NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF METHACRYLONITRILE

(CAS NO. 126-98-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

November 2001

NTP TR 497

NIH Publication No. 02-4431

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

FOREWORD

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

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

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

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

Details about ongoing and completed NTP studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov. Abstracts of all NTP Technical Reports and full versions of the most recent reports and other publications are available from the NIEHS' Environmental Health Information Service (EHIS) http://ehis.niehs.nih.gov (800-315-3010 or 919-541-3841). In addition, printed copies of these reports are available from EHIS as supplies last. A listing of all the NTP Technical Reports printed since 1982 appears on the inside back cover.

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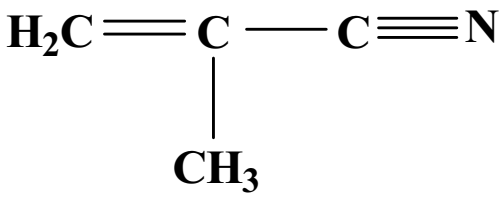
CONTENTS

ABSTRACT



METHACRYLONITRILE

CAS No. 126-98-7

Chemical Formula: C_4H_5N Molecular Weight: 67.09

Synonyms: 2-Cyanopropene; 2-cyano-1-propene; isobutenenitrile; isopropene cyanide; isopropenylnitrile; methylacrylonitrile; α-methylacrylonitrile; 2-methyl-2-propenenitrile

Methacrylonitrile is an unsaturated aliphatic nitrile. It is widely used in the preparation of homopolymers and copolymers, elastomers, and plastics and as a chemical intermediate in the preparation of acids, amides, amines, esters, and other nitriles. Methacrylonitrile is also used as a replacement for acrylonitrile in the manufacture of an acrylonitrile/butadiene/styrene-like polymer that provides improved barrier properties to gases such as carbon dioxide in carbonated beverage containers. Methacrylonitrile was nominated for study by the National Cancer Institute because of the potential for human exposure, structural similarity to the known carcinogen acrylonitrile, demonstrated toxic effects in several animal species, and a lack of toxicity and carcinogenicity data. Male and female F344/N rats and B6C3F$_1$ mice received methacrylonitrile (greater than 99% pure) in deionized water by gavage for 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, *Drosophila melanogaster*, rat and mouse bone marrow cells, and mouse peripheral blood erythrocytes.

2-Year Study in Rats

Groups of 50 male and 50 female rats were administered 0, 3, 10, or 30 mg methacrylonitrile/kg body weight in deionized water by gavage, 5 days per week for 104 to 105 weeks. This dose selection was based on the results of an NTP 13-week gavage study where rats were administered 0, 7.5, 15, 30, 60, or 120 mg methacrylonitrile/kg body weight. In the 13-week study, clinical signs of toxicity were observed early in the study. In addition, lower mean body weights and survival were observed in male and female rats administered 60 or 120 mg/kg.

In the 2-year study, survival of all dosed groups of rats was similar to that of the vehicle control groups. Mean body weights of the 30 mg/kg groups were less than those of the vehicle controls after weeks 21 and 37 for males and females, respectively. No changes in the incidences of neoplasms were attributed to exposure to methacrylonitrile. The incidences of olfactory epithelial atrophy and metaplasia of the nose were significantly

greater for 30 mg/kg males and females than for the vehicle controls. Increased incidences of cytoplasmic vacuolization occurred in the liver of males and females.

2-Year Study in Mice

Groups of 50 male and 50 female mice were administered methacrylonitrile in deionized water by gavage at doses of 0, 1.5, 3, or 6 mg/kg, 5 days per week for 104 to 105 weeks. This dose selection was based on the results of an NTP 13-week gavage study; where methacrylonitrile was administered at doses of 0, 0.75, 1.5, 3, 6, or 12 mg/kg for 32 days or 13 weeks. Mice administered 6 or 12 mg/kg exhibited clinical signs of toxicity. In addition, slight decreases in the mean body weight gains of 12 mg/kg male and female mice were observed at 13 weeks. Additionally, one 12 mg/kg male from the 32-day interim evaluation and one 12 mg/kg female from the 13-week study died during the first week of treatment; other deaths were accidental.

In the 2-year study, methacrylonitrile had no effect on survival. The mean body weights of all dosed groups were generally similar to those of the vehicle controls throughout the study. No neoplasms or nonneoplastic lesions were attributed to the methacrylonitrile administration.

Genetic Toxicology

Methacrylonitrile did not induce mutations in any of five strains of *Salmonella typhimurium*, with or without S9 activation, and did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* fed methacrylonitrile during the larval stage. Results of *in vivo* bone marrow micronucleus tests with methacrylonitrile in male rats and mice were also negative. Finally, no increase in the frequency of micronucleated erythrocytes was seen in peripheral blood of male or female mice treated with methacrylonitrile for 13 weeks by gavage.

Conclusions

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of methacrylonitrile in male or female F344/N rats administered 3, 10, or 30 mg/kg. There was *no evidence of carcinogenic activity* of methacrylonitrile in male or female $B6C3F_1$ mice administered 1.5, 3, or 6 mg/kg.

In male and female rats, methacrylonitrile administration caused significant increases in the incidences of nonneoplastic lesions of the nose and liver.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of the Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 10.

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses in water by gavage	0, 3, 10, or 30 mg/kg	0, 3, 10, or 30 mg/kg	0, 1.5, 3, or 6 mg/kg	0, 1.5, 3, or 6 mg/kg
Body weights	30 mg/kg group less than the vehicle control group	30 mg/kg group less than the vehicle control group	Dosed groups similar to the vehicle control group	Dosed groups similar to the vehicle control group
Survival rates	25/50, 34/50, 35/50, 31/50	38/50, 33/50, 34/50, 36/50	35/49, 43/50, 43/50, 22/50[a]	35/50, 35/50, 43/50, 25/50[a]
Nonneoplastic effects	Nose: olfactory epithelial atrophy (0/50, 0/50, 0/49, 48/50); olfactory epithelial metaplasia (0/50, 0/50, 0/49, 47/50) Liver: cytoplasmic vacuolization (14/50, 18/50, 23/50, 28/49)	Nose: olfactory epithelial atrophy (0/50, 0/50, 1/50, 19/50); olfactory epithelial metaplasia (0/50, 0/50, 0/50, 47/50) Liver: cytoplasmic vacuolization (7/50, 14/49, 17/48, 30/50)	None	None
Neoplastic effects	None	None	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, TA1535, and TA1537, with and without S9			
Sex-linked recessive lethal mutations *Drosophila melanogaster:*	Negative when administered in feed			
Micronucleated erythrocytes				
Rat bone marrow *in vivo*:	Negative			
Mouse bone marrow *in vivo*:	Negative			
Mouse peripheral blood *in vivo*:	Negative			

[a] Twenty-four males and 15 females in the 6 mg/kg groups died due to dosing accidents during week 69.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

For studies showing multiple chemical-related neoplastic effects that if considered individually would be assigned to different levels of evidence categories, the following convention has been adopted to convey completely the study results. In a study with clear evidence of carcinogenic activity at some tissue sites, other responses that alone might be deemed some evidence are indicated as "were also related" to chemical exposure. In studies with clear or some evidence of carcinogenic activity, other responses that alone might be termed equivocal evidence are indicated as "may have been" related to chemical exposure.

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on methacrylonitrile on 3 May 2001 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 3 May 2001, the draft Technical Report on the toxicology and carcinogenesis studies of methacrylonitrile received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

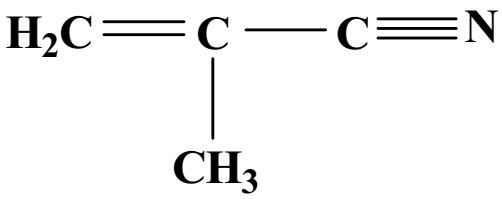
Dr. B.I. Ghanayem, NIEHS, introduced the toxicology and carcinogenesis studies of methacrylonitrile by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic and nonneoplastic lesions in rats and mice. Dr. Ghanayem also compared the toxicity and metabolism of methacrylonitrile to acrylonitrile. The proposed conclusion for the 2-year studies was *no evidence of carcinogenic activity* in male and female rats and mice.

Dr. Chatman, the first principal reviewer, questioned whether a maximum tolerated dose was achieved for the mouse study. Dr. Drinkwater, the second principal reviewer, also asked if a higher dose could have been tolerated by the mice and if the loss of some animals due to accidental deaths significantly reduced the sensitivity of the study. Dr. Dragan, the third principal reviewer, suggested that inhalation might have been a more appropriate route of exposure.

Dr. Ghanayem justified the selection of 6 mg/kg as the highest dose for mice by noting that in the precursor 13-week study, two mice that received 12 mg/kg died from acute toxicity. He also noted that on a molar basis, the highest dose in this study was double the lowest dose at which neoplasms were seen in mice in the companion acrylonitrile study. Dr. J.K. Haseman, NIEHS, noted that although the early deaths during week 69 reduced study sensitivity slightly, there was little evidence of a possible carcinogenic effect in male or female mice that might have been statistically significant with a few additional animals.

Dr. Chatman moved that a statement be added to the conclusion to indicate that mice may have been able to tolerate higher doses. Dr. Piegorsch seconded the motion. Dr. Drinkwater asked if data on cyanide levels were available to indicate that doses of 12 mg/kg would not have been tolerated. Dr. Ghanayem said that mortality, tremors, and convulsions were the indicators of acute toxicity. Dr. C.J. Portier, NIEHS, asked the panel for a more precise statement and asked if the implication was a conclusion of inadequate study. Dr. Hecht did not feel the study was inadequate because the goal of providing a comparison between methacrylonitrile and acrylonitrile was achieved. Dr. J.R. Bucher, NIEHS, said that the dose selection criteria used in this study followed the standard practice: because 12 mg/kg caused lethality and acute toxicity in a 13-week study, half that dose was chosen for the 2-year study. The motion to amend the conclusion failed by three yes votes to four no votes with one abstention (Dr. Klaunig). Dr. Davis then moved that the conclusions be accepted as written, *no evidence of carcinogenic activity*. Dr. Malarkey seconded the motion, which was approved by five yes votes to one no vote and two abstentions (Drs. Klaunig and Dragan).

INTRODUCTION



METHACRYLONITRILE

CAS No. 126-98-7

Chemical Formula: C_4H_5N Molecular Weight: 67.09

Synonyms: 2-Cyanopropene; 2-cyano-1-propene; isobutenenitrile; isopropene cyanide; isopropenylnitrile; methylacrylonitrile; α-methylacrylonitrile; 2-methyl-2-propenenitrile

Chemical and Physical Properties

Methacrylonitrile is an unsaturated aliphatic nitrile. The compound is a colorless liquid with a melting point of -35.8° C and a boiling point of 90° C. Methacrylonitrile is readily miscible with water, acetone, octane, and toluene at 20° to 25° C. The vapor pressure for methacrylonitrile is 40 torr at 13° C, 65 torr at 25° C, and 100 torr at 33° C (*Merck Index*, 1996).

Production, Use, and Human Exposure

Methacrylonitrile is prepared by the vapor-phase catalytic oxidation of methallylamine, by the dehydration of methacrylamide, or from the reaction of isopropylene oxide and ammonia. It is widely used in the preparation of homopolymers and copolymers, elastomers, and plastics and as a chemical intermediate in the preparation of acids, amides, amines, esters, and other nitriles (*Merck Index*, 1996). Methacrylonitrile is also used as a replacement for acrylonitrile in the manufacture of an acrylonitrile/butadiene/styrene-like polymer that provides improved barrier properties to gases such as carbon dioxide in carbonated beverage containers (Considine, 1974).

Methacrylonitrile has been designated as a hazardous waste by the United States Environmental Protection Agency (40 CFR, § 261.33). The estimated production capacity for methacrylonitrile in the United States was 1 to 10 million pounds in 1977 (USEPA, 1987). In 1978, an estimated 26,000 workers were potentially exposed to aliphatic nitriles each day in the United States (NIOSH, 1978). The National Occupational Exposure Survey conducted from 1980 to 1983 indicated that approximately 425 workers are exposed annually to methacrylonitrile (NIOSH, 1990). Additionally, methacrylonitrile has been identified as a component of the mainstream smoke of unfiltered cigarettes (3 µg/cigarette) made from air-cured or flue-cured tobaccos or a blend of these tobaccos (Baker *et al*., 1984). A time-weighted average threshold limit value of 1 ppm (2.7 mg/m^3) has been adopted by the American Conference of Governmental Industrial Hygienists (2000). The atmospheric odor threshold is reported to be 7 ppm (Amoore and Hautala,

1983). The concentration of methacrylonitrile-derived polymer in the methacrylonitrile-grafted butadiene copolymers used in the preparation of resinous and polymeric coating materials has been limited to 41%. Methacrylonitrile is also limited to 0.5 mg per square inch of food-contact surface in food packaging and to 50 ppm for chloroform-soluble coating components in water containers (21 CFR, Subpart C, § 175.300).

Absorption, Distribution, Metabolism, and Excretion

Experimental Animals

Methacrylonitrile is readily absorbed through the skin and respiratory and gastrointestinal tracts and is distributed to all tissues (Smyth *et al*., 1962; Pozzani *et al*., 1968; Tanii and Hashimoto, 1984; Farooqui and Mumtaz, 1991; Ghanayem *et al*., 1992).

Ghanayem *et al*. (1992) reported that methacrylonitrile elimination by rats is dose, strain, and dosing vehicle dependent. Male F344 rats were administered 1.15, 11.5, or 115 mg/kg methacrylonitrile in water by gavage. The primary route of elimination was in expired air as carbon dioxide. Rats administered 1.15 or 11.5 mg/kg exhaled 60% to 70% of the dose as carbon dioxide. In contrast, rats that received 115 mg/kg exhaled 25% of the dose as carbon dioxide and 40% of the dose as organic volatiles within 72 hours. The main constituents of the organic volatiles were methacrylonitrile and acetone. Evidence of saturation of methacrylonitrile metabolism was seen at 115 mg/kg. Urinary excretion accounted for 20% to 30% of the administered methacrylonitrile dose eliminated within 72 hours. In a study in which Sprague-Dawley rats were administered a gavage dose of 100 mg/kg methacrylonitrile in corn oil, 43% of the dose was eliminated in the urine as metabolites, 15% was eliminated in the feces, and 2.5% was exhaled as carbon dioxide (Cavazos *et al*., 1989). Ghanayem *et al*. (1992) observed that gavage administration of methacrylonitrile in corn oil rather than in water resulted in slower absorption and decreased elimination of unchanged methacrylonitrile.

Metabolite identification studies demonstrated that methacrylonitrile is metabolized via an epoxide intermediate, 1-cyano-1-methyloxirane (Figure 1). Studies in cytochrome P4502E1 (CYP2E1) knockout mice showed that although CYP2El is the principal enzyme responsible for the oxidative metabolism of methacrylonitrile, other cytochrome P450 enzymes are also involved (Ghanayem *et al*., 1999). 1-Cyano-1-methyloxirane was not identified *in vivo*; however, evidence based on the identity of methacrylonitrile metabolites in bile, urine, and expired air supports its formation in rats and mice. 1-Cyano-1-methyloxirane interacts with reduced glutathione, presumably via glutathione transferases, resulting in the formation of 1-(S-glutathionyl)-2-propanone (SGTP), which was identified in the bile of male F344 rats administered methacrylonitrile by gavage (Ghanayem and Burka, 1996). Catabolism of SGTP results in the formation of *N*-acetyl-S-(2-hydroxypropyl)-L-cysteine (NAHPC), which was identified in the urine of rats administered methacrylonitrile. Metabolism of 1-cyano-1-methyloxirane is considered the main pathway leading to cyanide release. Cyanide is converted to thiocyanate via rhodanese and excreted in urine. Approximately 13% of the administered dose was recovered as thiocyanate in the plasma and urine of rats administered methacrylonitrile (Cavazos *et al*., 1989; Farooqui *et al.*, 1992). Cyanide release from methacrylonitrile *in vivo* was reported to be species dependent (Farooqui *et al*., 1992). Administration of 100, 17, or 4 mg methacrylonitrile/kg body weight to rats, mice, or gerbils, respectively, resulted in the highest plasma concentrations of cyanide in gerbils, next highest in mice, and then lowest in rats. The high concentrations of cyanide in blood and the time to achieve maximum concentrations correlated well with the low LD_{50} of methacrylonitrile in gerbils and mice.

[^{14}C]-Acetone was identified in the expired breath of rats treated with [2-^{14}C]-methacrylonitrile (Ghanayem *et al.*, 1992). To explain the formation of this metabolite, it was suggested that SGTP may be the subject of a nucleophilic attack of glutathione on the sulfur atom resulting in the formation of glutathione disulfide and acetone. Alternatively, 1-cyano-1-methyloxirane may undergo reductive metabolism leading to the formation of acetone (Figure 1).

Another major metabolic pathway involves direct conjugation of parent methacrylonitrile with reduced glutathione, resulting in the formation of 1-(S-glutathionyl)-2-cyanopropane (SGTCP), which was identified in the bile of rats treated with methacrylonitrile by gavage (Ghanayem and Burka, 1996). This reaction may or may not be catalyzed by glutathione transferases. In contrast, the production of the direct conjugate of methacrylonitrile with glutathione is significantly less than that of the epoxide-glutathione conjugate.

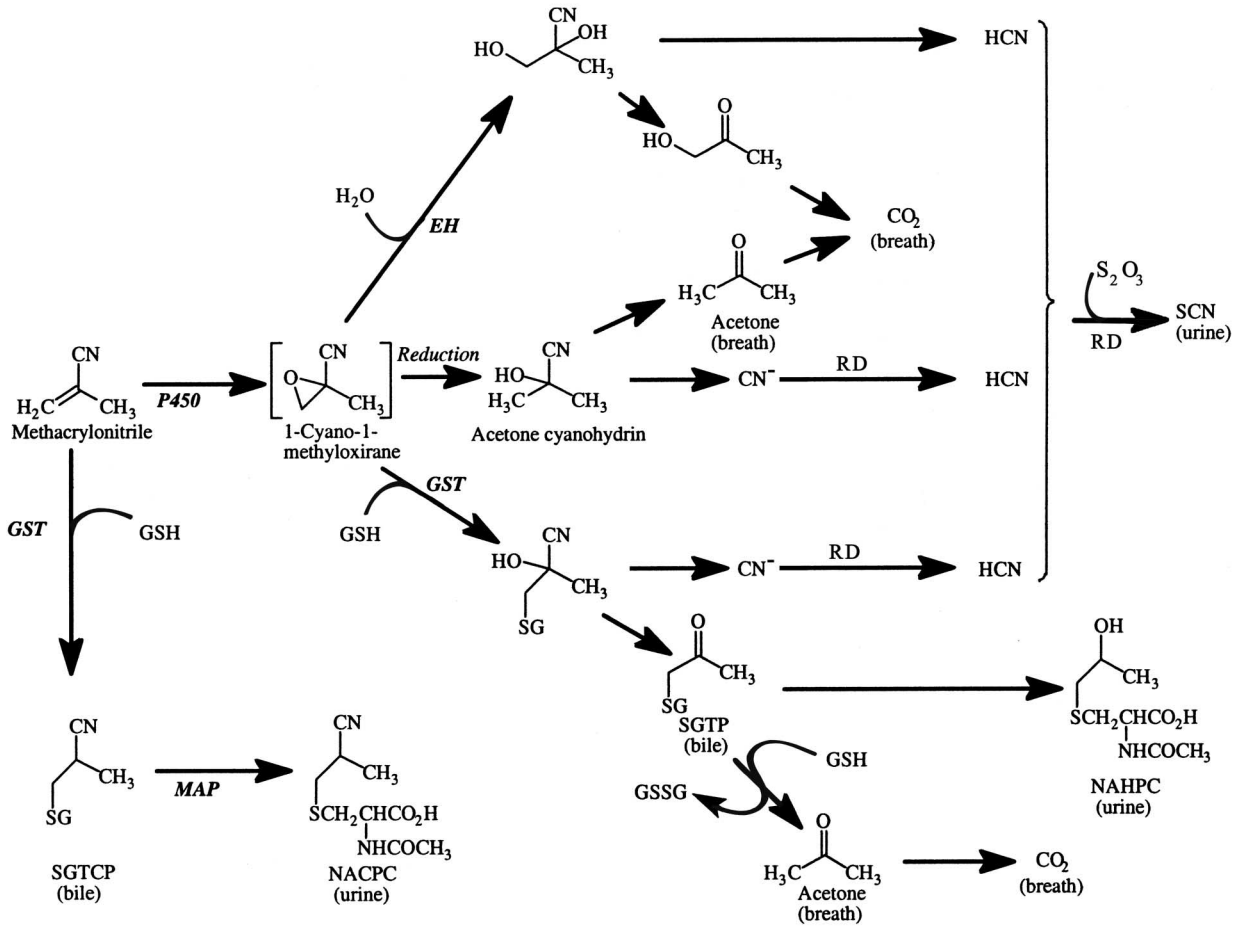


Figure 1
Metabolism of Methacrylonitrile in Rats and Mice
(Farooqui and Mumtaz, 1991; Ghanayem *et al*., 1992; Ghanayem and Burka, 1996)
SGTP=1-(S-glutathionyl)-2-propanone; NAHPC=*N*-acetyl-S-(2-hydroxypropyl)-L-cysteine; SGTCP =1-(S-glutathionyl)-2-cyanopropane; NACPC=*N*-acetyl-S-(2-cyanopropyl)-L-cysteine; GSH=reduced glutathione; GST=glutathione-S-transferase; EH=epoxide hydratase; RD=rhodanese; MAP=mercapturic acid pathway

Degradation of SGTCP produces *N*-acetyl-S-(2-cyanopropyl)-L-cysteine (NACPC), which was identified in the urine of methacrylonitrile-treated rats (Ghanayem *et al*., 1992).

F344/N rats and B6C3F$_1$ mice administered 1.15 or 11.5 mg/kg [2-^{14}C]-methacrylonitrile in a single gavage dose metabolized and excreted methacrylonitrile differently (Ghanayem *et al*., 1994). Rats and mice excreted 7% and 49%, respectively, of the 11.5 mg/kg dose as NAHPC. These data, in addition to earlier reports showing that a greater portion of the methacrylonitrile dose was converted to cyanide in mice than in rats (Farooqui *et al*., 1992), support the hypothesis that mice metabolize methacrylonitrile via the epoxide intermediate to a greater extent than do rats. Rats eliminated more [2-^{14}C]-methacrylonitrile-derived carbon dioxide than did mice, suggesting that rats may be more efficient in detoxifying methacrylonitrile oxidative intermediates (Ghanayem *et al*., 1994).

Elimination of methacrylonitrile in F344 rats occurs primarily in expired air and in urine. Male F344 rats administered [2-^{14}C]-methacrylonitrile intravenously at doses of 29, 58, or 116 mg/kg showed a terminal half-life of 39 minutes, suggesting that the potential for bioaccumulation is minimal (Demby *et al.*, 1993). This work also showed that clearance is higher at 29 mg/kg than at 58 or 116 mg/kg, further confirming that methacrylonitrile elimination is saturated at doses above 29 mg/kg. Within 24 hours, approximately 36% was exhaled as unchanged methacrylonitrile, 26% as carbon dioxide, 17% as acetone, and 16% was excreted in the urine as metabolites in male rats that received 58 mg/kg intravenously. Male F344 rats administered 58 mg/kg [2-^{14}C]-methacrylonitrile in water by gavage exhaled 18% of the dose as unchanged methacrylonitrile, 39% as carbon dioxide, and 13% as acetone within 24 hours after dosing. Twenty-two percent of the dose was eliminated in the urine as metabolites within 24 hours.

Concentrations of thiocyanate in blood and urine of male Sprague-Dawley rats increased following administration of a single 100 mg/kg dose of [2-^{14}C] methyl-2,3 [^{14}C] acrylonitrile in safflower oil by gavage (Cavazos *et al*., 1989). The thiocyanate concentration in plasma of these rats increased significantly from 26.3 µmol/L within 1 hour to 87 µmol/L within 6 hours. Five days after gavage dosing, the total urinary excretion of thiocyanate was approximately 12% of the administered methacrylonitrile dose, whereas the total urinary excretion of radioactivity was 43%.

Studies of the tissue distribution of radioactivity in rats treated with 11.5, 58, or 115 mg/kg [2-^{14}C]-methacrylonitrile showed that methacrylonitrile was distributed to all major tissues as a function of time (Ghanayem *et al*., 1992). The concentration of methacrylonitrile-derived radioactivity was dose dependent and was particularly high in the liver, kidney, urinary bladder, intestine, adrenal gland, and thymus. With the exception of the brain, the tissue/blood ratio of methacrylonitrile-derived radioactivity in rats receiving the median (58 mg/kg) methacrylonitrile dose was greater than 1.0 at 8, 24, and 72 hours after dosing. The concentration of methacrylonitrile-derived radioactivity was consistently higher in rats that received 115 mg/kg methacrylonitrile and declined as a function of time to reach a minimal concentration at 72 hours. The percentage of methacrylonitrile which remained in tissues of rats 72 hours after dosing was less than 3% of the administered dose. These data further confirmed that methacrylonitrile has a minimal potential for bioaccumulation.

Male Sprague-Dawley rats administered 100 mg/kg [2-^{14}C]-methacrylonitrile by gavage retained radioactivity in erythrocytes for more than 5 days after dosing, suggesting that methacrylonitrile binds to macromolecules (Cavazos *et al*., 1989). The peak concentration occurred 3 hours after exposure. Approximately 66% to 76% of the radioactivity in erythrocytes was localized in the protein fraction, which includes membrane proteins as well as globin from hemoglobin.

In a study to assess the role of CYP2E1 in methacrylonitrile metabolism and disposition, 12 mg/kg [2-^{14}C]-methacrylonitrile was administered by gavage to CYP2E1$^{-/-}$ mice, CYP2E1$^{-/-}$ mice pretreated with 1-aminobenzotriazole (a universal cytochrome P450 inhibitor), and wild-type mice (Ghanayem *et al*., 1999). Significant differences in the elimination of [2-^{14}C]-methacrylonitrile-derived radioactivity were found among the three groups. Exhalation of [2-^{14}C]-methacrylonitrile-derived organic volatiles in the 24 hours following dosing was 34% and 1% to 3% of the administered dose in CYP2E1$^{-/-}$ and wild-type mice, respectively. CYP2E1$^{-/-}$ mice exhaled a significantly smaller portion of the dose as organic volatiles as compared to CYP2E1$^{-/-}$ mice pretreated with 1-aminobenzotriazole, and a significantly greater percentage of the dose as [^{14}C]-carbon dioxide. High-performance liquid chromatography (HPLC) showed that parent methacrylonitrile was the only detectable constituent of the exhaled organic volatiles for all mice.

Exhalation of carbon dioxide derived from methacrylonitrile metabolism was three to five times greater in wild-type mice than in CYP2E1$^{-/-}$ mice. Further, urinary excretion of methacrylonitrile-derived radioactivity was significantly less in CYP2E1$^{-/-}$ mice than in wild-type mice. HPLC analysis revealed an approximate 50% decrease in the urinary excretion of NAHPC in CYP2E1$^{-/-}$ mice compared to wild-type mice. As noted earlier, NAHPC is formed via cytochrome P450-mediated metabolism (Figure 1). In contrast, a significant increase in the excretion of NACPC was seen in CYP2E1$^{-/-}$ mice compared to wild-type mice. As shown in Figure 1, NACPC is formed via metabolic pathways that do not involve cytochrome P450 enzymes. In CYP2E1$^{-/-}$ mice pretreated with 1-aminobenzotriazole (an inhibitor of P450 enzymes), less than 2% of the administered methacrylonitrile was eliminated as urinary NAHPC; this was associated with a significant increase in urinary excretion of NACPC. The concentrations of methacrylonitrile-derived radioactivity in tissues generally showed the following trend: wild-type mice > CYP2E1$^{-/-}$ mice > CYP2E1$^{-/-}$ mice pretreated with 1-aminobenzotriazole. This suggests a direct relationship between methacrylonitrile oxidative metabolism and the persistence of methacrylonitrile and/or its metabolites in various tissues. Therefore, it is suggested that methacrylonitrile-derived oxidative metabolites such as the epoxide intermediate have greater reactivity with mouse tissues than parent methacrylonitrile. It was concluded from these studies that although CYP2E1 is the primary enzyme involved in methacrylonitrile oxidative metabolism, other enzymes are also involved.

Humans

No information on the absorption, distribution, metabolism, or excretion of methacrylonitrile in humans was found in the literature.

TOXICITY

Experimental Animals

The toxicity of aliphatic nitriles has been attributed to the formation of epoxide intermediates, depletion of tissue glutathione, and the metabolic release of cyanide. The most studied compound in this class is acrylonitrile, which causes acetylcholine- and cyanide-like toxic effects and is a known rat carcinogen (Ghanayem *et al.*, 1985, 1991; IARC, 1999). The toxicity and carcinogenicity of acrylonitrile have been attributed at least partially to its oxidation to an epoxide intermediate (2-cyanoethylene oxide), cyanide release, and depletion of tissue glutathione (Tanii and Hashimoto, 1984; Ghanayem *et al*., 1985).

Methacrylonitrile has been shown to be acutely toxic in rats, mice, dogs, and rabbits by dermal, inhalation, intraperitoneal, ocular, and gavage routes of administration (McOmie, 1949; Smyth *et al*., 1962; Pozzani *et al*., 1968; Tanii and Hashimoto, 1984). The toxic effects of methacrylonitrile have also been attributed to the *in vivo* release of cyanide and depletion of glutathione (Willhite and Smith, 1981; Hartung, 1982). Silver *et al*. (1982) reported that the length of the carbon chain, presence of substituents at the α-carbon, position of the double bonds, and route of administration are important factors in influencing the release of cyanide from nitriles *in vivo*.

The LD_{50} values for methacrylonitrile vary widely depending on species and route of administration (Table 1). The LD_{50} values in 14-day inhalation studies with methacrylonitrile range from 36 ppm in A/J mice to 328 to 700 ppm in Harlan-Wistar rats (Pozzani *et al*., 1968). The LD_{50} values for gavage studies with methacrylonitrile range from 4 mg/kg in gerbils to 200 mg/kg in Harlan-Wistar rats.

The symptoms of methacrylonitrile toxicity are similar among animal species. In A/J mice, Harlan-Wistar rats, albino guinea pigs, and rabbits administered methacrylonitrile by inhalation for 14 days, death was preceded by a loss of consciousness and by tonic-clonic convulsions (Pozzani *et al.*, 1968). Male beagle dogs exposed to 13.5 ppm methacrylonitrile by inhalation for 13 weeks developed central nervous system effects manifested by tonic convulsions and by a loss of control of the hind limbs (Pozzani *et al*., 1968). Sprague-Dawley rats developed ataxia, tremors, convulsions, irregular breathing, salivation, vasodilation, and diarrhea within one hour of gavage administration of 100 mg/kg methacrylonitrile (Farooqui *et al.*, 1990). Dermal administration of methacrylonitrile to rabbits caused irritation consisting of slight erythema and discoloration at the site of application followed by lung congestion and death at doses greater than 2.0 mL/kg (McOmie, 1949). Intraperitoneal or gavage administration of 15 mg/kg methacrylonitrile has been observed to be lethal in mice (McOmie, 1949).

The time required for the onset of cyanide-related central nervous system toxicity in Albino-Swiss mice, Sprague-Dawley rats, and Mongolian gerbils varies (Farooqui *et al*., 1992). The peak blood concentration of cyanide occurred at 1 hour in mice and gerbils and at 3 hours in rats treated with methacrylonitrile by gavage

TABLE 1
Summary of Selected Animal LD_{50} Data for Methacrylonitrile

Species	Route	LD_{50}	Reference
Rat	Gavage	200 mg/kg	Pozzani *et al*., 1968
Rat	Inhalation	328 to 700 ppm	Pozzani *et al*., 1968
Mouse	Gavage	17 mg/kg	Tanii and Hashimoto, 1984
Mouse	Inhalation	36 ppm	Pozzani *et al*., 1968
Guinea pig	Inhalation	88 ppm	Pozzani *et al*., 1968
Rabbit	Dermal	268 mg/kg	Smyth *et al*., 1962
Gerbil	Gavage	4 mg/kg	Farooqui and Mumtaz, 1991

Administration of 0.3 mmol/kg methacrylonitrile by gavage in olive oil to male ddY mice pretreated with carbon tetrachloride resulted in a lower concentration of cyanide than that observed in the controls, significantly increased survival, and greatly reduced toxicity (Tanii and Hashimoto, 1984). These authors proposed that carbon tetrachloride decreased cyanide liberation from methacrylonitrile *in vivo*. Rabbits were resuscitated from a moribund condition induced by dermal exposure to 4 mL/kg methacrylonitrile using a 20 mg/kg intravenous dose of sodium nitrite, a cyanide antidote (McOmie, 1949).

As noted previously, depletion of endogenous glutathione by methacrylonitrile may be another mechanism of toxicity. Male Sprague-Dawley rats administered 100 mg/kg methacrylonitrile exhibited glutathione depletion in the liver (39% of the controls) and in the brain, heart, kidney, lung, and spleen (26% to 34% of the controls) (Day *et al*., 1988).

The National Toxicology Program (2000) has published the results of 13-week studies of methacrylonitrile in rats and mice. Methacrylonitrile was administered to F344/N rats at 0, 7.5, 15, 30, 60, or 120 mg/kg and to $B6C3F_1$ mice at 0, 0.75, 1.5, 3, 6, or 12 mg/kg body weight for 32 days or 13 weeks in water by gavage. Methacrylonitrile resulted in dose-dependent lethargy, tremors, lacrimation, convulsions, and abnormal breathing in both species. These effects were more pronounced in rats than in mice, but the apparent greater sensitivity of rats may be attributed to the higher doses used in rats. Body weight gain and mortality were gender dependent in rats, with males being more sensitive than females; mortality was 95% in males versus 5% in females in groups receiving 120 mg/kg. Methacrylonitrile administration also resulted in a dose-dependent decrease in body weight. Blood cyanide levels in rats suggested a correlation between the *in vivo* liberation of cyanide from methacrylonitrile and mortality, with male rats having higher blood cyanide levels than female rats. At present, it is not clear why blood cyanide levels are higher in females than in males dosed with methacrylonitrile. Changes in organ weights were also observed in animals treated with methacrylonitrile. Significant dose-dependent increases were observed in the stomach weights of rats and mice and the liver weight of rats. Significant decreases in thymus weights were also observed in rats and mice. These effects varied between rats and mice and as a function of time and methacrylonitrile dose. These changes in organ weights were not associated with histopathologic alterations.

At the 32-day interim evaluation and at the end of the 13-week gavage study (NTP, 2000), the nasal olfactory epithelium of rats was the only target of methacrylonitrile. Administration of methacrylonitrile caused dose-dependent increases in the incidences of necrosis and metaplasia in rats. The no-observed-adverse-effect level of methacrylonitrile in the olfactory epithelium of rats dosed for 13 weeks was 30 mg/kg. No nasal lesions were observed in mice treated with methacrylonitrile, which could have resulted from the lower dose used in mice as compared to rats.

Humans

Groups of human volunteers were exposed to methacrylonitrile by sequential inhalation of concentrations of 24, 14, 0, 7, 14, 24, 2, 0, and 2 ppm for 1.0 minute each with a 45-minute or longer interval between exposures (Pozzani *et al.*, 1968). Subjects exposed to 24 ppm experienced nose, throat, or eye irritation. The majority of the subjects (88% to 89%) could detect methacrylonitrile odor at 14 or 24 ppm.

Reproductive and Developmental Toxicity

Experimental Animals

After oral exposure to 50 mg methacrylonitrile/kg body weight per day during the first 2 weeks of gestation or to 100 mg/kg per day during only the second week of gestation, pregnant Sprague-Dawley rats aborted (Villarreal *et al*., 1988). A dose-dependent reduction in maternal body weight gain was also observed. At the end of gestation, rats exposed to methacrylonitrile developed dose-dependent, mild-to-severe edema in the fallopian tubes. Teratogenic effects such as exencephaly, encephalocele, and rib fusions and bifurcations may be attributed to cyanide release from aliphatic nitriles (Willhite *et al*., 1981). Based on the reproductive toxicity of methacrylonitrile, the lowest-observed-adverse-effect level appears to be 50 mg/kg (Farooqui and Mumtaz, 1991). Inhalation exposure to 100 ppm methacrylonitrile for 6 hours during days 6 and 20 of gestation resulted in no significant teratogenicity (Saillenfait *et al*., 1993).

The developmental effects of aliphatic nitriles (including methacrylonitrile) were investigated both *in vivo* and *in vitro* by Saillenfait and Sabate (2000). These studies showed that aliphatic nitriles produce concentration-dependent decreases in growth and differentiation and increases in the incidences of morphologically abnormal embryos *in vitro*. Day 10 rat embryos were cultured for 46 hours at methacrylonitrile concentrations up to 40 mM, and similar effects were observed (Saillenfait and Sabate, 2000). The presence of rat hepatic microsomes in the cultures enhanced these effects.

Reproductive toxicity studies showed that female rats administered 60 or 120 mg/kg methacrylonitrile by gavage had significantly longer estrous cycles than the vehicle control group. Furthermore, females in the 60 mg/kg group spent more time in the diestrus phase than the vehicle control animals (NTP, 2000).

Humans

No information on reproductive toxicity studies of methacrylonitrile in humans was found in the literature.

Carcinogenicity

Experimental Animals

No information on long-term studies of the carcinogenicity of methacrylonitrile in experimental animals was found in the literature.

The carcinogenicity of acrylonitrile, which is structurally similar to methacrylonitrile, has been investigated in rats in a number of studies, and reviews of these studies are available (USEPA, 1983; WHO, 1983; IARC, 1987, 1999; ATSDR, 1990). Collectively, these studies demonstrated that acrylonitrile is a multisite carcinogen in rats; the target organs, which varied from one study to another, included the brain, spinal cord, forestomach, small intestine, tongue, mammary gland, and Zymbal's gland. Administration of 20, 100, or 500 ppm acrylonitrile in drinking water to male Sprague-Dawley rats for 2 years resulted in a significant increase in the incidence of Zymbal's gland neoplasms (Gallagher *et al*., 1988). In another drinking water study, 100 or 500 ppm acrylonitrile administered to Fischer 344 rats resulted in increased incidences of brain and spinal cord neoplasms (Bigner *et al*., 1986). Inhalation (Maltoni *et al*., 1988) or gavage (Maltoni *et al*., 1977) exposure to acrylonitrile also caused increased incidences of neoplasms in Sprague-Dawley rats. No information on acrylonitrile carcinogenicity in any other animal species was available at the start of the current methacrylonitrile studies. However, the NTP has completed a study to assess the carcinogenicity of acrylonitrile in mice (NTP, 2001a). This study demonstrated that acrylonitrile is also a multisite carcinogen in male and female B6C3F_1 mice when administered at 2.5, 10, or 20 mg/kg by gavage; increases in the incidences of neoplasms were observed in the forestomach and harderian gland of male mice and in the forestomach, ovary, harderian gland, and lung of female mice.

Humans

While acrylonitrile is considered a possible human carcinogen (Group 2B), no epidemiology studies of methacrylonitrile in humans were found in the literature (IARC, 1999).

Genetic Toxicity

There are few mutagenicity studies on methacrylonitrile; however, the available evidence indicates that the chemical is not genotoxic. Negative results were obtained in tests for induction of gene mutations in *Salmonella typhimurium* (Zeiger *et al*., 1987) and sex-linked recessive lethal mutations in *Drosophila melanogaster* (Zimmering *et al*., 1989). Results included in a brief abstract also presented no evidence for mutagenicity in *Salmonella*, mouse lymphoma L5178Y cells, or *Drosophila* (Knaap *et al*., 1985).

In a male rat bone marrow micronucleus test, methacrylonitrile failed to induce a consistent, significant increase in the induction of micronuclei when administered in a series of three daily intraperitoneal injections of methacrylonitrile at 12 to 100 mg/kg body weight (NTP, 2000). Similarly, no induction of micronuclei was observed in the bone marrow of female mice treated in the same manner with 6.25 to 25 mg/kg methacrylonitrile (NTP, 2000).

Study Rationale

Methacrylonitrile was nominated by the National Cancer Institute for study because of the potential for human exposure, structural similarity to the known carcinogen acrylonitrile, demonstrated toxic effects in several animal species, and a lack of toxicity and carcinogenicity data on this chemical at the time of nomination.

Doses for the 2-year studies were selected based on the results of the earlier 13-week gavage studies of methacrylonitrile in rats and mice (NTP, 2000). Due to the mortality, early signs of acute neurotoxicity (including tremors and convulsions), body weight decreases, and blood cyanide levels at 60 and 120 mg/kg in male rats, doses for males in the 2-year study were set at 0, 3, 10, and 30 mg/kg. Similar results precluded use of 120 mg/kg in female rats. While females may have tolerated 60 mg/kg, there was concern about the relatively high cyanide levels (15-fold increase) and the acute neurotoxicity encountered early in the 13-week study. Therefore 0, 3, 10, and 30 mg/kg were also selected as doses for female rats.

In the 13-week mouse study with a 32-day interim sacrifice (NTP, 2000), methacrylonitrile was administered at doses of 0, 0.75, 1.5, 3, 6 and 12 mg/kg. At 12 mg/kg, methacrylonitrile caused slight decreases in mean body weight gain and one death in males and one in females during the first week of dosing. In addition, male mice that received 12 mg/kg became prostrate and exhibited tremors and ataxia early in the 13-week study. Female mice were more severely affected and exhibited irregular breathing and convulsions. Although the acute toxicity signs of methacrylonitrile encountered early during the 13-week study abated as dosing continued, there was concern over the use of 12 mg/kg for 2 years. Therefore, doses for the 2-year study in mice were set at 1.5, 3, and 6 mg/kg.

MATERIALS AND METHODS

Procurement and Characterization of Methacrylonitrile

Methacrylonitrile was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (00427ET). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory (Radian Corporation, Austin, TX), and the study laboratory (Appendix G). Reports on analyses performed in support of the methacrylonitrile studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a colorless liquid, was identified as methacrylonitrile using infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy and gas chromatography/mass spectrometry. The purity of lot 00427ET was determined using Karl Fischer water analysis and gas chromatography. Karl Fischer water analysis indicated 0.19% water. Gas chromatography indicated one major peak and one impurity with an area of 0.03% (by one system) or 0.04% (by a second system) of the total area. The overall purity was determined to be greater than 99%.

Accelerated stability studies of the bulk chemical were conducted by the analytical chemistry laboratory using gas chromatography to evaluate the potential for degradation during storage over the course of the study. No degradation of the bulk chemical was observed after storage for 14 days at 60° C. The bulk chemical was stored at room temperature, protected from light, in amber glass bottles in metal cans. Stability was monitored during the 2-year studies with gas chromatography. No degradation of the bulk chemical was detected during the studies.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared every 4 weeks through 3 January 1996 and every 2 weeks thereafter by mixing methacrylonitrile with deionized water (Table G2). Stability studies of a 0.15 mg/mL dose formulation were performed by the study laboratory with gas chromatography. Stability of dose formulations was confirmed for at least 35 days. Dose formulations were stored at 5° C in amber glass bottles during the study.

Periodic analyses of the dose formulations of methacrylonitrile were conducted at the study laboratory using gas chromatography. The dose formulations were analyzed approximately every 8 to 12 weeks (Table G3). All dose formulations analyzed for rats were within 10% of the target concentration, and 34 of 36 dose formulations analyzed for mice were within 10% of the target concentration with no value greater than 112% of the target concentration. Analysis of postadministration dosing solutions showed declines in methacrylonitrile concentrations that were attributed to volatilization. Typically, losses were greater in mouse dosing solutions than in rat dosing solutions. Efforts to minimize headspace in dosing bottles as well as the use of crimp-top bottles with septa decreased losses but did not eliminate them completely.

2-Year Studies

Study Design

Groups of 50 male and 50 female rats were administered methacrylonitrile in deionized water by gavage at doses of 0, 3, 10, or 30 mg/kg body weight, 5 days per week for 104 to 105 weeks. Groups of 50 male and 50 female mice were administered methacrylonitrile in deionized water by gavage at doses of 0, 1.5, 3, or 6 mg/kg, 5 days per week for 104 to 105 weeks.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY) for use in the 2-year studies. Rats and mice were quarantined for 11 (males) or 12 (females) days before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 6 weeks old

at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix I).

Animal Maintenance

Rats were housed two or three (males) or five (females) per cage and mice were housed individually (male) or five (females) per cage. Feed and water were available *ad libitum*. Cages were changed twice weekly (rats and female mice) or weekly (male mice), and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 2. Information on feed composition and contaminants is provided in Appendix H.

Clinical Examinations and Pathology

All animals were observed twice daily. Animals were weighed at the beginning of the studies, every 4 weeks, and at necropsy. Clinical findings were recorded on days 8 and 29, every 4 weeks thereafter, and at necropsy.

Five male and five female rats and mice per group were randomly selected for urine collection at 2 weeks and at 3, 12, and 18 months. The animals were placed individually into metabolism cages for urine collection immediately after dosing, and urine was collected over ice during a 24-hour period, after which the animals were returned to their regular cages. The volume of urine was recorded, and urine creatinine concentrations were determined using a Hitachi 911 chemistry analyzer (Boehringer Mannheim, Indianapolis, IN) and reagents supplied by the manufacturer. Urine samples were then stored frozen at -20° C or less until they were shipped to another facility for metabolite quantitation. The metabolites measured are listed in Table 2.

The methacrylonitrile urinary metabolites, *N*-acetyl-S-(2-cyanopropyl)-L-cysteine (NACPC) and *N*-acetyl-S-(2-hydroxypropyl)-L-cysteine (NAHPC), were measured using liquid chromatography coupled with tandem mass spectrometry at an analytical chemistry laboratory (Cedra Corporation; Austin, TX). The samples were extracted with acetonitrile and injected onto a strong anion exchange column (YKC 5 micron, 2.0 × 50 mm; YMC, Inc., Wilmington, NC). The mobile phase was 0.1% ammonium acetate in water, and the system was operated isocratically at 1.3 mL/minute. The mass spectrometer (Perkin Elmer Sciex, Norwalk, CT) monitored the peak areas of daughter ions at m/z 100 from the m/z 229 fragment of NACPC and the daughter ion m/z 91 from the m/z 220 fragment of NAHPC relative to the m/z 85 daughter ion of the m/z 215 fragment of the internal standard (*N*-acetyl-S-(2-cyanoethyl)-L-cysteine). The method was validated over the concentration range from 0.500 to 100 ug/mL based on a sample volume of 0.200 mL with acceptable precision, accuracy, and recovery.

Complete necropsies and microscopic examinations were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 2.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. 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 evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the bone marrow, liver, nose, pancreas, and thyroid gland of male and female rats; adrenal gland and spleen of male rats; clitoral gland of female rats; small intestine, kidney, and liver of male and female mice; adrenal gland, epididymis, lung, oral mucosa, pituitary gland, preputial gland, prostate gland, and salivary gland of male mice; and the mandibular lymph node, mesentery, ovary, and uterus of female mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists

experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al*. (1986).

TABLE 2
Experimental Design and Materials and Methods in the 2-Year Gavage Studies of Methacrylonitrile

Study Laboratory
Battelle Columbus Operations (Columbus, OH)

Strain and Species
F344/N rats
$B6C3F_1$ mice

Animal Source
Taconic Laboratory Animals and Services (Germantown, NY)

Time Held Before Studies
11 (males) or 12 days (females)

Average Age When Studies Began
6 weeks

Date of First Dose
Rats: 30 October 1995 (males) or 31 October 1995 (females)
Mice: 16 October 1995 (males) or 17 October 1995 (females)

Duration of Dosing
5 days/week for 104 to 105 weeks

Date of Last Dose
Rats: 24, 27-28 October 1997 (males) or 29-30 October 1997 (females)
Mice: 10, 13-14 October 1997 (males) or 14-16 October 1997 (females)

Necropsy Dates
Rats: 27-29 October 1997 (males) or 30-31 October 1997 (females)
Mice: 13-15 October 1997 (males) or 15-17 October 1997 (females)

Average Age at Necropsy
110 weeks

Size of Study Groups
50 males and 50 females

Method of Distribution
Animals were distributed randomly into groups of approximately equal initial mean body weights.

Animals per Cage
Rats: 2 or 3 (males) or 5 (females)
Mice: 1 (male) or 5 (females)

Method of Animal Identification
Tail tattoo

Diet
NTP-2000 nonirradiated pelleted diet from study initiation to 25 July 1996 for rats or 16 July 1996 for mice; irradiated pelleted diet until study termination (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum* and changed weekly. NTP-2000 meal feed provided during 24-hour urine collections at 12 and 18 months.

Water
Tap water (City of Columbus municipal supply) via automatic watering system (except when animals were housed in metabolism cages, when they drank out of polycarbonate bottles fitted with stainless steel caps and sipper tubes), available *ad libitum*.

TABLE 2
Experimental Design and Materials and Methods in the 2-Year Gavage Studies of Methacrylonitrile

Cages
Solid, polycarbonate (Lab Products, Inc., Maywood, NJ), rotated every 2 weeks and changed twice weekly (rats and female mice) or weekly (male mice)

Bedding
Sani-Chips® hardwood (P.J. Murphy Forest Products Corp., Montville, NJ), changed twice weekly (rats and female mice) or weekly (male mice)

Cage Filters
Spun-bonded polyester DuPont 2024 filter (Snow Filtration Co., Cincinnati, OH), changed every 2 weeks

Racks
Stainless steel, drawer-type (Lab Products, Inc., Maywood, NJ), rotated every 2 weeks

Animal Room Environment
Temperature: 72° ± 3° F
Relative humidity: 50% ± 15%
Room fluorescent light: 12 hours/day
Room air changes: 10/hour

Doses
Rats: 0, 3, 10, or 30 mg/kg in deionized water by gavage (dosing volume 5 mL/kg)
Mice: 0, 1.5, 3, or 6 mg/kg in deionized water by gavage (dosing volume 10 mL/kg)

Type and Frequency of Observation
Observed twice daily; animals were weighed at the beginning of the studies, every 4 weeks, and at necropsy. Clinical findings were recorded on days 8 and 29, every 4 weeks thereafter, and at necropsy.

Method of Sacrifice
Carbon dioxide asphyxiation

Necropsy
Necropsies were performed on all animals.

Urinalysis and Urinary Metabolite Analyses
At 2 weeks and at 3, 12, and 18 months, five male and five female rats and mice from each group were randomly selected and placed individually into metabolism cages for urine collection immediately after dosing. The urine was collected over ice during a 24-hour period, after which the animals were returned to their regular cages. Parameters evaluated include urine volume, creatinine, *N*-acetyl-S-(2-cyanopropyl)-L-cysteine and *N*-acetyl-S-(2-hydroxypropyl)-L-cysteine.

Histopathology
Complete histopathology was performed on all animals. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung with mainstem bronchi, lymph nodes (mandibular and mesenteric), mammary gland (except male mice), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

STATISTICAL METHODS

Survival Analyses

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

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, B4, C1, C4, D1, and D4 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F_1 mice (Portier *et al*., 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each dosed group with controls and a test for an overall dose-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions are represented as 1-P with the letter N added (e.g., P=0.99 is presented as P=0.01N).

Analysis of Continuous Variables

Urinalysis and toxicokinetic data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test [Williams' (1971, 1972) or Shirley's test] was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend [Dunnett's (1955) or Dunn's test]. Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

The concurrent control group represents the most valid comparison to the treated groups and is the only control group analyzed statistically in NTP bioassays. However, historical control data are often helpful in interpreting potential treatment-related effects, particularly for uncommon or rare neoplasm types. For meaningful comparisons, the conditions for studies in the historical database must be generally similar. Until recently, the NTP historical control database consisted of animals fed NIH-07 diet. In 1995, the NTP changed the diet fed to animals used in toxicity and carcinogenesis studies conducted by the NTP. This new diet (NTP-2000) contains less protein and more fiber and fat than the NIH-07 diet previously used (Rao, 1996, 1997). This dietary change was instituted primarily to increase longevity and decrease the incidence and/or severity of some spontaneous neoplasms and nonneoplastic lesions in the rats and mice used in NTP studies. These studies of methacrylonitrile are some of the first in which the animals on study were fed the NTP-2000 diet. Because the incidence of some neoplastic and nonneoplastic lesions may be affected by the dietary change, use of the existing historical control database (NIH-07 diet) may not be appropriate for all neoplasm types.

Currently, the database includes 11 (10 for male rats) studies by various routes in which the NTP-2000 diet was used. Based on the extensive NTP historical database using the NIH-07 diet, incidences of the vast majority of spontaneous neoplasms are not significantly different between control groups regardless of the route of administration. There is no reason to expect this to be different with the NTP-2000 diet. For example, control animals from dosed feed and dosed water studies are treated no differently and no differences in incidence of neoplasms are expected. Exceptions exist for some neoplasms/routes, and if comparisons are necessary for these neoplasm types, only studies with similar routes of administration will be used.

Quality Assurance Methods

The 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of methacrylonitrile was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sex-linked recessive lethal mutations in *Drosophila melanogaster,* and micronucleated erythrocytes in rat and mouse bone marrow and mouse peripheral blood. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of methacrylonitrile are part of a larger effort by the NTP to develop a comprehensive database that would permit a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). These short-term genetic toxicity tests were originally developed to clarify mechanisms of chemical-induced DNA damage growing out of the earlier electrophilicity/mutagenicity relationship proposed by Miller and Miller (1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). Therefore, the information obtained from these tests applies only to mutagenic carcinogens. For mutagenic carcinogens, the combination of DNA reactivity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in multiple species and genders of rodents and at multiple tissue sites (Ashby and Tennant, 1991). Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) and that there is no complementarity among the *in vitro* genetic toxicity tests (Tennant *et al*., 1987; Zeiger *et al.*, 1990). That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. Although other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity compared with the *Salmonella* test, these other tests can provide useful information on the types of

DNA and chromosomal effects induced by the chemical under investigation.

The predictivity for carcinogenicity of a positive response in the acute *in vivo* bone marrow chromosome aberration test or micronucleus test appears to be less than that in the *Salmonella* test (Shelby *et al*., 1993; Shelby and Witt, 1995). However, clearly positive results in long-term peripheral blood micronucleus tests are associated with high predictivity for rodent carcinogenicity (Witt *et al*., 2000); negative results in this assay do not correlate well with either negative or positive results in rodent carcinogenicity studies. Because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical. Most organic chemicals that are identified by the International Agency for Research on Cancer as human carcinogens, other than hormones, are genotoxic. The vast majority of these are detected by both the *Salmonella* assay and rodent bone marrow cytogenetics tests (Shelby, 1988; Shelby and Zeiger, 1990).

RESULTS

RATS

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 3 and in the Kaplan-Meier survival curves (Figure 2). Survival of dosed groups was similar to that of the vehicle control group for each sex.

Body Weights and Clinical Findings

Mean body weights of the 30 mg/kg groups were less than those of the vehicle controls after weeks 21 and 37 for males and females, respectively (Figure 3; Tables 4 and 5). There were no clinical findings related to methacrylonitrile administration.

TABLE 3
Survival of Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Male				
Animals initially in study	50	50	50	50
Accidental death[a]	0	0	0	1
Moribund	13	13	9	12
Natural deaths	12	3	6	6
Animals surviving to study termination	25	34	35[d]	31
Percent probability of survival at end of study[b]	50	68	70	63
Mean survival (days)[c]	665	698	690	684
Survival analysis[e]	P=0.592N	P=0.084N	P=0.062N	P=0.234N
Female				
Animals initially in study	50	50	50	50
Accidental deaths[a]	1	1	1	0
Moribund	4	10	9	7
Natural deaths	7	6	6	7
Animals surviving to study termination	38	33	34	36[d]
Percent probability of survival at end of study	78	67	70	72
Mean survival (days)	710	689	680	691
Survival analysis	P=0.878	P=0.312	P=0.408	P=0.577

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[d] Includes one animal that died during the last week of the study
[e] The result of the life table trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed group columns. A negative trend or lower mortality in a dosed group is indicated by **N**.

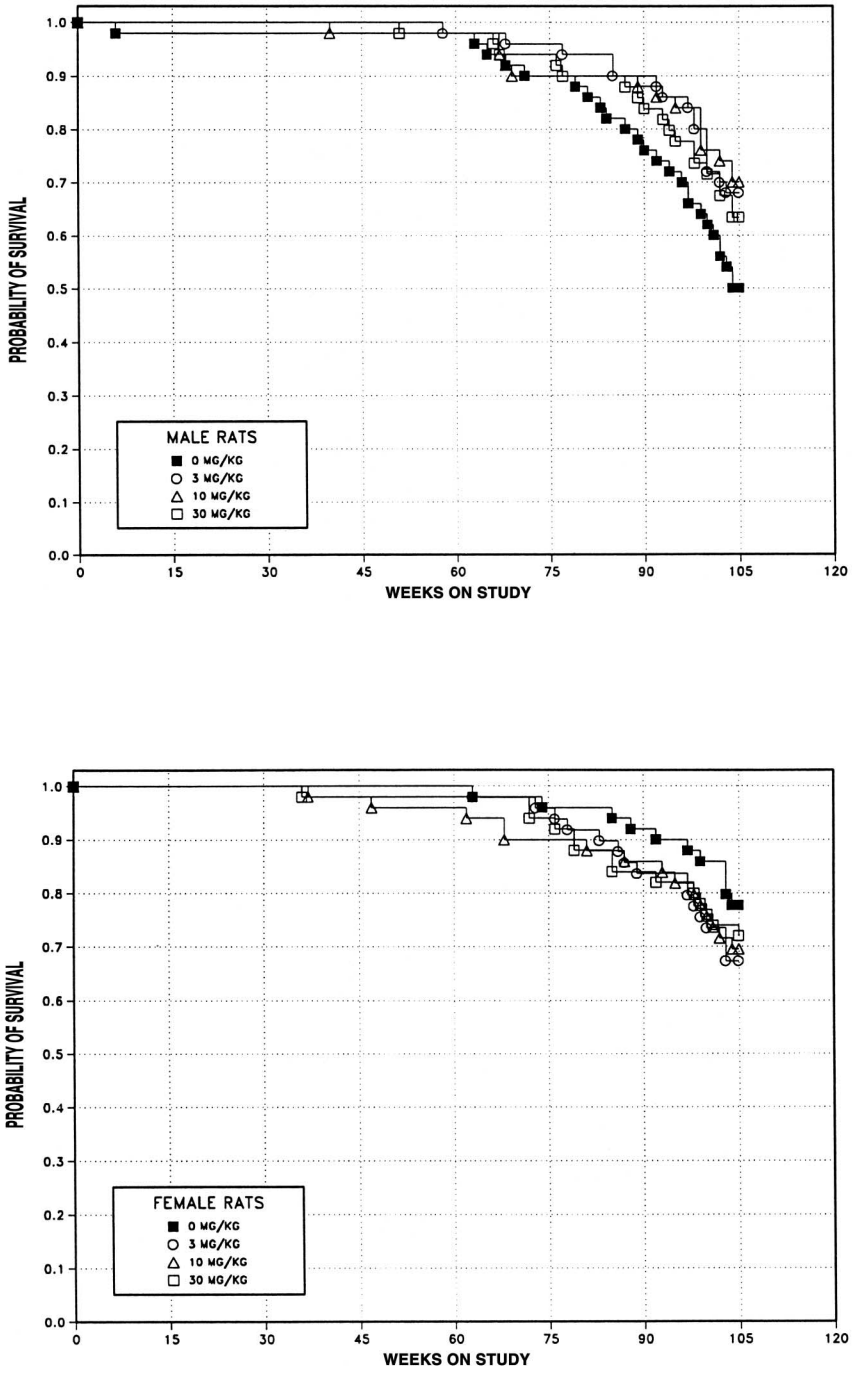


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Administered Methacrylonitrile by Gavage for 2 Years

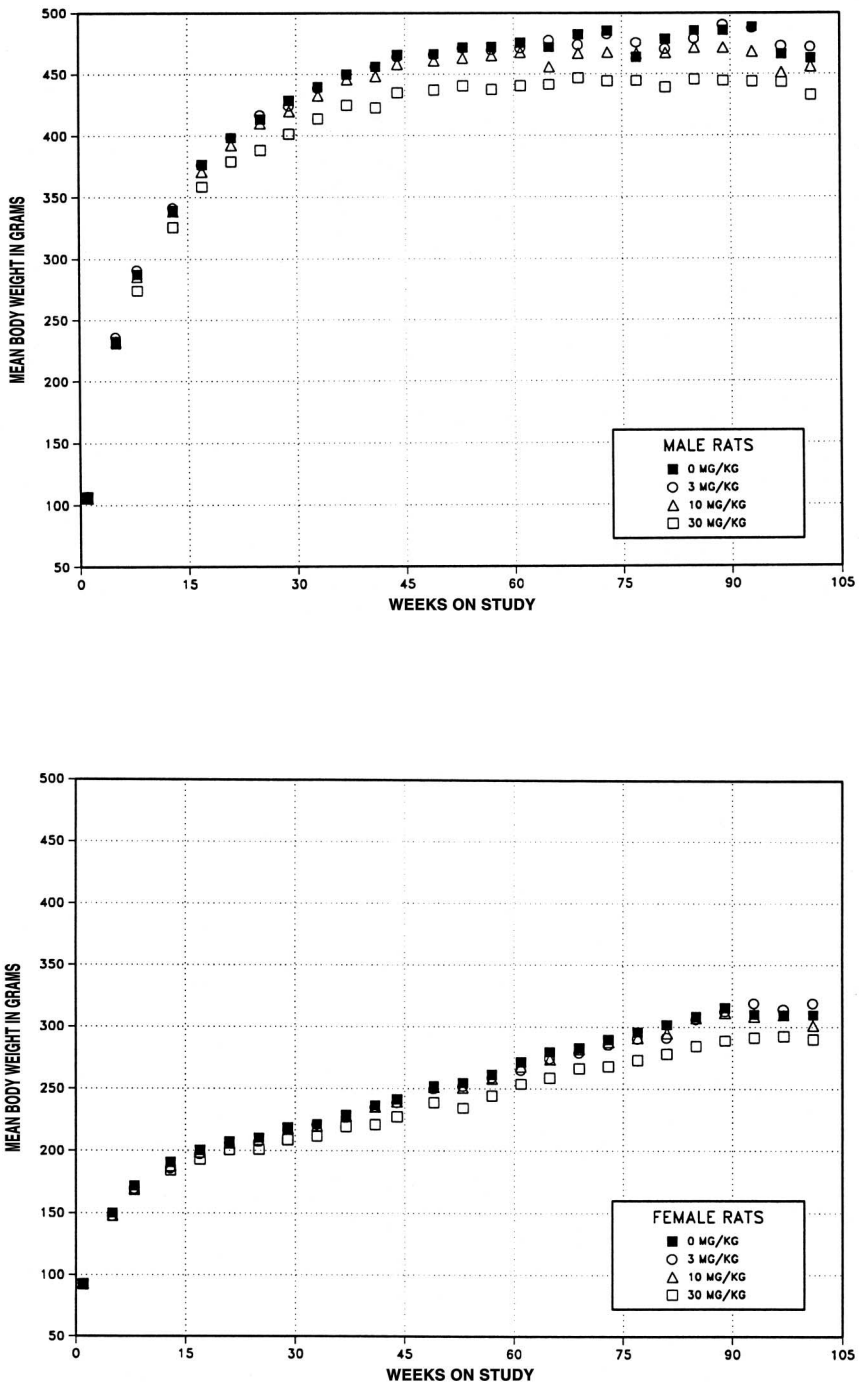


FIGURE 3
Growth Curves for Male and Female Rats
Administered Methacrylonitrile by Gavage for 2 Years

TABLE 4
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Methacrylonitrile

Weeks on Study	Vehicle Control		3 mg/kg			10 mg/kg			30 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	105	50	107	102	50	106	100	50	107	101	50
5	233	50	236	102	50	233	100	50	231	99	50
8	287	49	291	101	50	286	99	50	274	95	50
13	339	49	342	101	50	339	100	50	326	96	50
17	377	49	376	100	50	371	99	50	359	95	50
21	399	49	398	100	50	393	99	50	379	95	50
25	413	49	417	101	50	410	99	50	388	94	50
29	429	49	424	99	50	420	98	50	401	94	50
33	440	49	439	100	50	433	98	50	414	94	50
37	450	49	450	100	50	446	99	50	425	94	50
41	456	49	456	100	50	448	98	49	423	93	50
44	466	49	464	100	50	458	98	49	435	93	50
49	466	49	466	100	50	461	99	49	437	94	50
53	472	49	471	100	50	463	98	49	441	93	49
57	472	49	470	100	50	465	99	49	438	93	49
61	476	49	471	99	49	468	98	49	440	93	49
65	472	48	478	101	49	456	97	49	442	94	49
69	482	46	474	98	48	467	97	46	447	93	47
73	485	45	483	100	48	468	96	45	444	92	47
77	464	45	476	103	48	467	101	45	445	96	44
81	478	44	470	98	47	467	98	45	439	92	44
85	486	41	479	99	47	471	97	45	445	92	44
89	486	39	490	101	45	472	97	44	444	92	43
93	488	37	488	100	44	468	96	43	444	91	41
97	466	35	473	101	43	451	97	42	443	95	38
101	463	30	472	102	36	456	99	38	433	94	35
Mean for weeks											
1-13	241		244	102		241	100		235	98	
14-52	433		432	100		427	99		407	94	
53-101	476		477	100		465	98		442	93	

TABLE 5
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of Methacrylonitrile

Weeks on Study	Vehicle Control		3 mg/kg			10 mg/kg			30 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	92	50	92	100	50	93	101	50	93	101	50
5	150	50	148	99	50	148	99	50	148	98	50
8	172	50	169	99	50	169	99	50	168	98	50
13	191	50	186	98	50	188	99	50	184	97	50
17	200	50	197	99	50	199	99	50	193	97	50
21	207	50	206	99	50	206	99	50	201	97	50
25	210	50	207	99	50	209	100	50	201	96	50
29	218	50	217	99	50	218	100	50	209	96	50
33	221	50	221	100	50	220	100	50	212	96	50
37	229	50	227	99	50	228	100	50	220	96	49
41	237	50	235	100	50	235	99	49	221	94	49
44	242	50	239	99	50	239	99	49	227	94	49
49	252	50	250	99	49	252	100	48	239	95	49
53	255	50	252	99	49	251	99	48	234	92	49
57	261	50	259	99	49	258	99	48	244	94	49
61	271	50	265	98	49	268	99	48	254	94	49
65	280	49	274	98	48	274	98	47	259	93	49
69	283	49	279	99	48	282	100	45	266	94	49
73	290	49	285	99	48	288	99	45	268	93	47
77	296	48	291	98	46	291	98	44	273	92	46
81	302	48	291	97	45	295	98	44	278	92	44
85	308	48	306	99	44	307	100	43	284	92	44
89	315	46	313	99	42	311	99	42	289	92	42
93	310	45	319	103	41	308	100	42	291	94	41
97	310	45	314	102	41	310	100	40	292	94	41
101	310	42	319	103	36	301	97	37	290	94	38
Mean for weeks											
1-13	151		149	99		150	100		148	99	
14-52	224		222	99		223	100		214	96	
53-101	292		290	99		288	99		271	93	

Urinalysis and Urinary Metabolite Analyses

No biologically significant differences in urine volume or urinary creatinine concentrations were observed between dosed and vehicle control rats at 2 weeks or at 3, 12, or 18 months (Table F1). Urinary excretion of *N*-acetyl-S-(2-cyanopropyl)-L-cysteine and *N*-acetyl-S-(2-hydroxypropyl)-L-cysteine increased in male and female rats as a function of dose. When normalized to creatine, the concentration of *N*-acetyl-S-(2-cyanopropyl)-L-cysteine was generally greater in males than in females. In females, the concentrations of *N*-acetyl-S-(2-hydroxypropyl)-L-cysteine were generally greater than those of *N*-acetyl-S-(2-cyanopropyl)-L-cysteine. However, the opposite is generally observed in male rats.

Pathology and Statistical Analyses

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

Nose: The incidences of olfactory epithelial atrophy and metaplasia were significantly greater in 30 mg/kg males and females than those in the vehicle controls (Tables 6, A5, and B4). The average severity of atrophy ranged from minimal to mild. These lesions were observed in levels II and III of the nasal cavity. Routinely examined nasal cavity levels in NTP toxicity and carcinogenicity studies are: level I, excised immediately posterior to the upper incisor teeth; level II, excised through the level of the incisive papilla anterior to the first palatial ridge; and level III, excised through the middle of the second molar teeth. Levels I and II contain the naso- and maxilloturbinates that, along with the nasal passages (meatuses) and septum, are lined by ciliated respiratory-type epithelium. Level III encompasses the olfactory region of the nose with ethmoid turbinates and meatuses lined entirely by specialized olfactory neuroepithelium. The atrophy involved the dorsal meatus in level II and the ethmoid turbinates and lateral walls of level III. The epithelium was thinner, with columnar sustentacular cells predominating. For the finding diagnosed as metaplasia of the olfactory epithelium (Plates 1 through 4), there was complete loss of sensory and sustentacular cells, which were replaced by thin, pseudostratified, ciliated, nonciliated cuboidal, or columnar epithelial cells. This change was also present along the nasal septum, primarily in level II.

TABLE 6
Incidences of Nonneoplastic Lesions of the Nose in Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Male				
Number Examined Microscopically	50	50	49	50
Olfactory Epithelium, Atrophy[a]	0	0	0	48** (1.5)[b]
Olfactory Epithelium, Metaplasia	0	0	0	47** (2.1)
Female				
Number Examined Microscopically	50	50	50	50
Olfactory Epithelium, Atrophy	0	0	1 (2.0)	19** (1.7)
Olfactory Epithelium, Metaplasia	0	0	0	47** (1.6)

** Significantly different ($P \leq 0.01$) from the vehicle group by the Poly-3 test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Other Organs: The incidences of diffuse cytoplasmic vacuolization (positively stained in periodic acid Schiff reaction), consistent with glycogen infiltration in the liver, were significantly greater in 30 mg/kg males (vehicle control, 14/50; 3 mg/kg, 18/50; 10 mg/kg, 23/50; 30 mg/kg, 28/49; Table A5) and in all dosed groups of females (7/50, 14/49, 17/48, 30/50; Table B4) than those in the vehicle controls. The severities of this lesion in dosed groups of rats were generally slightly greater than those in the vehicle controls (males: 1.6, 2.1, 2.2, 2.6; females: 1.3, 1.4, 1.3, 2.7). Glycogen accumulates in hepatocytes as glucose increases in the blood of portal veins (Cheville, 1994). Hepatocytic glycogen accumulation is known to occur following exposure to certain chemicals. Cortisol and other corticosteroids are important stimulants of hepatic glycogen synthesis. In the case of clavulanate treatment, it was suggested that the increase in hepatic glycogen in the rats represents an adaptive response to the extensive hepatic metabolism of this compound in this species (Jackson *et al*., 1985). The incidences of pancreatic exocrine gland hyperplasia were increased in all dosed groups of males (4/50, 10/49, 11/50, 12/50; Table A5). No effect of methacrylonitrile on the incidences of pancreatic exocrine gland neoplasms was noted. The incidences of pancreatic acinar hyperplasia in the NTP historical control data vary considerably. Relatively high incidences of this lesion were reported in 2-year studies with the following compounds: pentachloroanisole (38%; NTP, 1993), titanocene dichloride (24%; NTP, 1991), and salicylazosulfapyridine (32%; NTP, 1997). The incidences of acinar hyperplasia noted in the dosed groups in the current study are within the historical control range (NTP, 2001b) and therefore are not considered related to treatment. The incidence of bone marrow hyperplasia, mostly composed of mixed myeloid and erythroid cells, was increased in 30 mg/kg females (12/50, 11/50, 12/50, 25/50; Table B4).

Mononuclear Cell Leukemia: There was a negative trend in the incidence of mononuclear cell leukemia in male rats (20/50, 20/50, 14/50, 12/50; Table A3). The incidence in 30 mg/kg males was significantly less than that in the vehicle controls and was slightly below the historical range in controls given NTP-2000 diet [300/609 (47.3% ± 10.5%); range 32%-68%; Table A4]. Because the decrease in the incidence of mononuclear cell leukemia was confined to males, was not associated with spleen toxicity or a decrease in body weights, and because methacrylonitrile is nongenotoxic (Elwell *et al.,* 1996), the decreased incidences of mononuclear cell leukemia in males were not considered related to methacrylonitrile administration.

MICE

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 7 and in the Kaplan-Meier survival curves (Figure 4). There were no significant effects of methacrylonitrile on survival. In the 6 mg/kg groups, 24 males and 15 females were accidentally overdosed with 60 mg/kg methacrylonitrile and died during week 69.

Body Weights and Clinical Findings

The mean body weights of all dosed groups were generally similar to those of the vehicle controls throughout the study (Tables 8 and 9; Figure 5). There were no clinical findings related to methacrylonitrile administration.

TABLE 7
Survival of Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Male				
Animals initially in study	50	50	50	50
Accidental deaths[a]	0	0	0	25
Missing[a]	1	0	0	0
Moribund	5	2	3	0
Natural deaths	9	5	4	3
Animals surviving to study termination	35[d]	43	43[e]	22
Percent probability of survival at end of study[b]	71	86	86	88
Mean survival (days)[c]	692	715	708	591
Survival analysis[f]	P=0.099N	P=0.139N	P=0.143N	P=0.191N
Female				
Animals initially in study	50	50	50	50
Accidental deaths[a]	0	0	0	15
Moribund	1	2	3	3
Natural deaths	14	13	4	7
Animals surviving to study termination	35[d]	35	43	25
Percent probability of survival at end of study	70	70	86	73
Mean survival (days)	700	680	716	619
Survival analysis	P=0.563N	P=1.000	P=0.097N	P=0.978N

[a] Censored from survival analyses. Accidental deaths, except one male rat, were due to dosing accidents.
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[d] Includes one animal that died during the last week of the study
[e] Includes two animals that died during the last week of the study
[f] The result of the life table trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed group columns. A negative trend or lower mortality in a dosed group is indicated by **N**.

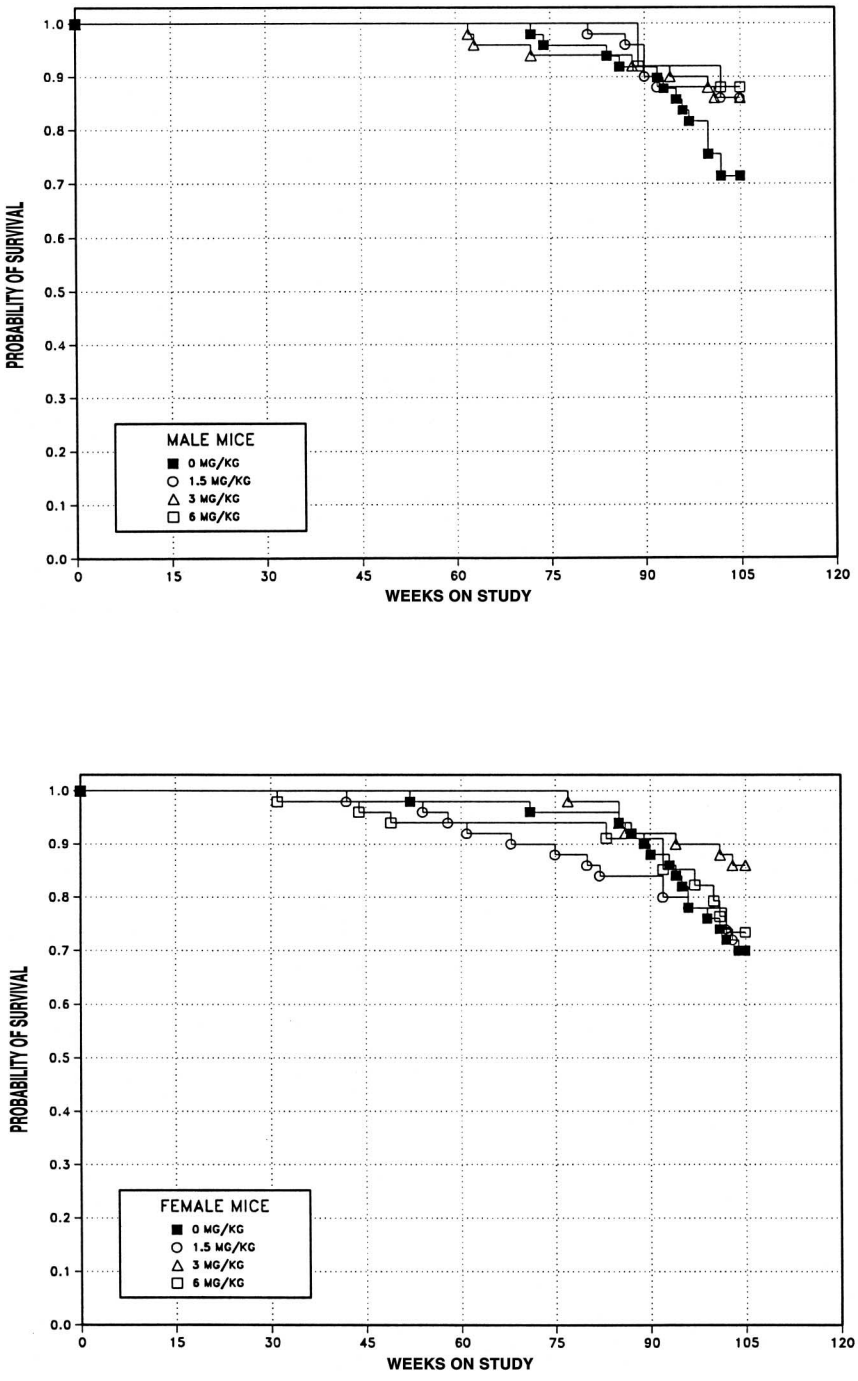


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Administered Methacrylonitrile by Gavage for 2 Years

TABLE 8
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of Methacrylonitrile

Weeks on Study	Vehicle Control		1.5 mg/kg			3 mg/kg			6 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	21.8	50	22.0	101	50	21.7	100	50	21.9	101	50
5	27.8	50	27.4	99	50	26.6	96	50	26.8	96	49
9	32.3	50	32.9	102	50	31.4	97	50	30.6	95	49
13	36.3	49	36.4	100	50	34.8	96	50	34.3	95	49
17	39.3	49	39.4	100	50	38.3	98	50	36.6	93	49
21	44.5	49	43.9	99	50	43.0	97	50	40.5	91	49
25	46.5	49	45.9	99	50	44.9	97	50	42.4	91	49
29	47.7	49	47.1	99	50	46.6	98	50	44.1	93	49
33	48.9	49	48.0	98	50	47.7	98	50	45.2	92	49
37	49.2	49	48.7	99	50	48.5	99	50	46.8	95	49
41	49.4	49	48.8	99	50	49.0	99	50	46.9	95	49
45	50.3	49	49.2	98	50	49.7	99	50	47.6	95	49
49	50.1	49	49.7	99	50	50.0	100	50	48.2	96	49
53	50.6	49	50.2	99	50	50.7	100	50	48.8	96	49
57	50.6	49	50.4	100	50	51.1	101	50	49.1	97	49
61	50.2	49	50.4	100	50	51.4	102	50	49.5	99	49
65	49.9	49	50.3	101	50	51.4	103	48	49.5	99	49
69	50.0	49	50.5	101	50	51.3	103	48	49.6	99	49
73	48.6	48	49.5	102	50	50.2	103	47	48.3	99	25
77	47.7	47	48.8	102	50	50.1	105	47	47.9	100	25
81	47.5	47	48.2	102	50	49.9	105	47	48.0	101	25
85	47.4	46	48.8	103	49	50.2	106	47	48.1	102	25
89	45.6	45	47.5	104	48	48.9	107	46	47.3	104	25
93	43.4	44	46.3	107	44	47.2	109	46	46.7	108	23
97	44.7	41	47.4	106	44	48.0	107	45	47.0	105	23
101	42.5	37	45.4	107	44	45.6	107	44	44.6	105	23
Mean for weeks											
1-13	29.6		29.7	100		28.6	97		28.4	96	
14-52	47.3		46.7	99		46.4	98		44.3	94	
53-101	47.6		48.7	102		49.7	104		48.0	101	

TABLE 9
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of Methacrylonitrile

Weeks on Study	Vehicle Control		1.5 mg/kg			3 mg/kg			6 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	18.4	50	18.5	101	50	18.6	101	50	18.3	100	50
5	22.7	50	22.9	101	50	22.9	101	50	22.2	98	50
9	26.2	50	26.2	100	50	27.0	103	50	25.5	97	50
13	30.0	50	30.2	101	50	32.2	107	50	29.0	97	50
17	34.0	50	35.0	103	50	36.2	107	50	34.3	101	50
21	38.9	50	39.5	102	50	41.6	107	50	38.9	100	50
25	42.1	50	42.9	102	50	44.8	106	50	42.3	101	50
29	44.8	50	45.7	102	50	48.0	107	50	44.6	100	50
32	47.6	50	48.4	102	50	50.2	106	50	46.1	97	49
37	50.6	50	51.4	102	50	53.0	105	50	49.6	98	49
41	52.6	50	52.8	100	50	54.3	103	50	51.3	98	49
45	54.2	50	54.4	100	49	55.3	102	50	53.0	98	48
49	56.0	50	56.6	101	49	57.2	102	50	54.6	98	48
53	57.7	49	57.5	100	49	57.9	100	50	56.3	98	47
57	58.0	49	58.3	101	48	57.9	100	50	56.7	98	47
61	57.9	49	57.7	100	47	58.8	102	50	56.8	98	47
65	57.3	49	57.8	101	46	57.9	101	50	56.1	98	47
69	58.1	49	58.8	101	45	58.8	101	50	57.2	99	47
73	57.4	48	58.6	102	45	58.0	101	50	56.2	98	32
77	57.2	48	58.9	103	44	57.9	101	49	55.6	97	32
81	57.6	48	59.1	103	43	57.0	99	49	55.8	97	32
85	56.9	48	59.1	104	42	55.8	98	49	55.6	98	31
89	55.7	46	58.3	105	42	56.5	101	46	54.0	97	31
93	55.5	43	56.8	102	40	55.5	100	46	53.6	97	29
97	57.4	39	56.7	99	39	56.4	98	45	53.4	93	29
101	53.2	38	53.6	101	39	53.8	101	45	51.4	97	27
Mean for weeks											
1-13	24.3		24.5	101		25.2	104		23.8	98	
14-52	46.8		47.4	101		49.0	105		46.1	99	
53-101	56.9		57.8	102		57.1	100		55.3	97	

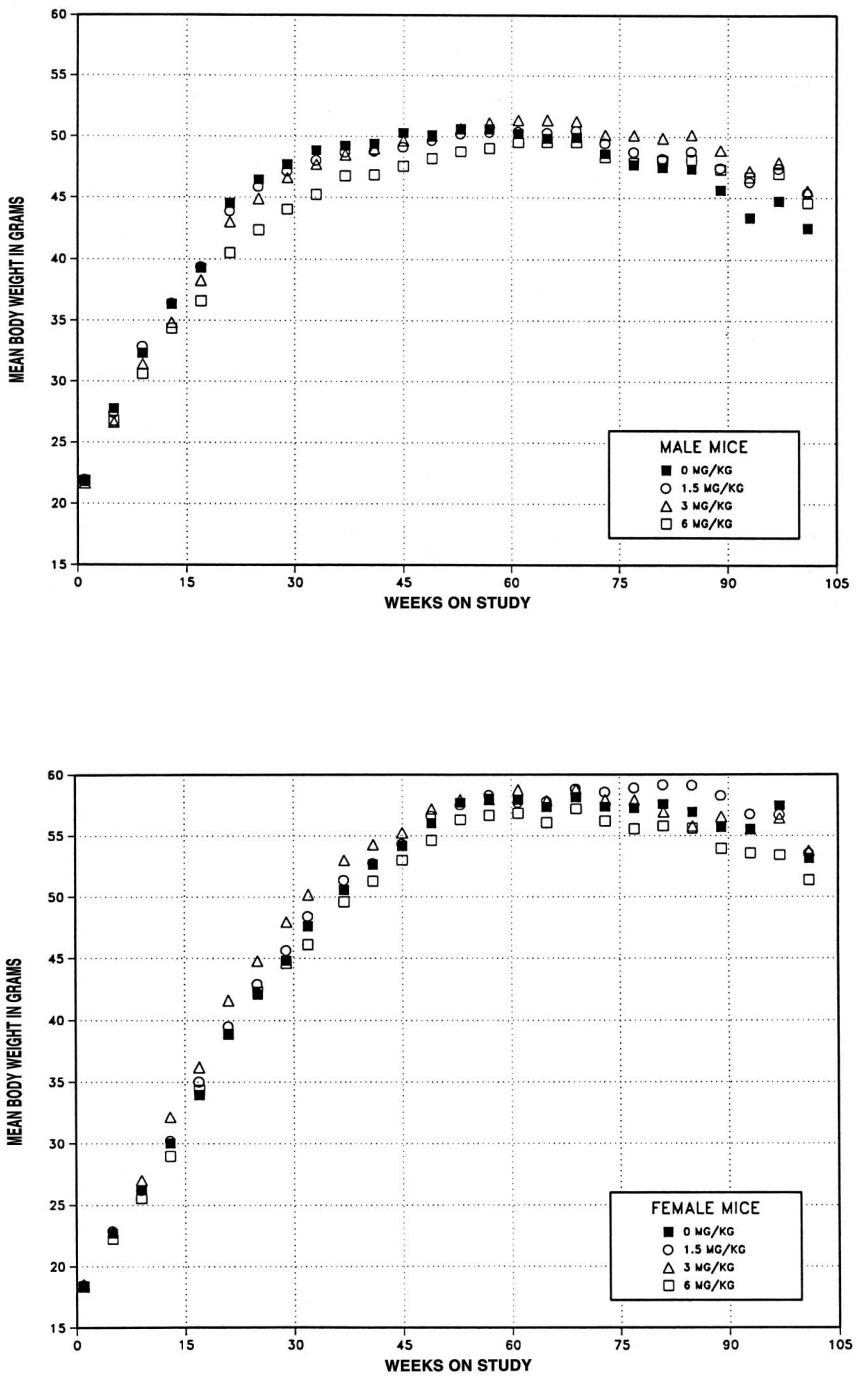


FIGURE 5
Growth Curves for Male and Female Mice Administered Methacrylonitrile by Gavage for 2 Years

Urinalysis and Urinary Metabolite Analyses

No biologically significant differences in urine volume or urinary creatinine concentrations were observed between dosed and vehicle control mice at 2 weeks or at 3, 12, or 18 months (Table F2). Urinary excretion of *N*-acetyl-S-(2-cyanopropyl)-L-cysteine and *N*-acetyl-S-(2-hydroypropyl)-L-cysteine increased in male and female mice in a dose-dependent manner. In contrast to the observations in rats, the concentrations of *N*-acetyl-S-(2-cyanopropyl)-L-cysteine were generally greater in female than in male mice. Further, the concentrations of *N*-acetyl-S-(2-hydroypropyl)-L-cysteine were significantly greater at all time points and doses than the corresponding values for *N*-acetyl-S-(2-cyano-propyl)-L-cysteine in male and female mice.

Pathology and Statistical Analyses

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix C for male mice and Appendix D for female mice. No neoplasms or nonneoplastic lesions in mice were attributed to methacrylonitrile administration.

GENETIC TOXICOLOGY

Methacrylonitrile (100 to 10,000 µg/plate) did not induce mutations in *Salmonella typhimurium* strain TA97, TA98, TA100, TA1535, or TA1537 (Table E1; Zeiger *et al*., 1987). All tests were performed with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9. No induction of sex-linked recessive lethal mutations was observed in germ cells of male *Drosophila melanogaster* fed medium containing 6,000 ppm methacrylonitrile during the larval stage (Table E2; Zimmering *et al.*, 1989). In the male rat bone marrow micronucleus test, an initial trial showed a significant induction of micronuclei in the 25 mg/kg group; however, a second trial showed no induction of micronuclei in bone marrow polychromatic erythrocytes and the test was determined to be negative overall (Table E3). Also, no increase in the frequency of micronucleated polychromatic erythrocytes was observed in the bone marrow of male mice treated with 6.25 to 25 mg/kg methacrylonitrile (Table E4). Consistent with the negative results seen with the short-term bone marrow tests in rats and mice, the results of a 13-week peripheral blood micronucleus test in male and female mice showed no evidence of methacrylonitrile-induced genetic damage (Table E5). In conclusion, this battery of short-term *in vitro* and *in vivo* tests showed no evidence of genotoxicity of methacrylonitrile.

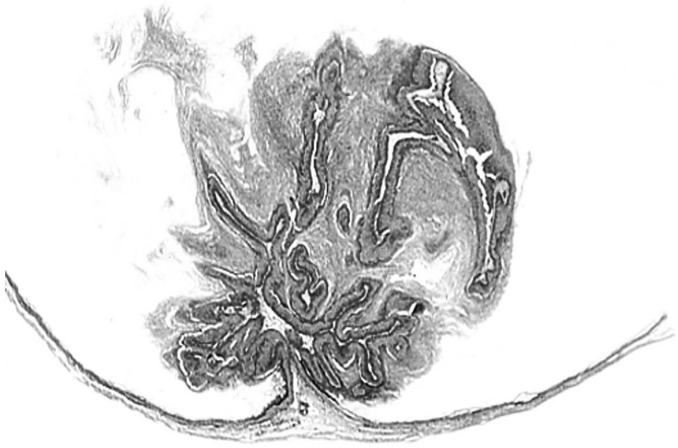


PLATE 1
Squamous cell papilloma in the forestomach of a male B6C3F$_1$ mouse given 20 mg acrylonitrile/kg body weight per day by gavage for 2 years. Note the central stalk with secondary branches. H&E; 5×

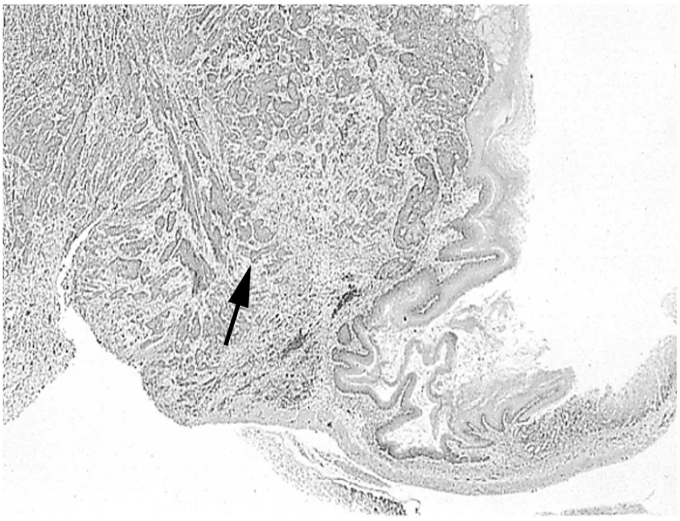


PLATE 2
Squamous cell carcinoma in the forestomach of a male B6C3F$_1$ mouse given 20 mg acrylonitrile/kg body weight per day by gavage for 2 years. Note (arrow) the invasion of neoplastic cells into the submucosa. H&E; 5×

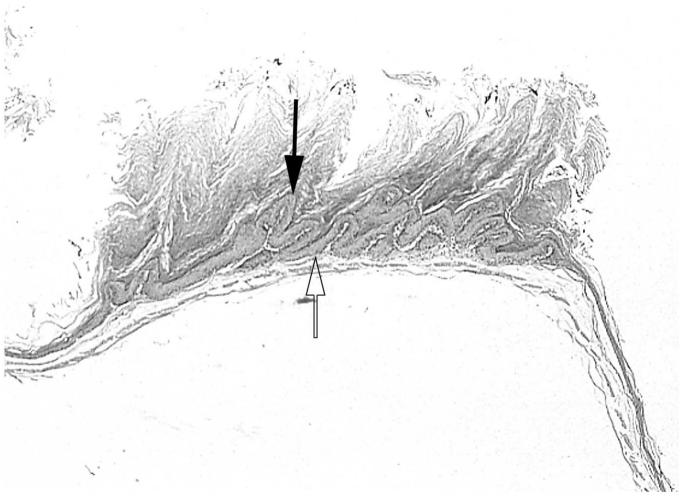


PLATE 3
Squamous cell hyperplasia in the forestomach of a male B6C3F$_1$ mouse given 20 mg acrylonitrile/kg body weight per day by gavage for 2 years. Note the thickened epithelium forming endophytic pegs (open arrow). Dark arrow indicates undulating folds. H&E; 10×

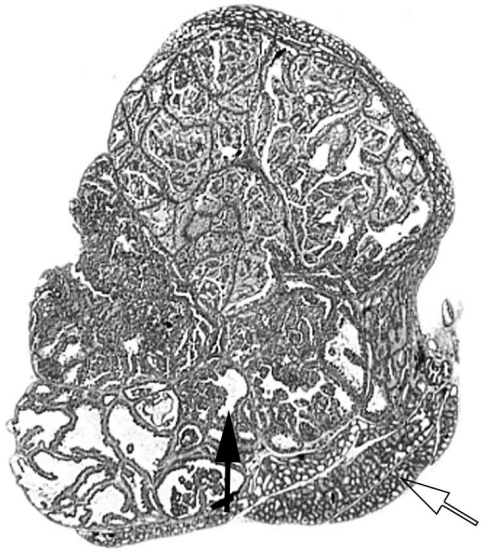


PLATE 4
Adenoma in the harderian gland of a male B6C3F$_1$ mouse given 20 mg acrylonitrile/kg body weight per day by gavage for 2 years. Note the distinct nodule compressing the surrounding alveoli. Dark arrow-adenoma, open arrow-normal harderian gland tissue. H&E; 3.3×

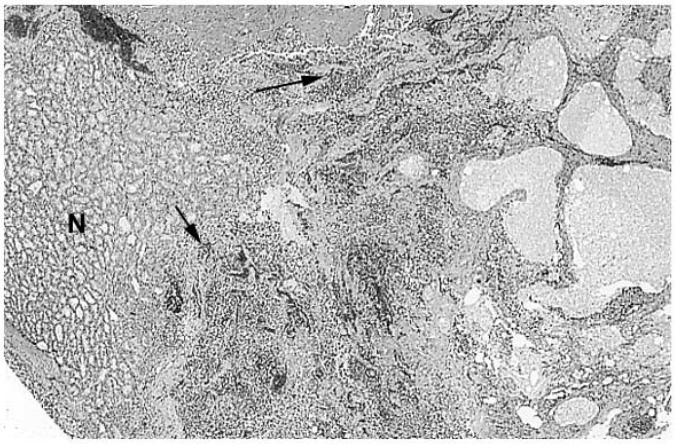


PLATE 5
Carcinoma in the harderian gland of a male B6C3F$_1$ mouse given 20 mg acrylonitrile/kg body weight per day by gavage for 2 years. Note the carcinoma (arrows) adjacent to the gland (N=normal gland). H&E; 8×

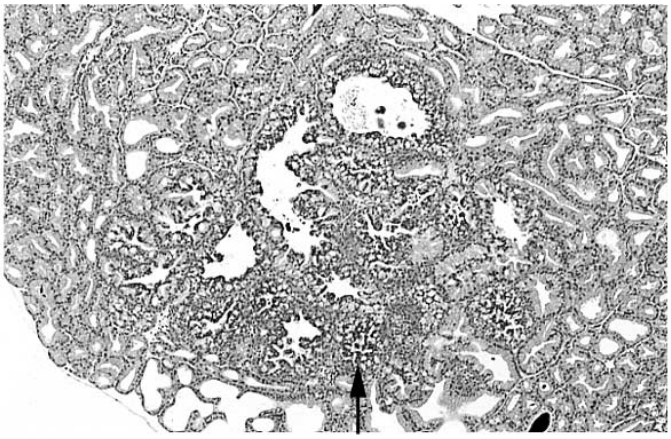


PLATE 6
Marked hyperplasia in the harderian gland of a male B6C3F$_1$ mouse given 20 mg acrylonitrile/kg body weight per day by gavage for 2 years. Note the focus of tinctorially distinct cells (arrow) with no evidence of compression of the surrounding alveoli. H&E; 16×

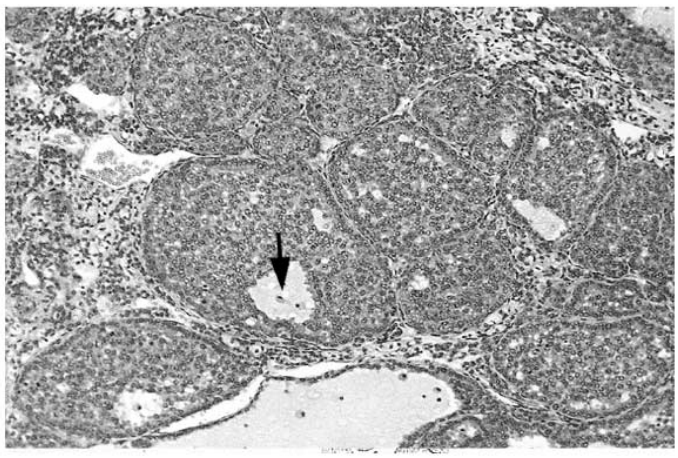


PLATE 7
Granulosa cell tumor in the ovary of a female B6C3F$_1$ mouse given 20 mg acrylonitrile/kg body weight per day by gavage for 2 years. The tumor cells, which have scanty cytoplasm, are forming varying sized pseudofollicular structures. The characteristic Call-Exner bodies (cell-free area, see arrow) are also present. H&E; 10×

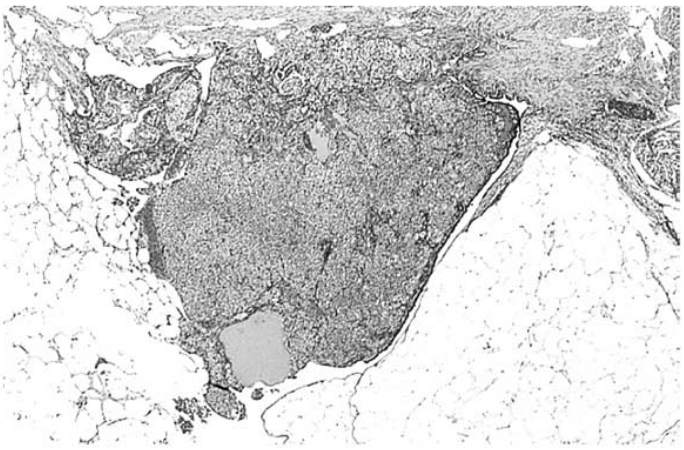


PLATE 8
Severe atrophy in the ovary of a female B6C3F$_1$ mouse given 20 mg acrylonitrile/kg body weight per day by gavage for 2 years. Note the absence of follicles and corpora lutea and a predominance of interstitial tissue. H&E; 10×

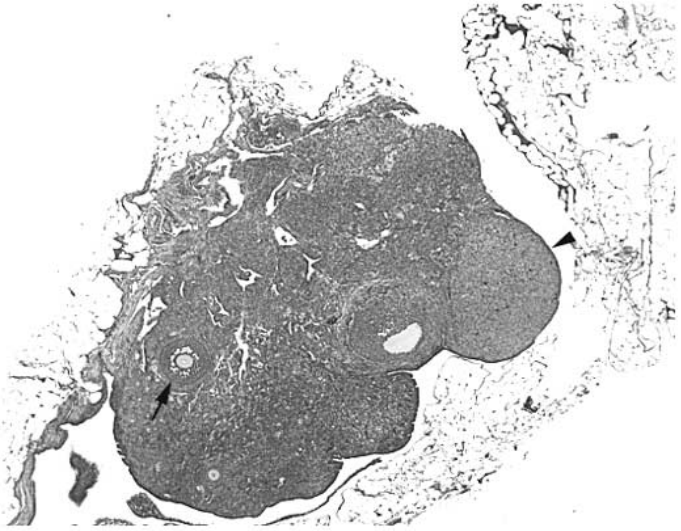


PLATE 9
Ovary of a vehicle control female B6C3F$_1$ mouse from the 2-year study of acrylonitrile. Note presence of follicle (arrow) and corpus luteum (arrowhead). H&E; 10×

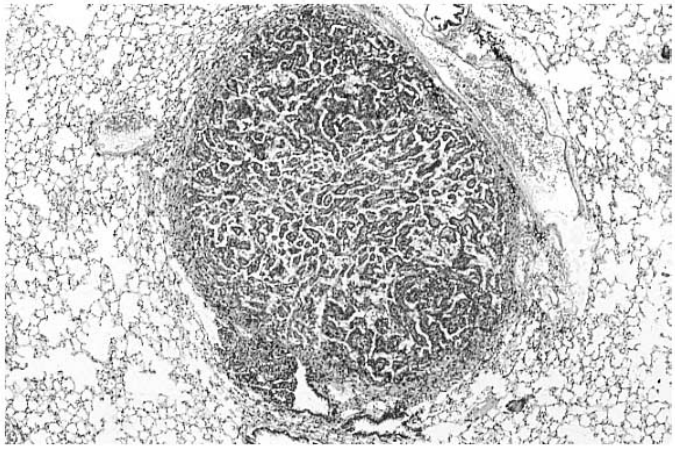


PLATE 10
Alveolar/bronchiolar adenoma in a female B6C3F$_1$ mouse given 20 mg acrylonitrile/kg body weight per day by gavage for 2 years. Note a distinct and compressing nodule distorting the underlying alveolar structure. H&E; 13.2×

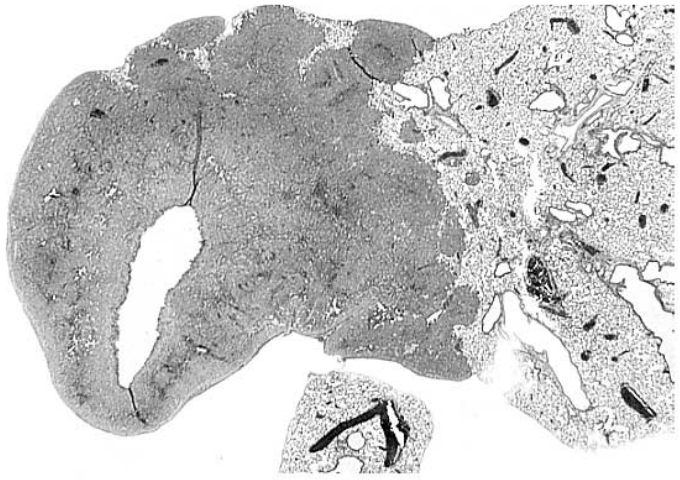


PLATE 11
Alveolar/bronchiolar carcinoma in a female B6C3F$_1$ mouse given 20 mg acrylonitrile/kg body weight per day by gavage for 2 years. H&E; 25×

DISCUSSION AND CONCLUSIONS

The National Cancer Institute nominated methacrylonitrile for study by the NTP because of its high production volume and extensive use, lack of chronic and carcinogenicity data, and structural similarity to the known rat and probable human carcinogen (IARC, 1999), acrylonitrile. Methacrylonitrile was initially evaluated for toxicity in 13-week gavage studies (NTP, 2000). The doses for the current 2-year studies were selected based on the results of the 13-week studies.

In the 2-year study in F344/N rats, methacrylonitrile was administered by gavage to groups of 50 males and 50 females at doses of 0, 3, 10, and 30 mg/kg, 5 days per week for 104 to 105 weeks. No chemical-related neoplasms were observed in rats at the end of the 2-year study. However, incidences of olfactory epithelial atrophy and metaplasia of the nose were significantly greater for 30 mg/kg males and females than for the vehicle controls. Findings of olfactory epithelial lesions in rats in the 2-year study are consistent with the findings at the 32-day interim evaluation and at the end of the 13-week study (NTP, 2000). The rat olfactory epithelium of the nasal cavity was the primary target of methacrylonitrile in the 60 and 120 mg/kg groups, and lesions consisted of necrotic and metaplastic effects. No lesions were observed at 30 mg/kg in the 13-week study, which may be attributed to the relatively shorter duration of dosing. This site- and species-specific toxicity may be attributed to the disposition of methacrylonitrile in rats and the high levels of cytochrome P4502E1 in the olfactory mucosa (Wang *et al*., 1999). Metabolism and disposition studies indicated that a major route of methacrylonitrile elimination was in the expired air as parent methacrylonitrile and its metabolite acetone. Demby *et al.* (1993) demonstrated that saturation of methacrylonitrile metabolism occurs at doses greater than 29 mg/kg, which contributes to exhalation of parent compound in the expired air. Rats administered 115 mg methacrylonitrile/kg body weight exhaled approximately 35% of the dose as parent compound (Ghanayem *et al*., 1992). Evidence also indicates that methacrylonitrile, and/or its metabolite acetone, causes overexpression of CYP2E1 in the nasal tissue, which may lead to increased *in situ* metabolism of expired methacrylonitrile to reactive cytotoxic metabolites (Wang *et al*., 1999). Early uptake and persistence of methacrylonitrile-derived radioactivity in the nasal tissue was observed in rats for up to 24 hours using whole body autoradiography (Ahmed *et al.*, 1996).

In the 2-year study in B6C3F$_1$ mice, methacrylonitrile was administered to groups of 50 males and 50 females at 0, 1.5, 3, or 6 mg/kg by gavage. No neoplasms or nonneoplastic lesions in mice were attributed to methacrylonitrile administration.

At approximately 15 months on study, some male and female mice in the 6 mg/kg group were accidentally exposed to 10-fold higher concentrations of methacrylonitrile, resulting in the death of 24 male and 15 female mice. This early mortality somewhat reduced the sensitivity of the study for detecting carcinogenic effects. However, 44% and 50% of male and female mice, respectively, survived to study termination, and survival rates in the other dosed and control groups ranged from 70% to 86%. There was no evidence of carcinogenic effects that might have been statistically significant ($P \leq 0.05$) in male or female mice had there only been a few more surviving animals in the 6 mg/kg groups (see Tables C3 and D3). Therefore, this study is still considered adequate for assessing the potential carcinogenic activity of methacrylontrile in the B6C3F$_1$ mouse.

Methacrylonitrile was negative in a number of mutagenicity tests. Methacrylonitrile was nonmutagenic with and without S9 bioactivating enzymes in several strains of *Salmonella typhimurium* (TA97, TA98, TA100, TA1535, and TA1537) at concentrations ranging from 100 to 10,000 µg/plate (Table E1; Zeiger *et al*., 1987). Methacrylonitrile also failed to induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* treated during the larval stage by feeding at approximately 6,000 ppm (Table E2; Zimmering *et al.*, 1989). Intraperitoneal injection of methacrylonitrile to male rats (12-100 mg/kg) or male mice (6.25-25 mg/kg) resulted in no increases in the induction of micronucleated bone marrow polychromatic

erythrocytes (Tables E3 and E4). Metha-crylonitrile also failed to increase the frequency of micronucleated normochromatic erythrocytes in the peripheral blood of mice that received 0.75 to 12 mg/kg methacrylonitrile by gavage for 13 weeks (Table E5).

The absence of neoplastic lesions in methacrylonitrile treated rats and mice raised the question of whether the doses of methacrylonitrile used in the present study were sufficiently challenging. Methacrylonitrile was nominated for carcinogenicity testing in part because of its structural similarity to acrylonitrile, a multisite carcinogen in rats (USEPA, 1983; IARC, 1987; WHO, 1983; ATSDR, 1990). Administration of acrylonitrile to Spartan rats by gavage at 0, 0.1, or 10.0 mg/kg body weight increased the incidences of tumors in the brain, forestomach, and Zymbal's gland (BioDynamics, Inc., 1980). In another study, administration of 5 mg acrylonitrile/kg body weight in olive oil by gavage resulted in increased forestomach tumors (Maltoni *et al*., 1977 and 1988). In a companion study to the present methacrylonitrile study, acrylonitrile was a multisite carcinogen in mice at doses as low as 2.5 mg/kg (NTP, 2001). Doses of methacrylonitrile used in this 2-year rat study are significantly higher than acrylonitrile doses known to be carcinogenic to rats. In mice, doses for the 2-year study were the highest that could be given, and twice the highest dose (12 mg/kg) used in the 2-year study increased mortality in the 13-week study. No neoplastic effects were seen for methacrylonitrile, while lower doses of acrylonitrile (on a molar basis) produced neoplasms at several sites in male and female rats and mice. It is therefore possible to conclude that doses of methacrylonitrile used in the present studies were adequate. It is well established that metabolism is a prerequisite for the expression of toxicity and carcinogenicity of aliphatic nitriles. Three mechanisms are implicated in the toxicity and carcinogenicity of both acrylonitrile and methacrylonitrile: cyanide release, reaction with tissue glutathione (GSH), and reaction with DNA. Cyanide release may account for the acute toxicity (Benz *et al*., 1990) and there is some evidence that methacrylonitrile is metabolized more rapidly to cyanide than acrylonitrile (Tanii and Hashimoto, 1984). This may explain the greater sensitivity of mice to methacrylonitrile than to acrylonitrile, as evidenced by the use of lower doses in mice treated with methacrylonitrile than with acrylonitrile.

Conjugation may lower the concentration of GSH in various tissues and expose critical macromolecules to nucleophilic attacks (Ghanayem *et al*., 1985). Methacrylonitrile is less potent than acrylonitrile as a depleter of GSH (Day *et al*., 1988). A greater percentage of the administered acrylonitrile dose was eliminated in urine as GSH-derived mercapturic acids, and methacrylonitrile appeared to react less rapidly with tissue nucleophiles, based on differences in the concentration of the radioactivity at the site of administration. For example, the highest concentration of acrylonitrile-derived radioactivity was detected in the stomach, also a target of acrylonitrile toxicity and carcinogenicity (Burka *et al*., 1994).

Reaction with DNA may be the most significant factor in relation to the chronic toxicity of aliphatic nitriles. It is well established that acrylonitrile does not react directly with DNA very efficiently (Guengerich *et al*., 1981) and the mutagenic/carcinogenic effect of this chemical may be attributed to the 2-cyanoethylene oxide. This epoxide intermediate has been shown to react with DNA *in vitro* (Guengerich *et al*., 1981; Solomon *et al*., 1993). Although there are no studies available that measured direct methacrylonitrile reactivity with DNA, it is expected that methacrylonitrile will be less reactive than acrylonitrile, because the methyl group may electronically destabilize the anionic intermediate of the Michael addition. Additionally, the reactivity of the epoxide intermediate of methacrylonitrile may be less than 2-cyanoethylene oxide because a nucleophilic attack may be hindered by the methyl group on the adjacent carbon.

In summary, although a greater portion of an administered methacrylonitrile dose is metabolized via the epoxide intermediate, there is evidence that the epoxide from methacrylonitrile is broken down and eliminated more efficiently than 2-cyanoethylene oxide (as evidenced by the significantly greater exhalation of CO_2 by animals treated with methacrylonitrile than with acrylonitrile). In addition, there is the possibility that a nucleophilic attack of the DNA by the epoxide intermediate of methacrylonitrile may be hindered by the methyl group and contribute to lower reactivity than for acrylonitrile.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of methacrylonitrile in male or female F344/N rats

administered 3, 10, or 30 mg/kg. There was *no evidence of carcinogenic activity* of methacrylonitrile in male or female B6C3F$_1$ mice administered 1.5, 3, or 6 mg/kg.

In male and female rats, methacrylonitrile administration caused significant increases in the incidences of nonneoplastic lesions of the nose and liver.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of the Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 10.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF METHACRYLONITRILE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Methacrylonitrile[a]

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund	13	13	9	12
Natural deaths	12	3	6	6
Survivors				
Died last week of study			1	
Terminal sacrifice	25	34	34	31
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Polyp adenomatous	1 (2%)		1 (2%)	
Intestine large, rectum	(50)	(50)	(50)	(50)
Polyp adenomatous		1 (2%)		1 (2%)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Polyp adenomatous		1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)	(50)
Polyp adenomatous			1 (2%)	
Liver	(50)	(50)	(50)	(49)
Hepatocellular adenoma	1 (2%)	2 (4%)		
Histiocytic sarcoma				1 (2%)
Mesentery	(13)	(13)	(11)	(12)
Fat, sarcoma	1 (8%)			
Fat, schwannoma malignant				1 (8%)
Pancreas	(50)	(49)	(50)	(50)
Adenoma	2 (4%)		1 (2%)	2 (4%)
Mixed tumor benign			1 (2%)	
Salivary glands	(50)	(50)	(50)	(50)
Neural crest tumor				1 (2%)
Schwannoma malignant	2 (4%)		1 (2%)	1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma				1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Carcinoma	1 (2%)			
Tongue				(1)
Squamous cell papilloma				1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Osteosarcoma, metastatic, bone		1 (2%)		
Schwannoma malignant				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	2 (4%)		
Osteosarcoma, metastatic, bone		1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Endocrine System (continued)				
Adrenal medulla	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, bone		1 (2%)		
Pheochromocytoma malignant	1 (2%)	1 (2%)	2 (4%)	
Pheochromocytoma benign	2 (4%)	6 (12%)	6 (12%)	2 (4%)
Bilateral, pheochromocytoma benign	1 (2%)	1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma		2 (4%)	1 (2%)	1 (2%)
Carcinoma		2 (4%)		
Parathyroid gland	(46)	(46)	(50)	(50)
Adenoma			1 (2%)	1 (2%)
Pituitary gland	(50)	(50)	(50)	(50)
Adenoma	17 (34%)	18 (36%)	11 (22%)	20 (40%)
Craniopharyngioma				1 (2%)
Osteosarcoma, metastatic, bone		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(50)
Schwannoma malignant, metastatic, skin	1 (2%)			
Bilateral, C-cell, adenoma	1 (2%)	2 (4%)	1 (2%)	
C-cell, adenoma	8 (16%)	10 (20%)	7 (14%)	6 (12%)
C-cell, carcinoma	1 (2%)	1 (2%)	1 (2%)	
Follicular cell, adenoma	1 (2%)		2 (4%)	
Follicular cell, carcinoma		1 (2%)	1 (2%)	2 (4%)
General Body System				
Tissue NOS		(1)	(1)	
Chemodectoma benign			1 (100%)	
Osteosarcoma, metastatic, bone		1 (100%)		
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)	(49)
Adenoma	2 (4%)	1 (2%)	4 (8%)	4 (8%)
Carcinoma	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Prostate	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			1 (2%)
Seminal vesicle	(50)	(50)	(50)	(50)
Testes	(50)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)
Bilateral, interstitial cell, adenoma	34 (68%)	40 (80%)	43 (86%)	45 (90%)
Interstitial cell, adenoma	6 (12%)	5 (10%)	4 (8%)	1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Lymph node	(7)	(3)	(3)	(4)
Osteosarcoma, metastatic, bone		1 (33%)		
Inguinal, fibrosarcoma, metastatic, skin				1 (25%)
Mediastinal, histiocytic sarcoma				1 (25%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Hematopoietic System (continued)				
Lymph node, mandibular	(49)	(50)	(49)	(49)
Neural crest tumor, metastatic, lymph node, mandibular				1 (2%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Carcinoma	1 (2%)			
Histiocytic sarcoma				1 (2%)
Spleen	(50)	(50)	(50)	(49)
Hemangiosarcoma		1 (2%)	1 (2%)	
Histiocytic sarcoma				1 (2%)
Leiomyoma		1 (2%)		
Thymus	(49)	(47)	(45)	(50)
Integumentary System				
Mammary gland	(46)	(50)	(49)	(49)
Fibroadenoma	2 (4%)	6 (12%)	2 (4%)	8 (16%)
Fibroadenoma, multiple		1 (2%)		
Skin	(49)	(50)	(50)	(50)
Basal cell adenoma			1 (2%)	
Basal cell carcinoma			1 (2%)	
Carcinoma, metastatic, nose				1 (2%)
Hemangiosarcoma		1 (2%)		
Keratoacanthoma		4 (8%)	3 (6%)	2 (4%)
Keratoacanthoma, multiple	1 (2%)	1 (2%)		
Sarcoma		1 (2%)		
Squamous cell carcinoma	1 (2%)			
Subcutaneous tissue, fibroma	3 (6%)	3 (6%)	2 (4%)	5 (10%)
Subcutaneous tissue, fibroma, multiple		1 (2%)		
Subcutaneous tissue, fibrosarcoma			1 (2%)	2 (4%)
Subcutaneous tissue, fibrous histiocytoma				1 (2%)
Subcutaneous tissue, lipoma	1 (2%)		1 (2%)	
Subcutaneous tissue, neural crest tumor, metastatic, skin				1 (2%)
Subcutaneous tissue, schwannoma malignant, metastatic, salivary glands	2 (4%)			1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteoma		1 (2%)		
Cranium, osteosarcoma	1 (2%)			
Vertebra, osteosarcoma		1 (2%)		
Skeletal muscle	(1)	(1)		
Rhabdomyosarcoma	1 (100%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)	
Carcinoma, metastatic, Zymbal's gland		1 (2%)		
Oligodendroglioma malignant		1 (2%)		
Meninges, osteosarcoma, metastatic, bone	1 (2%)			
Spinal cord	(1)	(2)	(1)	(1)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		3 (6%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma			1 (2%)	
Histiocytic sarcoma				1 (2%)
Osteosarcoma, metastatic, bone		1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)	
Schwannoma malignant, metastatic, skin	1 (2%)			
Mediastinum, osteosarcoma, metastatic, bone		1 (2%)		
Nose	(50)	(50)	(49)	(50)
Osteosarcoma, metastatic, bone		1 (2%)		
Respiratory epithelium, squamous cell carcinoma				1 (2%)
Special Senses System				
Zymbal's gland		(2)		(1)
Adenoma		1 (50%)		
Carcinoma		1 (50%)		1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Renal tubule, adenoma		1 (2%)		1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	20 (40%)	20 (40%)	14 (28%)	12 (24%)
Mesothelioma malignant			2 (4%)	2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	49	50	49	49
Total primary neoplasms	116	146	124	133
Total animals with benign neoplasms	47	49	49	47
Total benign neoplasms	85	114	95	104
Total animals with malignant neoplasms	29	30	24	26
Total malignant neoplasms	31	32	29	28
Total animals with metastatic neoplasms	3	2	1	4
Total metastatic neoplasms	5	10	1	5
Total animals with uncertain neoplasms - benign or malignant				1
Total uncertain neoplasms				1

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	0 3 8	4 3 9	4 5 3	4 7 4	4 9 3	5 4 9	5 6 3	5 7 9	5 8 4	6 0 7	6 1 7	6 2 9	6 3 9	6 5 7	6 6 8	6 7 4	7 7 4	6 9 1	6 9 7	7 0 1	7 0 8	7 1 0	7 1 6	7 2 4	7 2 4
Carcass ID Number	0 1 3	0 2 6	0 0 9	0 2 7	0 3 1	0 0 7	0 3 6	0 2 9	0 3 4	0 0 4	0 0 2	0 4 3	0 3 5	0 3 7	0 0 8	0 0 1	0 1 4	0 0 5	0 4 5	0 0 3	0 1 1	0 2 5	0 2 1	0 3 9	0 4 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																							X		
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery		+									+	+							+	+			+	+	
Fat, sarcoma											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant							X						X												
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																							X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X		X	X		X	X			X			X			X					X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin													X												
Bilateral, C-cell, adenoma								X																	
C-cell, adenoma														X							X				
C-cell, carcinoma																			X						
Follicular cell, adenoma												X													

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 1 2	0 1 7	0 2 3	0 4 0	0 4 9	0 5 0	0 0 6	0 1 0	0 1 8	0 3 0	0 3 3	0 4 6	0 1 5	0 1 6	0 1 9	0 2 0	0 2 2	0 2 4	0 2 8	0 3 2	0 3 8	0 4 1	0 4 2	0 4 4	0 4 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																									X	1
Mesentery								+			+						+			+			+		+	13
Fat, sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X							X	2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										2
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma		X																								1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																							X			1
Pheochromocytoma benign	X																	X								2
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X		X	X	X			X			X					X					X	17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, skin																										1
Bilateral, C-cell, adenoma																										1
C-cell, adenoma	X									X					X		X			X			X			8
C-cell, carcinoma																										1
Follicular cell, adenoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	0 3 8	4 3 9	4 5 3	4 7 4	4 9 3	5 4 9	5 6 3	5 7 9	5 8 4	6 0 7	6 1 7	6 2 9	6 3 9	6 5 7	6 6 8	6 7 4	6 7 4	6 9 1	6 9 7	7 0 1	7 0 8	7 1 0	7 1 6	7 2 4	7 2 4
Carcass ID Number	0 1 3	0 2 6	0 0 9	0 2 7	0 3 1	0 0 7	0 3 6	0 2 9	0 3 4	0 0 4	0 0 2	0 4 3	0 3 5	0 3 7	0 0 8	0 0 1	0 1 4	0 0 5	0 4 5	0 0 3	0 1 1	0 2 5	0 2 1	0 3 9	0 4 8
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X				X				X			X	X			X		X	X		X		X	X
Interstitial cell, adenoma							X				X										X		X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node										+	+	+							+	+				+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																								X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma, multiple								X																	
Squamous cell carcinoma																	X								
Subcutaneous tissue, fibroma																				X					
Subcutaneous tissue, lipoma					X																				
Subcutaneous tissue, schwannoma malignant, metastatic, salivary glands							X						X												
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, osteosarcoma				X																					
Skeletal muscle					+																				
Rhabdomyosarcoma					X																				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, osteosarcoma, metastatic, bone				X																					
Peripheral nerve			+																						
Spinal cord			+																						

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 1 2	0 1 7	0 2 3	0 4 0	0 4 9	0 5 0	0 6	0 1 0	0 1 8	0 3 0	0 3 3	0 4 6	0 1 5	0 1 6	0 1 9	0 2 0	0 2 2	0 2 4	0 2 8	0 3 2	0 3 8	0 4 1	0 4 2	0 4 4	0 4 7	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X							X						2
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		34
Interstitial cell, adenoma							X																		X	6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										7
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																								X		1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	46
Fibroadenoma																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Keratoacanthoma, multiple																										1
Squamous cell carcinoma																										1
Subcutaneous tissue, fibroma														X			X									3
Subcutaneous tissue, lipoma																										1
Subcutaneous tissue, schwannoma malignant, metastatic, salivary glands																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, osteosarcoma																										1
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meninges, osteosarcoma, metastatic, bone																										1
Peripheral nerve																										1
Spinal cord																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	0 3 8	4 3 9	4 5 3	4 7 4	4 9 3	5 4 9	5 6 3	5 7 9	5 8 4	6 0 7	6 1 7	6 2 9	6 3 9	6 5 7	6 6 8	6 7 4	6 7 4	6 9 1	6 9 7	7 0 1	7 0 8	7 1 0	7 1 6	7 2 4	7 2 4
Carcass ID Number	0 1 3	0 2 6	0 0 9	0 2 7	0 3 1	0 0 7	0 3 6	0 2 9	0 3 4	0 0 4	0 0 2	0 4 3	0 3 5	0 3 7	0 0 8	0 0 1	0 1 4	0 0 5	0 4 5	0 0 3	0 1 1	0 1 5	0 2 1	0 3 9	0 4 8
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																				+					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X	X		X		X		X			X	X	X	X		X	X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 1 2	0 1 7	0 2 3	0 4 0	0 4 9	0 5 0	0 0 6	0 1 0	0 1 8	0 3 0	0 3 3	0 4 6	0 1 5	0 1 6	0 1 9	0 2 0	0 2 2	0 2 4	0 2 8	0 3 2	0 3 8	0 4 1	0 4 2	0 4 4	0 4 7	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X	X			X	X							X	X						X		X	20

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	40	44	53	58	59	64	64	67	68	68	69	69	69	71	71	72	72	72	73	73	73	73	73	73
	00	04	36	89	92	41	45	44	81	83	96	97	77	70	16	29	29	29	30	00	00	30	00	30
Carcass ID Number	08	07	08	05	09	07	07	08	06	09	00	05	07	08	09	08	06	09	05	05	06	07	08	08
	87	00	00	44	99	11	66	88	22	22	00	99	77	44	44	11	67	96	55	57	00	33	55	66
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous							X																	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																								
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																					X			
Mesentery						+				+									+		+		+	+
Pancreas	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																X								
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X																			
Osteosarcoma, metastatic, bone																X								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																X								
Pheochromocytoma malignant			X																					
Pheochromocytoma benign													X									X		
Bilateral, pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X			X		
Carcinoma																								
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X					X	X	X	X							X			X	
Osteosarcoma, metastatic, bone																X								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																								
C-cell, adenoma								X				X			X		X				X			
C-cell, carcinoma																								
Follicular cell, carcinoma											X													
General Body System																								
Tissue NOS																+								
Osteosarcoma, metastatic, bone																X								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	09090	09097	00551	00552	00553	00556	00558	00561	00563	00564	00565	00566	00568	00572	00574	00575	00578	00579	00582	00583	00589	00591	00593	00595	00598	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																												1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous			X																									1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma							X																					2
Mesentery					+								+				+	+		+				+			+	13
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																												
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																												1
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X						2
Osteosarcoma, metastatic, bone																												1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																												1
Pheochromocytoma malignant																												1
Pheochromocytoma benign	X							X								X						X						6
Bilateral, pheochromocytoma benign										X																		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																												2
Carcinoma																X						X						2
Parathyroid gland	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X							X		X		X	X	X			X	X			X	X		X			18
Osteosarcoma, metastatic, bone																												1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma			X	X																								2
C-cell, adenoma							X								X		X						X				X	10
C-cell, carcinoma								X																				1
Follicular cell, carcinoma																												1
General Body System																												
Tissue NOS																												1
Osteosarcoma, metastatic, bone																												1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	40	44	53	58	59	64	64	67	68	68	69	69	69	69	71	71	72	72	72	73	73	73	73	73	73
	00	47	36	89	92	41	45	44	81	83	96	97	77	97	10	16	29	99	99	30	00	00	00	00	00
Carcass ID Number	08	07	08	05	09	07	07	08	06	09	00	05	07	08	09	08	06	06	09	05	05	06	07	08	08
	87	70	00	44	99	11	66	88	22	22	00	99	77	44	44	11	67	79	66	55	57	00	33	55	86
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X	X	X		X	X	X	X						X	X	X	X	X	X	X	X	X		X
Interstitial cell, adenoma										X	X	X		X										X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+								+									
Osteosarcoma, metastatic, bone																X									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Leiomyoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma											X			X											
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Keratoacanthoma								X	X																X
Keratoacanthoma, multiple																									
Sarcoma																									
Subcutaneous tissue, fibroma						X																			
Subcutaneous tissue, fibroma, multiple									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteoma																							X		
Vertebra, osteosarcoma																X									
Skeletal muscle																			+						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland														X											
Oligodendroglioma malignant	X																								
Peripheral nerve		+						+																	
Spinal cord		+						+																	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	09090	09097	09051	09052	09053	09056	09058	09061	09063	09064	09065	09066	09068	09072	09074	09075	09078	09079	09082	09083	09089	09091	09093	09095	09098	Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Carcinoma								X																		1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	40
Interstitial cell, adenoma																										5
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node										+																3
Osteosarcoma, metastatic, bone																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																			X							1
Leiomyoma										X																1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma		X	X													X									X	6
Fibroadenoma, multiple											X															1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																		X								1
Keratoacanthoma																								X		4
Keratoacanthoma, multiple																		X								1
Sarcoma				X																						1
Subcutaneous tissue, fibroma											X						X									3
Subcutaneous tissue, fibroma, multiple																										1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteoma																										1
Vertebra, osteosarcoma																										1
Skeletal muscle																										1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Oligodendroglioma malignant																										1
Peripheral nerve																										2
Spinal cord																										2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	4 0 0	4 7 4	5 3 6	5 8 9	5 9 2	6 4 1	6 4 5	6 7 4	6 8 1	6 8 3	6 9 6	6 9 7	6 9 7	6 9 7	7 1 0	7 1 6	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 8 7	0 7 0	0 8 0	0 5 4	0 9 9	0 7 1	0 7 6	0 8 8	0 6 2	0 9 2	1 0 0	0 5 9	0 7 7	0 8 4	0 9 4	0 8 1	0 6 7	0 6 9	0 9 6	0 5 5	0 5 7	0 6 0	0 7 3	0 8 5	0 8 6
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X																	
Osteosarcoma, metastatic, bone																X									
Mediastinum, osteosarcoma, metastatic, bone																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																X									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland														+											
Adenoma																									
Carcinoma														X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																	X								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X	X	X	X			X		X		X	X						X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	09090	09097	00551	00552	00553	00556	00558	00661	00663	00664	00665	00666	00668	00672	00774	00775	00778	00779	00782	00783	00789	00791	00793	00795	00798	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X												X												3
Osteosarcoma, metastatic, bone																										1
Mediastinum, osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye															+											1
Zymbal's gland																			+							2
Adenoma																			X							1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X		X	X				X			X		X					X	X					20

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 10 mg/kg

Number of Days on Study	27 64	44 64	44 67	44 74	48 40	61 07	64 22	66 22	68 27	68 88	68 89	68 91	69 12	71 22	72 22	72 29	72 29	72 99	72 99	72 99	72 99	72 99	72 99	72 99	72 99	73 30
Carcass ID Number	11 14	11 01	11 45	11 29	11 43	11 08	11 34	11 23	12 28	10 33	11 15	13 33	14 22	13 25	14 11	10 24	10 25	10 58	11 20	13 36	13 38	13 39	15 50	11 01
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																				X						
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																										
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery										+		+														+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X				
Mixed tumor benign																					X					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																				X						
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																										
Pheochromocytoma benign																							X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X			X	X	X										X					X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																										
C-cell, adenoma		X						X		X													X			
C-cell, carcinoma																X										
Follicular cell, adenoma																										
Follicular cell, carcinoma							X																			
General Body System																										
Tissue NOS																										
Chemodectoma benign																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 10 mg/kg

Number of Days on Study	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	11012	11013	11026	11006	11007	11009	11010	11016	11017	11019	11021	11022	11024	11025	11027	11030	11031	11032	11037	11040	11044	11046	11047	11048	11049	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous							X																			1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+		+	+				+				+							+				+	+		11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Mixed tumor benign																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant												X										X				2
Pheochromocytoma benign		X						X	X							X			X							6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X					X							X	X				X							11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma				X																						1
C-cell, adenoma							X											X		X						7
C-cell, carcinoma																										1
Follicular cell, adenoma								X		X																2
Follicular cell, carcinoma																										1
General Body System																										
Tissue NOS																							+			1
Chemodectoma benign																							X			1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 10 mg/kg

Number of Days on Study	2 7 6	4 6 4	4 6 4	4 7 4	4 8 0	6 1 7	6 4 2	6 6 2	6 8 7	6 8 8	6 8 9	6 9 1	7 1 2	7 2 2	7 2 2	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0
Carcass ID Number	1 1 4	1 0 1	1 0 4 5	1 2 9	1 4 3	1 0 8	1 3 4	1 2 3	1 2 8	1 0 3	1 1 5	1 3 3	1 4 2	1 3 5	1 4 1	1 0 2	1 0 4	1 0 5	1 1 8	1 2 0	1 3 6	1 3 8	1 3 9	1 5 0	1 1 1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X					X				
Carcinoma			X							X															
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X			X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	
Interstitial cell, adenoma			X			X													X						X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+				+	+												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Basal cell carcinoma														X											
Keratoacanthoma																						X		X	
Subcutaneous tissue, fibroma																X									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Peripheral nerve				+																					
Spinal cord				+																					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 10 mg/kg

Number of Days on Study	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	11012	11013	11026	10066	10007	10009	11010	11016	11017	11019	12021	12022	12024	12025	12027	13010	13011	13012	13027	14004	14004	14006	14007	14008	14009		Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma												X											X				4
Carcinoma		X																									3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		43
Interstitial cell, adenoma																											4
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node																											3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma							X																				1
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+		45
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Fibroadenoma		X									X																2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Basal cell adenoma																									X		1
Basal cell carcinoma																											1
Keratoacanthoma		X																									3
Subcutaneous tissue, fibroma					X																						2
Subcutaneous tissue, fibrosarcoma	X																										1
Subcutaneous tissue, lipoma																			X								1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Astrocytoma malignant				X																							1
Peripheral nerve																											1
Spinal cord																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma											X																1
Alveolar/bronchiolar carcinoma											X																1
Pheochromocytoma malignant, metastatic, adrenal medulla												X															1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 10 mg/kg

Number of Days on Study	2 7 6	4 6 4	4 6 4	4 7 4	4 8 0	6 1 7	6 4 2	6 6 2	6 8 7	6 8 8	6 8 9	6 9 1	7 1 2	7 2 2	7 2 2	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0
Carcass ID Number	1 1 4	1 0 1	1 4 5	1 2 9	1 4 3	1 0 8	1 3 4	1 2 3	1 2 8	1 0 3	1 1 5	1 3 3	1 4 2	1 3 5	1 4 1	1 0 2	1 0 4	1 0 5	1 1 8	1 2 0	1 3 6	1 3 8	1 3 9	1 5 0	1 1 1
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X		X		X	X	X	X	X										
Mesothelioma malignant																									

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 10 mg/kg

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Total
Carcass ID Number	1	1	2	0	0	0	1	1	1	1	2	2	2	2	2	3	3	3	3	4	4	4	4	4	4	Tissues/
	2	3	6	6	7	9	0	6	7	9	1	2	4	5	7	0	1	2	7	0	4	6	7	8	9	Tumors
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X						X			X									X			X	X	14
Mesothelioma malignant					X		X																			2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 30 mg/kg

Number of Days on Study	3 5 1	4 5 6	4 6 6	5 3 0	5 3 0	5 3 3	6 0 3	6 1 8	6 2 4	6 4 5	6 5 7	6 6 2	6 8 0	6 8 1	6 9 9	7 0 8	7 1 0	7 2 2	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 6 9	1 5 4	1 9 2	1 8 7	1 8 9	1 8 8	1 5 9	1 5 1	1 6 4	2 0 0	1 7 7	1 9 6	1 7 1	1 8 1	1 5 5	1 9 4	1 9 5	1 6 1	1 8 0	1 5 3	1 5 8	1 6 3	1 7 6	1 8 5	1 9 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									X
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Mesentery							+			+												+		+	
Fat, schwannoma malignant																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neural crest tumor																									
Schwannoma malignant								X																	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma															X										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign													X							X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X		X		X		X		X		X	X		X			
Craniopharyngioma								X																	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma		X										X								X					
Follicular cell, carcinoma																									
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 30 mg/kg

Number of Days on Study	729	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	19 99	15 02	17 00	17 02	17 05	18 03	18 06	15 06	15 07	16 00	16 02	16 05	16 06	16 07	16 08	17 03	17 04	17 08	17 09	18 02	18 04	19 00	19 01	19 03	19 07	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Mesentery	+	+				+	+						+	+							+				+	12
Fat, schwannoma malignant							X																			1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																X				2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neural crest tumor															X											1
Schwannoma malignant																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																									+	1
Squamous cell papilloma																									X	1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Schwannoma malignant													X													1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X				X	X		X		X	X	X	X			X	X	X				X			20
Craniopharyngioma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X						X			X										6
Follicular cell, carcinoma		X															X									2
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 30 mg/kg

Number of Days on Study	3 5 1	4 5 6	4 6 6	5 3 0	5 3 0	5 3 3	6 0 3	6 1 8	6 2 4	6 4 5	6 5 7	6 6 2	6 8 0	6 8 1	6 9 9	7 0 8	7 1 0	7 2 2	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 6 9	1 5 4	1 9 2	1 8 7	1 8 9	1 8 8	1 5 9	1 5 1	1 6 4	2 0 0	1 7 7	1 9 6	1 7 1	1 8 1	1 5 5	1 9 4	1 9 5	1 6 1	1 8 0	1 5 3	1 5 8	1 6 3	1 7 6	1 8 5	1 9 8
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Carcinoma			X									X													
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Bilateral, interstitial cell, adenoma		X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Interstitial cell, adenoma																								X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Lymph node		+					+											+							
Inguinal, fibrosarcoma, metastatic, skin							X																		
Mediastinal, histiocytic sarcoma		X																							
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neural crest tumor, metastatic, lymph node, mandibular																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma													X								X			X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, nose													X												
Keratoacanthoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma							X							X											
Subcutaneous tissue, fibrous histiocytoma									X																
Subcutaneous tissue, neural crest , tumor, metastatic, skin																									
Subcutaneous tissue, schwannoma malignant, metastatic, salivary glands								X																	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																		+							
Spinal cord																		+							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 30 mg/kg

Number of Days on Study	729	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	19 99	15 92	17 90	17 72	17 75	18 83	18 86	15 66	15 67	16 00	16 02	16 25	16 66	16 67	16 68	17 33	17 74	17 78	17 89	18 24	18 40	19 01	19 13	19 97		Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		49
Adenoma									X				X					X								4
Carcinoma																										2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma															X											1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma									X																	1
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		45
Interstitial cell, adenoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Histiocytic sarcoma																										1
Lymph node																								+		4
Inguinal, fibrosarcoma, metastatic, skin																										1
Mediastinal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Neural crest tumor, metastatic, lymph node, mandibular															X											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Histiocytic sarcoma																										1
Spleen	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Fibroadenoma				X							X		X							X			X			8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma, metastatic, nose																										1
Keratoacanthoma																						X		X		2
Subcutaneous tissue, fibroma										X	X					X	X		X							5
Subcutaneous tissue, fibrosarcoma																										2
Subcutaneous tissue, fibrous histiocytoma																										1
Subcutaneous tissue, neural crest tumor, metastatic, skin															X											1
Subcutaneous tissue, schwannoma malignant, metastatic, salivary glands																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Peripheral nerve																										1
Spinal cord																										1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 30 mg/kg

Number of Days on Study	351	456	466	530	530	533	603	618	624	645	657	662	680	681	699	708	710	722	726	729	729	729	729	729	729
Carcass ID Number	169	154	192	187	189	188	159	151	164	200	177	196	171	181	155	194	195	161	180	153	158	163	176	185	198
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Histiocytic sarcoma		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory epithelium, squamous cell carcinoma													X												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Leukemia mononuclear	X						X								X	X		X		X					
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Methacrylonitrile: 30 mg/kg

Number of Days on Study	729	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	19999	15202	17370	17702	17705	18303	18806	15606	15507	16070	16202	16505	16606	16707	16608	17303	17404	17808	17909	18202	18404	19000	19101	19303	19907	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory epithelium, squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Zymbal's gland															M						+					1
Carcinoma																					X					1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Renal tubule, adenoma															X											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear				X							X				X				X					X	X	12
Mesothelioma malignant					X				X																	2

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	3/50 (6%)	7/50 (14%)	6/50 (12%)	2/50 (4%)
Adjusted rate[b]	7.3%	15.5%	13.5%	4.6%
Terminal rate[c]	2/25 (8%)	6/34 (18%)	6/35 (17%)	1/31 (3%)
First incidence (days)	716	697	729 (T)	680
Poly-3 test[d]	P=0.167N	P=0.199	P=0.283	P=0.475N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	4/50 (8%)	8/50 (16%)	8/50 (16%)	2/50 (4%)
Adjusted rate	9.8%	17.5%	18.0%	4.6%
Terminal rate	3/25 (12%)	6/34 (18%)	8/35 (23%)	1/31 (3%)
First incidence (days)	716	536	729 (T)	680
Poly-3 test	P=0.101N	P=0.235	P=0.217	P=0.311N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	0.0%	6.6%	2.3%	2.3%
Terminal rate	0/25 (0%)	2/34 (6%)	1/35 (3%)	1/31 (3%)
First incidence (days)	—[e]	674	729 (T)	729 (T)
Poly-3 test	P=0.559N	P=0.138	P=0.516	P=0.510
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	0.0%	6.6%	2.3%	2.3%
Terminal rate	0/25 (0%)	2/34 (6%)	1/35 (3%)	1/31 (3%)
First incidence (days)	—	674	729 (T)	729 (T)
Poly-3 test	P=0.559N	P=0.138	P=0.516	P=0.510
Mammary Gland: Fibroadenoma				
Overall rate	2/50 (4%)	7/50 (14%)	2/50 (4%)	8/50 (16%)
Adjusted rate	4.9%	15.4%	4.5%	18.5%
Terminal rate	0/25 (0%)	5/34 (15%)	2/35 (6%)	7/31 (23%)
First incidence (days)	724	696	729 (T)	680
Poly-3 test	P=0.089	P=0.105	P=0.664N	P=0.053
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	0/50 (0%)	4/50 (8%)	1/50 (2%)	1/50 (2%)
Adjusted rate	0.0%	8.9%	2.3%	2.3%
Terminal rate	0/25 (0%)	4/34 (12%)	1/35 (3%)	0/31 (0%)
First incidence (days)	—	729 (T)	729 (T)	680
Poly-3 test	P=0.436N	P=0.073	P=0.516	P=0.511
Pituitary Gland: Adenoma				
Overall rate	17/50 (34%)	18/50 (36%)	11/50 (22%)	20/50 (40%)
Adjusted rate	38.0%	39.1%	23.6%	45.4%
Terminal rate	8/25 (32%)	13/34 (38%)	7/35 (20%)	14/31 (45%)
First incidence (days)	453	592	464	624
Poly-3 test	P=0.242	P=0.547	P=0.100N	P=0.312
Preputial Gland: Adenoma				
Overall rate	2/50 (4%)	1/50 (2%)	4/50 (8%)	4/49 (8%)
Adjusted rate	4.9%	2.2%	9.0%	9.5%
Terminal rate	2/25 (8%)	1/34 (3%)	4/35 (11%)	3/30 (10%)
First incidence (days)	729 (T)	729 (T)	729 (T)	681
Poly-3 test	P=0.169	P=0.466N	P=0.376	P=0.352

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Preputial Gland: Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	2/49 (4%)
Adjusted rate	2.4%	2.2%	6.6%	4.6%
Terminal rate	0/25 (0%)	1/34 (3%)	1/35 (3%)	0/30 (0%)
First incidence (days)	579	729 (T)	464	466
Poly-3 test	P=0.402	P=0.741N	P=0.338	P=0.514
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	7/50 (14%)	6/49 (12%)
Adjusted rate	7.2%	4.4%	15.4%	13.9%
Terminal rate	2/25 (8%)	2/34 (6%)	5/35 (14%)	3/30 (10%)
First incidence (days)	579	729 (T)	464	466
Poly-3 test	P=0.132	P=0.461N	P=0.196	P=0.263
Skin: Keratoacanthoma				
Overall rate	1/50 (2%)	5/50 (10%)	3/50 (6%)	2/50 (4%)
Adjusted rate	2.4%	11.0%	6.8%	4.6%
Terminal rate	0/25 (0%)	3/34 (9%)	3/35 (9%)	2/31 (7%)
First incidence (days)	579	674	729 (T)	729 (T)
Poly-3 test	P=0.450N	P=0.124	P=0.331	P=0.514
Skin: Keratoacanthoma or Squamous Cell Carcinoma				
Overall rate	2/50 (4%)	5/50 (10%)	3/50 (6%)	2/50 (4%)
Adjusted rate	4.8%	11.0%	6.8%	4.6%
Terminal rate	0/25 (0%)	3/34 (9%)	3/35 (9%)	2/31 (7%)
First incidence (days)	579	674	729 (T)	729 (T)
Poly-3 test	P=0.352N	P=0.253	P=0.530	P=0.682N
Skin: Keratoacanthoma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma				
Overall rate	2/50 (4%)	5/50 (10%)	5/50 (10%)	2/50 (4%)
Adjusted rate	4.8%	11.0%	11.2%	4.6%
Terminal rate	0/25 (0%)	3/34 (9%)	4/35 (11%)	2/31 (7%)
First incidence (days)	579	674	722	729 (T)
Poly-3 test	P=0.349N	P=0.253	P=0.243	P=0.682N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	3/50 (6%)	4/50 (8%)	2/50 (4%)	5/50 (10%)
Adjusted rate	7.3%	8.8%	4.5%	11.6%
Terminal rate	2/25 (8%)	2/34 (6%)	2/35 (6%)	5/31 (16%)
First incidence (days)	701	641	729 (T)	729 (T)
Poly-3 test	P=0.308	P=0.557	P=0.464N	P=0.383
Skin (Subcutaneous Tissue): Fibrous Histiocytoma, Fibrosarcoma, or Sarcoma				
Overall rate	0/50 (0%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	2.2%	2.3%	6.8%
Terminal rate	0/25 (0%)	1/34 (3%)	1/35 (3%)	0/31 (0%)
First incidence (days)	—	729 (T)	729 (T)	603
Poly-3 test	P=0.070	P=0.519	P=0.516	P=0.132
Skin (Subcutaneous Tissue): Fibroma, Fibrous Histiocytoma, Fibrosarcoma, or Sarcoma				
Overall rate	3/50 (6%)	5/50 (10%)	3/50 (6%)	8/50 (16%)
Adjusted rate	7.3%	11.0%	6.8%	18.2%
Terminal rate	2/25 (8%)	3/34 (9%)	3/35 (9%)	5/31 (16%)
First incidence (days)	701	641	729 (T)	603
Poly-3 test	P=0.078	P=0.416	P=0.625N	P=0.121

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Testes: Adenoma				
Overall rate	40/50 (80%)	45/50 (90%)	47/50 (94%)	46/50 (92%)
Adjusted rate	89.1%	92.6%	98.7%	95.8%
Terminal rate	25/25 (100%)	32/34 (94%)	35/35 (100%)	30/31 (97%)
First incidence (days)	439	474	464	456
Poly-3 test	P=0.152	P=0.394	P=0.024	P=0.155
Thyroid Gland (C-cell): Adenoma				
Overall rate	9/50 (18%)	12/50 (24%)	8/50 (16%)	6/50 (12%)
Adjusted rate	21.6%	26.4%	17.6%	13.6%
Terminal rate	6/25 (24%)	9/34 (27%)	5/35 (14%)	4/31 (13%)
First incidence (days)	579	674	464	456
Poly-3 test	P=0.116N	P=0.391	P=0.420N	P=0.247N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	10/50 (20%)	13/50 (26%)	9/50 (18%)	6/50 (12%)
Adjusted rate	23.9%	28.6%	19.8%	13.6%
Terminal rate	6/25 (24%)	10/34 (29%)	6/35 (17%)	4/31 (13%)
First incidence (days)	579	674	464	456
Poly-3 test	P=0.072N	P=0.399	P=0.417N	P=0.171N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted rate	2.4%	2.2%	6.7%	4.6%
Terminal rate	0/25 (0%)	0/34 (0%)	2/35 (6%)	2/31 (7%)
First incidence (days)	629	696	642	729 (T)
Poly-3 test	P=0.401	P=0.740N	P=0.335	P=0.515
All Organs: Mononuclear Cell Leukemia				
Overall rate	20/50 (40%)	20/50 (40%)	14/50 (28%)	12/50 (24%)
Adjusted rate	46.4%	42.9%	30.9%	26.9%
Terminal rate	9/25 (36%)	13/34 (38%)	7/35 (20%)	7/31 (23%)
First incidence (days)	584	589	642	351
Poly-3 test	P=0.030N	P=0.450N	P=0.096N	P=0.043N
All Organs: Benign Neoplasms				
Overall rate	47/50 (94%)	49/50 (98%)	49/50 (98%)	47/50 (94%)
Adjusted rate	97.8%	99.7%	99.9%	97.2%
Terminal rate	25/25 (100%)	34/34 (100%)	35/35 (100%)	30/31 (97%)
First incidence (days)	439	474	464	456
Poly-3 test	P=0.405N	P=0.540	P=0.489	P=0.700N
All Organs: Malignant Neoplasms				
Overall rate	29/50 (58%)	30/50 (60%)	24/50 (48%)	26/50 (52%)
Adjusted rate	62.4%	62.0%	51.9%	54.7%
Terminal rate	11/25 (44%)	18/34 (53%)	15/35 (43%)	14/31 (45%)
First incidence (days)	474	400	464	351
Poly-3 test	P=0.243N	P=0.569N	P=0.206N	P=0.291N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	50/50 (100%)	49/50 (98%)	49/50 (98%)
Adjusted rate	100.0%	100.0%	99.9%	98.0%
Terminal rate	25/25 (100%)	34/34 (100%)	35/35 (100%)	30/31 (97%)
First incidence (days)	439	400	464	351
Poly-3 test	P=0.218N	P=1.000	P=1.000N	P=0.504N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, lung, pancreatic islets, pituitary gland, preputial gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE A4
Historical Incidence of Mononuclear Cell Leukemia in Control Male F344/N Rats

Study	Incidence in Controls
Historical Incidence in Controls Given NTP-2000 Diet[a]	
Citral (feed)	68/100
p,p′-Dichlorodiphenyl sulfone (feed)	27/50
Indium phosphide (inhalation)	16/50
60-Hz Magnetic fields (whole body exposure)	50/100
Methacrylonitrile (gavage)	20/50
Naphthalene (inhalation)	26/49
o-Nitrotoluene (feed)	30/60
p-Nitrotoluene (feed)	24/50
Sodium nitrite (drinking water)	17/50
Vanadium pentoxide (inhalation)	22/50
Overall Historical Incidence in Controls Given NTP-2000 Diet	
Total (%)	300/609 (49.3%)
Mean ± standard deviation	47.3% ± 10.5%
Range	32%-68%
Historical Incidence in Water Gavage Controls Given NIH-07 Diet at Battelle Columbus Laboratories[b]	
Scopolamine hydrobromide trihydrate	33/50 (66.0%)

[a] Data as of 18 January 2001; includes data for lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemia
[b] Data as of 21 December 1999; includes data for lymphocytic, monocytic, and undifferentiated leukemia

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Methacrylonitrile[a]

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund	13	13	9	12
Natural deaths	12	3	6	6
Survivors				
Died the last week of the study			1	
Terminal sacrifice	25	34	34	31
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)	
Parasite metazoan		1 (2%)	1 (2%)	
Pigmentation			1 (2%)	
Intestine large, rectum	(50)	(50)	(50)	(50)
Parasite metazoan	10 (20%)	8 (16%)	7 (14%)	5 (10%)
Intestine large, cecum	(49)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)			
Epithelium, atrophy			1 (2%)	
Intestine small, duodenum	(50)	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)	1 (2%)	
Parasite metazoan		1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)	(50)
Inflammation, chronic active			2 (4%)	
Intestine small, ileum	(50)	(50)	(49)	(50)
Inflammation, chronic active			2 (4%)	
Parasite metazoan	1 (2%)			
Liver	(50)	(50)	(50)	(49)
Angiectasis	2 (4%)	4 (8%)	7 (14%)	4 (8%)
Basophilic focus	26 (52%)	33 (66%)	35 (70%)	13 (27%)
Clear cell focus	8 (16%)	16 (32%)	16 (32%)	4 (8%)
Congestion	1 (2%)		1 (2%)	
Cyst				1 (2%)
Degeneration, cystic	3 (6%)	7 (14%)	5 (10%)	6 (12%)
Eosinophilic focus	10 (20%)	8 (16%)	9 (18%)	7 (14%)
Fatty change	23 (46%)	18 (36%)	21 (42%)	9 (18%)
Hematopoietic cell proliferation				1 (2%)
Hepatodiaphragmatic nodule	8 (16%)	5 (10%)	9 (18%)	6 (12%)
Inclusion body intracytoplasmic				1 (2%)
Inflammation, chronic active	16 (32%)	21 (42%)	29 (58%)	10 (20%)
Mixed cell focus	16 (32%)	23 (46%)	22 (44%)	10 (20%)
Necrosis	4 (8%)	1 (2%)		3 (6%)
Thrombosis		1 (2%)		
Vacuolization cytoplasmic	14 (28%)	18 (36%)	23 (46%)	28 (57%)
Bile duct, fibrosis	1 (2%)			
Bile duct, hyperplasia	42 (84%)	48 (96%)	48 (96%)	36 (73%)
Mesentery	(13)	(13)	(11)	(12)
Artery, inflammation, chronic active	1 (8%)			
Fat, inflammation, chronic active	8 (62%)	12 (92%)	11 (100%)	9 (75%)
Fat, mineralization		1 (8%)		
Fat, necrosis	1 (8%)	1 (8%)		1 (8%)

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

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Alimentary System (continued)				
Pancreas	(50)	(49)	(50)	(50)
Cytoplasmic alteration	2 (4%)		3 (6%)	
Fibrosis		1 (2%)		
Hyperplasia	4 (8%)	10 (20%)	11 (22%)	12 (24%)
Acinus, atrophy	10 (20%)	13 (27%)	12 (24%)	14 (28%)
Artery, inflammation, chronic active	1 (2%)		1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Erosion	1 (2%)			
Hyperkeratosis	1 (2%)			
Hyperplasia	3 (6%)	3 (6%)		1 (2%)
Inflammation, chronic active	1 (2%)	1 (2%)		
Perforation	1 (2%)			
Ulcer	2 (4%)	2 (4%)	2 (4%)	
Epithelium, hyperplasia			1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Erosion	3 (6%)		5 (10%)	2 (4%)
Mineralization	1 (2%)			
Ulcer	4 (8%)			
Cardiovascular System				
Blood vessel	(50)	(49)	(50)	(50)
Inflammation, chronic active	1 (2%)	1 (2%)		
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	43 (86%)	48 (96%)	41 (82%)	46 (92%)
Fibrosis	1 (2%)		1 (2%)	
Thrombosis	3 (6%)	1 (2%)	1 (2%)	3 (6%)
Artery, inflammation, chronic active	1 (2%)			
Endocardium, hyperplasia				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Angiectasis	5 (10%)	3 (6%)	12 (24%)	9 (18%)
Atrophy	1 (2%)		1 (2%)	
Degeneration, cystic			1 (2%)	
Hematopoietic cell proliferation				2 (4%)
Hyperplasia	9 (18%)	10 (20%)	11 (22%)	8 (16%)
Necrosis			1 (2%)	
Pigmentation			1 (2%)	
Thrombosis			1 (2%)	
Vacuolization cytoplasmic	8 (16%)	3 (6%)	3 (6%)	5 (10%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	11 (22%)	5 (10%)	7 (14%)	7 (14%)
Mineralization		1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)		1 (2%)
Parathyroid gland	(46)	(46)	(50)	(50)
Fibrosis		1 (2%)		
Hyperplasia, focal			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Endocrine System (continued)				
Pituitary gland	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)		3 (6%)	
Atrophy	1 (2%)		1 (2%)	
Cyst	5 (10%)	5 (10%)	7 (14%)	1 (2%)
Hyperplasia	13 (26%)	17 (34%)	16 (32%)	10 (20%)
Craniopharyngeal duct, hyperplasia		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	23 (46%)	29 (58%)	35 (70%)	29 (58%)
Follicle, cyst	1 (2%)			
Follicular cell, hyperplasia	3 (6%)			1 (2%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)		1 (2%)	
Preputial gland	(50)	(50)	(50)	(49)
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic active	41 (82%)	45 (90%)	46 (92%)	45 (92%)
Prostate	(50)	(50)	(50)	(50)
Atrophy		1 (2%)	1 (2%)	3 (6%)
Cyst	1 (2%)			
Hyperplasia			5 (10%)	2 (4%)
Inflammation	25 (50%)	25 (50%)	17 (34%)	24 (48%)
Seminal vesicle	(50)	(50)	(50)	(50)
Atrophy	1 (2%)	2 (4%)	1 (2%)	4 (8%)
Inflammation, chronic active	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Atrophy	6 (12%)	6 (12%)	5 (10%)	2 (4%)
Mineralization	1 (2%)			
Necrosis			1 (2%)	
Interstitial cell, hyperplasia	9 (18%)	6 (12%)	4 (8%)	3 (6%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia	17 (34%)	14 (28%)	19 (38%)	20 (40%)
Myelofibrosis	1 (2%)			
Lymph node	(7)	(3)	(3)	(4)
Mediastinal, congestion	1 (14%)			
Mediastinal, ectasia			1 (33%)	
Mediastinal, inflammation, chronic active			1 (33%)	
Renal, congestion			1 (33%)	
Renal, ectasia		1 (33%)		
Renal, inflammation, chronic active			1 (33%)	
Lymph node, mandibular	(49)	(50)	(49)	(49)
Ectasia	1 (2%)	4 (8%)	1 (2%)	4 (8%)
Hyperplasia	1 (2%)			
Hyperplasia, plasma cell	2 (4%)	1 (2%)		2 (4%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Hematopoietic System (continued)				
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Congestion	1 (2%)			
Ectasia	2 (4%)	3 (6%)	1 (2%)	4 (8%)
Inflammation, chronic active			2 (4%)	
Spleen	(50)	(50)	(50)	(49)
Accessory spleen			1 (2%)	
Angiectasis		1 (2%)		
Fibrosis	6 (12%)	4 (8%)	4 (8%)	4 (8%)
Hematopoietic cell proliferation	4 (8%)	3 (6%)	3 (6%)	7 (14%)
Hemorrhage	1 (2%)			
Hyperplasia, histiocytic				1 (2%)
Necrosis	1 (2%)		1 (2%)	1 (2%)
Capsule, fibrosis		1 (2%)		
Capsule, inflammation, chronic active				1 (2%)
Thymus	(49)	(47)	(45)	(50)
Cyst	1 (2%)			
Integumentary System				
Mammary gland	(46)	(50)	(49)	(49)
Galactocele		5 (10%)		1 (2%)
Hyperplasia	2 (4%)	3 (6%)	4 (8%)	4 (8%)
Skin	(49)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Hyperkeratosis			2 (4%)	1 (2%)
Hyperplasia			2 (4%)	
Inflammation, chronic active			1 (2%)	1 (2%)
Parakeratosis			1 (2%)	
Subcutaneous tissue, fibrosis			1 (2%)	
Subcutaneous tissue, inflammation, chronic active			1 (2%)	
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hydrocephalus				1 (2%)
Necrosis	2 (4%)		1 (2%)	
Artery, inflammation, chronic active	1 (2%)			
Spinal cord	(1)	(2)	(1)	(1)
Hemorrhage				1 (100%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)		
Congestion		2 (4%)	1 (2%)	
Edema		1 (2%)		
Hemorrhage	4 (8%)		2 (4%)	
Inflammation, chronic active	3 (6%)	3 (6%)	4 (8%)	6 (12%)
Leukocytosis			1 (2%)	
Alveolar epithelium, hyperplasia	3 (6%)	8 (16%)	6 (12%)	4 (8%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Respiratory System (continued)				
Nose	(50)	(50)	(49)	(50)
Abscess				1 (2%)
Inflammation, chronic active	6 (12%)	7 (14%)	6 (12%)	6 (12%)
Thrombosis	2 (4%)	1 (2%)		1 (2%)
Olfactory epithelium, atrophy				48 (96%)
Olfactory epithelium, metaplasia				47 (94%)
Special Senses System				
Eye	(1)	(1)		
Cataract		1 (100%)		
Degeneration	1 (100%)			
Lens, mineralization		1 (100%)		
Retina, atrophy		1 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst		2 (4%)	1 (2%)	
Fibrosis			1 (2%)	
Infarct	1 (2%)		1 (2%)	
Inflammation, chronic active	13 (26%)	25 (50%)	22 (44%)	18 (36%)
Mineralization				1 (2%)
Nephropathy	44 (88%)	48 (96%)	46 (92%)	47 (94%)
Pigmentation		2 (4%)	3 (6%)	1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)		
Inflammation, chronic active		1 (2%)		

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF METHACRYLONITRILE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Methacrylonitrile[a]

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	1	1	1	
Moribund	4	10	9	7
Natural deaths	7	6	6	7
Survivors				
Died the last week of the study				1
Terminal sacrifice	38	33	34	35
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Periesophageal tissue, lipoma				1 (2%)
Intestine large, colon	(50)	(50)	(50)	(50)
Polyp adenomatous		1 (2%)		1 (2%)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Intestine small, ileum	(50)	(50)	(50)	(50)
Liver	(50)	(49)	(48)	(50)
Hepatocellular adenoma	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Mesentery	(7)	(2)	(8)	(4)
Lipoma				1 (25%)
Fat, histiocytic sarcoma			1 (13%)	
Pancreas	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Salivary glands	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Tongue				(1)
Squamous cell papilloma				1 (100%)
Cardiovascular System				
Blood vessel	(49)	(50)	(50)	(50)
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma benign	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma		1 (2%)	1 (2%)	
Parathyroid gland	(48)	(47)	(46)	(47)
Adenoma	1 (2%)			
Pituitary gland	(50)	(50)	(50)	(50)
Adenoma	12 (24%)	14 (28%)	19 (38%)	14 (28%)
Carcinoma	1 (2%)			
Pars intermedia, adenoma				1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, C-cell, adenoma				1 (2%)
C-cell, adenoma	3 (6%)	8 (16%)	5 (10%)	7 (14%)
C-cell, carcinoma	2 (4%)	1 (2%)	1 (2%)	
Follicular cell, carcinoma	1 (2%)			
General Body System				
None				
Genital System				
Clitoral gland	(49)	(48)	(50)	(48)
Adenoma	2 (4%)			
Carcinoma	1 (2%)	2 (4%)	1 (2%)	
Hemangiosarcoma	1 (2%)			
Ovary	(50)	(50)	(50)	(50)
Granulosa cell tumor malignant	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Uterus	(50)	(50)	(50)	(50)
Adenoma				1 (2%)
Carcinoma		1 (2%)		
Deciduoma benign				1 (2%)
Leiomyosarcoma				1 (2%)
Polyp stromal	6 (12%)	8 (16%)	9 (18%)	8 (16%)
Polyp stromal, multiple				3 (6%)
Sarcoma stromal			1 (2%)	2 (4%)
Cervix, polyp stromal	1 (2%)			
Cervix, sarcoma stromal		1 (2%)		
Vagina				(2)
Leiomyoma				1 (50%)
Sarcoma stromal				1 (50%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Lymph node	(6)	(1)	(5)	(1)
Lymph node, mandibular	(50)	(49)	(50)	(50)
Carcinoma, metastatic, mammary gland	1 (2%)			
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Spleen	(50)	(50)	(50)	(50)
Thymus	(48)	(49)	(47)	(47)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Carcinoma	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Fibroadenoma	16 (32%)	17 (34%)	10 (20%)	16 (32%)
Fibroadenoma, multiple	5 (10%)	9 (18%)	9 (18%)	2 (4%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Integumentary System (continued)				
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma	1 (2%)	1 (2%)		
Squamous cell papilloma	1 (2%)			
Subcutaneous tissue, fibroma				2 (4%)
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland	1 (2%)			
Glioma malignant			1 (2%)	
Oligodendroglioma benign	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma				2 (4%)
Carcinoma, metastatic, mammary gland	1 (2%)		1 (2%)	
Carcinoma, metastatic, thyroid gland	2 (4%)			
Histiocytic sarcoma			1 (2%)	
Nephroblastoma, metastatic, kidney				1 (2%)
Special Senses System				
Zymbal's gland			(1)	
Adenoma			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Nephroblastoma				1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Transitional epithelium, papilloma			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Leukemia mononuclear	21 (42%)	19 (38%)	16 (32%)	19 (38%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[c]	45	45	42	46
Total primary neoplasms	84	88	79	89
Total animals with benign neoplasms	35	38	34	37
Total benign neoplasms	53	63	57	64
Total animals with malignant neoplasms	26	21	21	24
Total malignant neoplasms	31	25	22	25
Total animals with metastatic neoplasms	5		1	1
Total metastatic neoplasms	5		1	1

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	4 3 8	5 1 4	5 8 9	6 1 6	6 4 1	6 7 4	6 7 9	6 9 0	7 1 6	7 1 8	7 1 9	7 2 8	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	2 0 3	2 2 7	2 2 4	2 1 1	2 4 2	2 3 0	2 1 6	2 4 5	2 4 1	2 3 5	2 4 0	2 4 4	2 0 1	2 0 6	2 0 9	2 1 4	2 1 7	2 2 0	2 2 1	2 2 2	2 2 3	2 2 8	2 3 1	2 3 2	2 3 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma			X																						
Mesentery		+						+							+			+	+						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign										X															
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X	X		X											X	
Carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenoma																									
Carcinoma	X																								
Hemangiosarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																						X			

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 3 9	2 4 6	2 4 7	2 4 8	2 5 0	2 0 2	2 0 4	2 0 5	2 0 7	2 0 8	2 1 0	2 1 2	2 1 3	2 1 5	2 1 8	2 1 9	2 2 5	2 2 6	2 2 9	2 3 3	2 3 4	2 3 7	2 3 8	2 4 3	2 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery									+	+																7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																X										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X		X		X					X			X	X			X			X			12
Carcinoma									X																	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma						X												X		X						3
C-cell, carcinoma																							X	X		2
Follicular cell, carcinoma		X																								1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X											X														2
Carcinoma																										1
Hemangiosarcoma																			X							1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	4 3 8	5 1 4	5 8 9	6 1 6	6 4 1	6 7 4	6 7 9	6 9 0	7 1 6	7 1 8	7 1 9	7 2 8	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	2 0 3	2 2 7	2 2 4	2 1 1	2 4 2	2 3 0	2 1 6	2 4 5	2 4 1	2 3 5	2 4 0	2 4 4	2 0 1	2 0 6	2 0 9	2 1 4	2 1 7	2 2 0	2 2 1	2 2 2	2 2 3	2 2 8	2 3 1	2 3 2	2 3 6
Genital System (continued)																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal												X								X					
Cervix, polyp stromal				X																					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+				+		+											+						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Fibroadenoma							X					X	X			X			X			X	X		X
Fibroadenoma, multiple																								X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Squamous cell papilloma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Oligodendroglioma benign																				X					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland																									
Carcinoma, metastatic, thyroid gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye										+										+					+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X	X	X	X		X	X	X					X			X	X	X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 3 9	2 4 6	2 4 7	2 4 8	2 5 0	2 0 2	2 0 4	2 0 5	2 0 7	2 0 8	2 1 0	2 1 2	2 1 3	2 1 5	2 1 8	2 1 9	2 2 5	2 2 6	2 2 9	2 3 3	2 3 4	2 3 7	2 3 8	2 4 3	2 4 9	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal												X					X				X	X				6
Cervix, polyp stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																+					+					6
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																X										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																1
Carcinoma										X						X							X			3
Fibroadenoma	X	X				X	X			X			X											X	X	16
Fibroadenoma, multiple				X					X		X				X											5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma											X															1
Squamous cell papilloma				X																						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland									X																	1
Oligodendroglioma benign																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland										X																1
Carcinoma, metastatic, thyroid gland		X																					X			2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye									+																	4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X				X		X			X			X	X					X			X		21

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	3 2 8	4 4 1	5 0 5	5 2 7	5 4 0	5 7 5	5 9 9	6 0 9	6 1 7	6 7 9	6 7 9	6 8 6	6 9 0	6 9 7	7 1 5	7 2 1	7 2 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	2 9 0	2 6 9	2 8 9	2 9 8	2 7 0	2 8 3	2 7 6	2 7 1	2 9 3	2 8 1	2 9 2	2 6 8	2 7 9	2 6 3	2 6 5	2 9 1	2 9 9	2 5 1	2 5 2	2 5 9	2 6 1	2 7 2	2 7 4	2 7 5	2 7 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+																						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign		X																X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X						X	X		X	X					X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma			X																	X		X		X	
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Polyp stromal																					X	X	X		X
Cervix, sarcoma stromal		X																							

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 8 2	2 8 6	2 8 7	2 8 8	3 0 0	2 5 3	2 5 4	2 5 5	2 5 6	2 5 7	2 5 8	2 6 0	2 6 2	2 6 4	2 6 6	2 6 7	2 7 3	2 7 8	2 8 0	2 8 4	2 8 5	2 9 4	2 9 5	2 9 6	2 9 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																	X									1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery	+																									2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign									X																	3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X			X		X	X					X	X	X					X				14
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X	X						X							X									8
C-cell, carcinoma																			X							1
General Body System																										
None																										
Genital System																										
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																				X					X	2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																			X							1
Polyp stromal						X		X															X	X		8
Cervix, sarcoma stromal																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	3 2 8	4 4 1	5 0 5	5 2 7	5 4 0	5 7 5	5 9 9	6 0 9	6 1 7	6 7 9	6 7 9	6 8 6	6 9 0	6 9 7	7 1 5	7 2 1	7 2 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	2 9 0	2 6 9	2 8 9	2 9 8	2 7 0	2 8 3	2 7 6	2 7 1	2 9 3	2 8 1	2 9 2	2 6 8	2 7 9	2 6 3	2 6 5	2 9 1	2 9 9	2 5 1	2 5 2	2 5 9	2 6 1	2 7 2	2 7 4	2 7 5	2 7 7
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node														+											
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma								X																	
Fibroadenoma				X		X		X				X			X				X	X					
Fibroadenoma, multiple										X															X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma								X																	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve														+											
Spinal cord														+											
Respiratory System																									
Larynx																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Lacrimal gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X	X	X	X	X	X			X	X		X		X							

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	28262	28866	28867	28868	30300	25053	25554	25555	25566	25577	25588	26600	26602	26604	26606	26607	27303	27808	28080	28404	28805	29294	29295	29296	29297	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Fibroadenoma			X					X		X		X		X	X				X	X		X		X		17
Fibroadenoma, multiple	X			X	X	X	X		X																X	9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Larynx																	+									1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																								+		1
Lacrimal gland																	+									1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X			X									X				X	X	X	X				19

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: 10 mg/kg

Number of Days on Study	2 5 6	3 2 5	4 3 4	4 7 0	4 7 0	5 0 8	5 6 2	6 0 3	6 5 1	6 6 1	6 8 6	6 9 0	6 9 6	7 0 4	7 1 1	7 2 4	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	3 3 7	3 0 5	3 2 6	3 0 2	3 0 9	3 5 0	3 3 8	3 3 9	3 4 1	3 4 8	3 2 8	3 2 3	3 1 0	3 4 5	3 0 8	3 1 5	3 0 1	3 0 3	3 0 4	3 0 7	3 1 1	3 1 6	3 1 8	3 1 9	3 2 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Mesentery					+			+	+			+				+	+								
Fat, histiocytic sarcoma																X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X			X	X	X						X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																								X	
C-cell, carcinoma																X									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal				X																X	X				
Sarcoma stromal															X										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: 10 mg/kg

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 2 1	3 2 2	3 2 4	3 2 5	3 3 2	3 3 3	3 4 0	3 4 2	3 4 3	3 4 6	3 0 6	3 1 2	3 1 3	3 1 4	3 1 7	3 2 7	3 2 9	3 3 0	3 3 1	3 3 4	3 3 5	3 3 6	3 4 4	3 4 7	3 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Mesentery	+																			+						8
Fat, histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign	X																X									2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																1
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X					X		X	X	X		X	X	X	X				X	X	X	X			19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X	X								X			X													5
C-cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																		X								1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal				X								X	X	X								X	X			9
Sarcoma stromal																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: 10 mg/kg

Number of Days on Study	2 5 6	3 2 5	4 3 4	4 7 0	4 7 0	5 0 8	5 6 2	6 0 3	6 5 1	6 6 1	6 8 6	6 9 0	6 9 6	7 0 4	7 1 1	7 2 4	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	3 3 0 7	3 0 5	3 2 6	3 0 2	3 0 9	3 5 0	3 3 8	3 3 9	3 4 1	3 4 8	3 2 8	3 2 3	3 1 0	3 4 5	3 0 8	3 1 5	3 0 1	3 0 3	3 0 4	3 0 7	3 1 1	3 1 6	3 1 8	3 1 9	3 2 0
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Lymph node								+	+	+			+												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																				X					
Fibroadenoma									X			X						X						X	X
Fibroadenoma, multiple										X						X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant			X																						
Peripheral nerve				+																					
Spinal cord				+																					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland																				X					
Histiocytic sarcoma																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye															+										
Zymbal's gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Leukemia mononuclear							X	X	X	X	X	X	X	X					X					X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: 10 mg/kg

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 2 1	3 2 2	3 2 4	3 2 5	3 3 2	3 3 3	3 4 0	3 4 2	3 4 3	3 4 6	3 0 6	3 1 2	3 1 3	3 1 4	3 1 7	3 2 7	3 2 9	3 3 0	3 3 1	3 3 4	3 3 5	3 3 6	3 4 4	3 4 7	3 4 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node								+																		5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Fibroadenoma		X					X									X			X						X	10
Fibroadenoma, multiple					X	X		X					X	X	X						X					9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																										1
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																										1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye															+			+								3
Zymbal's gland										+																1
Adenoma										X																1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma																						X				1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear					X	X	X		X								X							X		16

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: 30 mg/kg

Number of Days on Study	24 49 50 52 54 55 58 59 64 68 69 69 70 73 73 73 73 73 73 73 73 73 73 73 73
Carcass ID Number	357 360 395 361 379 355 400 308 377 366 359 385 352 389 351 356 362 363 364 365 368 369 371 372 374
Alimentary System	
Esophagus	+ +
Periesophageal tissue, lipoma	
Intestine large, colon	+ +
Polyp adenomatous	
Intestine large, rectum	+ +
Intestine large, cecum	+ +
Intestine small, duodenum	+ +
Intestine small, jejunum	+ +
Intestine small, ileum	+ +
Liver	+ +
Mesentery	+
Lipoma	X
Pancreas	+ +
Salivary glands	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ +
Tongue	+
Squamous cell papilloma	X
Cardiovascular System	
Blood vessel	+ +
Heart	+ +
Endocrine System	
Adrenal cortex	+ +
Adrenal medulla	+ +
Pheochromocytoma benign	
Islets, pancreatic	+ +
Parathyroid gland	+ + + + + M + + + + + + + + + + + + + + + + + + +
Pituitary gland	+ +
Adenoma	X X X X
Pars intermedia, adenoma	
Thyroid gland	+ +
Bilateral, C-cell, adenoma	X
C-cell, adenoma	X X X
General Body System	
None	
Genital System	
Clitoral gland	+ + + + + + + + + + + + + + + + M + + + + + + + + +
Ovary	+ +
Uterus	+ +
Adenoma	X
Deciduoma benign	
Leiomyosarcoma	X
Polyp stromal	X X
Polyp stromal, multiple	X X
Sarcoma stromal	X X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: 30 mg/kg

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 7 6	3 7 8	3 8 4	3 8 7	3 8 8	3 9 1	3 9 6	3 9 7	3 9 9	3 5 3	3 5 4	3 5 8	3 6 7	3 7 0	3 7 3	3 7 5	3 8 1	3 8 2	3 8 3	3 8 6	3 9 0	3 9 2	3 9 3	3 9 4	3 9 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Periesophageal tissue, lipoma													X													1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous										X																1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+														+							+				4
Lipoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																X										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X			X	X				X	X		X			X			X			X			X		14
Pars intermedia, adenoma				X																						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																										1
C-cell, adenoma			X											X						X		X				7
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Deciduoma benign																							X			1
Leiomyosarcoma																										1
Polyp stromal			X			X		X					X					X					X			8
Polyp stromal, multiple														X												3
Sarcoma stromal																										2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: 30 mg/kg

Number of Days on Study	24 49 50 52 54 55 58 59 64 68 69 69 70 73 73 73 73 73 73 73 73 73 73 73 73
Carcass ID Number	357 360 395 361 397 355 400 408 437 466 459 485 525 489 515 516 623 644 655 668 689 711 712 744
Genital System (continued)	
Vagina	+
Leiomyoma	
Sarcoma stromal	X
Hematopoietic System	
Bone marrow	+ +
Lymph node	+
Lymph node, mandibular	+ +
Lymph node, mesenteric	+ +
Spleen	+ +
Thymus	+ + + + + + + + M + + M + + + + + + + + + + + + +
Integumentary System	
Mammary gland	+ +
Carcinoma	X
Fibroadenoma	X X X X X X X X X
Fibroadenoma, multiple	X
Skin	+ +
Subcutaneous tissue, fibroma	
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Peripheral nerve	+
Spinal cord	+
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X
Nephroblastoma, metastatic, kidney	X
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	
Urinary System	
Kidney	+ +
Nephroblastoma	X
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X X X X X X X X X X X X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Methacrylonitrile: 30 mg/kg

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 7 7 6	3 7 8	3 8 4	3 8 8 7	3 8 8	3 9 1	3 9 6	3 9 9 7	3 9 9 9	3 5 3	3 5 5 4	3 5 8	3 6 7	3 7 0	3 7 3	3 7 5	3 8 1	3 8 2	3 8 3	3 8 6	3 9 0	3 9 2	3 9 3	3 9 4	3 9 8	Total Tissues/ Tumors
Genital System (continued)																										
Vagina																		+								2
Leiomyoma																		X								1
Sarcoma stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Fibroadenoma	X	X	X		X				X	X		X														16
Fibroadenoma, multiple																								X		2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma															X				X							2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Nephroblastoma, metastatic, kidney																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye												+														1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nephroblastoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X	X								X		X			X			X	X	X	19

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	1/50 (2%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate[b]	2.1%	6.8%	4.7%	2.3%
Terminal rate[c]	0/38 (0%)	2/33 (6%)	2/34 (6%)	1/36 (3%)
First incidence (days)	718	441	731 (T)	731 (T)
Poly-3 test[d]	P=0.440N	P=0.288	P=0.471	P=0.748
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	3/49 (6%)	2/48 (4%)	1/50 (2%)	0/48 (0%)
Adjusted rate	6.5%	4.8%	2.3%	0.0%
Terminal rate	2/37 (5%)	2/31 (7%)	1/34 (3%)	0/34 (0%)
First incidence (days)	438	731 (T)	731 (T)	—[e]
Poly-3 test	P=0.090N	P=0.549N	P=0.333N	P=0.137N
Mammary Gland: Fibroadenoma				
Overall rate	21/50 (42%)	26/50 (52%)	19/50 (38%)	18/50 (36%)
Adjusted rate	44.9%	57.0%	43.5%	39.5%
Terminal rate	19/38 (50%)	20/33 (61%)	15/34 (44%)	13/36 (36%)
First incidence (days)	679	527	651	499
Poly-3 test	P=0.155N	P=0.165	P=0.531N	P=0.378N
Mammary Gland: Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	1/50 (2%)
Adjusted rate	6.4%	2.3%	2.3%	2.3%
Terminal rate	3/38 (8%)	0/33 (0%)	1/34 (3%)	1/36 (3%)
First incidence (days)	731 (T)	609	731 (T)	731 (T)
Poly-3 test	P=0.344N	P=0.326N	P=0.335N	P=0.326N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	23/50 (46%)	26/50 (52%)	20/50 (40%)	19/50 (38%)
Adjusted rate	49.1%	57.0%	45.7%	41.7%
Terminal rate	21/38 (55%)	20/33 (61%)	16/34 (47%)	14/36 (39%)
First incidence (days)	679	527	651	499
Poly-3 test	P=0.147N	P=0.289	P=0.455N	P=0.304N
Pituitary Gland: Adenoma				
Overall rate	12/50 (24%)	14/50 (28%)	19/50 (38%)	14/50 (28%)
Adjusted rate	25.7%	31.6%	43.9%	31.3%
Terminal rate	10/38 (26%)	10/33 (30%)	16/34 (47%)	13/36 (36%)
First incidence (days)	718	609	690	527
Poly-3 test	P=0.418	P=0.347	P=0.052	P=0.358
Pituitary Gland: Adenoma or Carcinoma				
Overall rate	13/50 (26%)	14/50 (28%)	19/50 (38%)	14/50 (28%)
Adjusted rate	27.8%	31.6%	43.9%	31.3%
Terminal rate	11/38 (29%)	10/33 (30%)	16/34 (47%)	13/36 (36%)
First incidence (days)	718	609	690	527
Poly-3 test	P=0.478	P=0.434	P=0.082	P=0.446

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Thyroid Gland (C-cell): Adenoma				
Overall rate	3/50 (6%)	8/50 (16%)	5/50 (10%)	8/50 (16%)
Adjusted rate	6.4%	18.1%	11.6%	17.7%
Terminal rate	3/38 (8%)	7/33 (21%)	5/34 (15%)	5/36 (14%)
First incidence (days)	731 (T)	505	731 (T)	527
Poly-3 test	P=0.184	P=0.083	P=0.313	P=0.089
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	9/50 (18%)	6/50 (12%)	8/50 (16%)
Adjusted rate	10.7%	20.3%	13.9%	17.7%
Terminal rate	5/38 (13%)	8/33 (24%)	5/34 (15%)	5/36 (14%)
First incidence (days)	731 (T)	505	724	527
Poly-3 test	P=0.377	P=0.164	P=0.444	P=0.257
Uterus: Stromal Polyp				
Overall rate	7/50 (14%)	8/50 (16%)	9/50 (18%)	11/50 (22%)
Adjusted rate	14.9%	18.3%	20.6%	24.8%
Terminal rate	5/38 (13%)	8/33 (24%)	8/34 (24%)	8/36 (22%)
First incidence (days)	616	731 (T)	470	693
Poly-3 test	P=0.155	P=0.437	P=0.332	P=0.176
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	7/50 (14%)	9/50 (18%)	10/50 (20%)	13/50 (26%)
Adjusted rate	14.9%	20.3%	22.8%	28.7%
Terminal rate	5/38 (13%)	8/33 (24%)	8/34 (24%)	8/36 (22%)
First incidence (days)	616	441	470	549
Poly-3 test	P=0.079	P=0.345	P=0.242	P=0.085
All Organs: Mononuclear Cell Leukemia				
Overall rate	21/50 (42%)	19/50 (38%)	16/50 (32%)	19/50 (38%)
Adjusted rate	42.2%	40.3%	35.5%	41.2%
Terminal rate	12/38 (32%)	9/33 (27%)	8/34 (24%)	12/36 (33%)
First incidence (days)	438	527	562	500
Poly-3 test	P=0.539N	P=0.505N	P=0.323N	P=0.540N
All Organs: Benign Neoplasms				
Overall rate	35/50 (70%)	38/50 (76%)	34/50 (68%)	37/50 (74%)
Adjusted rate	73.2%	80.4%	76.3%	78.0%
Terminal rate	29/38 (76%)	28/33 (85%)	28/34 (82%)	28/36 (78%)
First incidence (days)	589	441	470	499
Poly-3 test	P=0.461	P=0.271	P=0.457	P=0.378
All Organs: Malignant Neoplasms				
Overall rate	26/50 (52%)	21/50 (42%)	21/50 (42%)	24/50 (48%)
Adjusted rate	52.3%	43.8%	45.7%	49.3%
Terminal rate	17/38 (45%)	10/33 (30%)	10/34 (29%)	13/36 (36%)
First incidence (days)	438	441	434	246
Poly-3 test	P=0.526	P=0.263N	P=0.330N	P=0.462N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	45/50 (90%)	45/50 (90%)	42/50 (84%)	46/50 (92%)
Adjusted rate	90.0%	92.0%	89.9%	92.0%
Terminal rate	33/38 (87%)	30/33 (91%)	30/34 (88%)	32/36 (89%)
First incidence (days)	438	441	434	246
Poly-3 test	P=0.487	P=0.499	P=0.626N	P=0.500

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Methacrylonitrile[a]

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	1	1	1	
Moribund	4	10	9	7
Natural deaths	7	6	6	7
Survivors				
Died the last week of the study				1
Terminal sacrifice	38	33	34	35
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Periesophageal tissue, hemorrhage		1 (2%)	2 (4%)	
Intestine large, rectum	(50)	(50)	(50)	(50)
Parasite metazoan	2 (4%)	5 (10%)	5 (10%)	4 (8%)
Intestine large, cecum	(50)	(50)	(50)	(50)
Inflammation, chronic active				1 (2%)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Fibrosis				1 (2%)
Liver	(50)	(49)	(48)	(50)
Angiectasis		1 (2%)	2 (4%)	1 (2%)
Basophilic focus	43 (86%)	43 (88%)	35 (73%)	39 (78%)
Clear cell focus	4 (8%)	2 (4%)	1 (2%)	3 (6%)
Degeneration			1 (2%)	
Degeneration, cystic	1 (2%)		1 (2%)	
Eosinophilic focus			3 (6%)	
Fatty change	21 (42%)	13 (27%)	11 (23%)	7 (14%)
Hepatodiaphragmatic nodule	9 (18%)	7 (14%)	8 (17%)	12 (24%)
Hyperplasia		1 (2%)		
Inflammation, chronic active	31 (62%)	27 (55%)	27 (56%)	27 (54%)
Mixed cell focus	2 (4%)	7 (14%)	8 (17%)	5 (10%)
Necrosis	2 (4%)	3 (6%)	1 (2%)	
Thrombosis	2 (4%)		3 (6%)	
Vacuolization cytoplasmic	7 (14%)	14 (29%)	17 (35%)	30 (60%)
Bile duct, hyperplasia	14 (28%)	5 (10%)	13 (27%)	9 (18%)
Mesentery	(7)	(2)	(8)	(4)
Fat, inflammation, chronic active	5 (71%)	1 (50%)	2 (25%)	1 (25%)
Fat, necrosis	1 (14%)	1 (50%)	4 (50%)	2 (50%)
Pancreas	(50)	(50)	(50)	(50)
Cytoplasmic alteration			1 (2%)	
Hyperplasia	1 (2%)		1 (2%)	1 (2%)
Acinus, atrophy	8 (16%)	4 (8%)	7 (14%)	10 (20%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema	1 (2%)	1 (2%)		
Hyperplasia	1 (2%)	1 (2%)		1 (2%)
Inflammation, chronic active	1 (2%)	2 (4%)	1 (2%)	
Ulcer			1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Erosion	1 (2%)	1 (2%)	2 (4%)	5 (10%)
Mineralization			1 (2%)	
Ulcer	1 (2%)			1 (2%)

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

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	24 (48%)	19 (38%)	16 (32%)	21 (42%)
Fibrosis	1 (2%)			
Thrombosis		1 (2%)	2 (4%)	1 (2%)
Epicardium, inflammation, chronic active	1 (2%)			
Pericardium, inflammation, chronic active			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Angiectasis	23 (46%)	6 (12%)	12 (24%)	19 (38%)
Degeneration			1 (2%)	
Hemorrhage	1 (2%)			
Hyperplasia	7 (14%)	6 (12%)	10 (20%)	7 (14%)
Hypertrophy		1 (2%)		
Necrosis				2 (4%)
Thrombosis				1 (2%)
Vacuolization cytoplasmic	4 (8%)	1 (2%)	2 (4%)	6 (12%)
Capsule, fibrosis	1 (2%)			
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)		3 (6%)	1 (2%)
Pituitary gland	(50)	(50)	(50)	(50)
Angiectasis	6 (12%)	4 (8%)	3 (6%)	5 (10%)
Cyst	19 (38%)	13 (26%)	14 (28%)	15 (30%)
Hyperplasia	20 (40%)	23 (46%)	16 (32%)	16 (32%)
Craniopharyngeal duct, hyperplasia	1 (2%)			
Pars nervosa, hyperplasia	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	36 (72%)	25 (50%)	37 (74%)	32 (64%)
General Body System				
None				
Genital System				
Clitoral gland	(49)	(48)	(50)	(48)
Cyst	1 (2%)	4 (8%)	5 (10%)	1 (2%)
Hyperplasia	10 (20%)	7 (15%)	10 (20%)	2 (4%)
Inflammation, chronic active	6 (12%)	2 (4%)	5 (10%)	8 (17%)
Ovary	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		
Cyst			1 (2%)	
Mineralization			1 (2%)	
Follicle, cyst	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Periovarian tissue, cyst	4 (8%)	3 (6%)	2 (4%)	3 (6%)
Uterus	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Hydrometra	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Inflammation, chronic active		2 (4%)		
Cervix, fibrosis	1 (2%)		1 (2%)	1 (2%)
Cervix, inflammation, chronic active			3 (6%)	1 (2%)
Endometrium, hyperplasia, cystic	4 (8%)	1 (2%)	3 (6%)	3 (6%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Atrophy	1 (2%)	1 (2%)		1 (2%)
Hyperplasia	12 (24%)	11 (22%)	12 (24%)	25 (50%)
Myelofibrosis	1 (2%)			
Lymph node	(6)	(1)	(5)	(1)
Mediastinal, hyperplasia			1 (20%)	
Lymph node, mandibular	(50)	(49)	(50)	(50)
Ectasia	1 (2%)	1 (2%)		1 (2%)
Hyperplasia			1 (2%)	
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Ectasia		1 (2%)		1 (2%)
Spleen	(50)	(50)	(50)	(50)
Accessory spleen				1 (2%)
Fibrosis	1 (2%)	1 (2%)	1 (2%)	
Hematopoietic cell proliferation	1 (2%)	8 (16%)	7 (14%)	5 (10%)
Capsule, necrosis				1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Galactocele	13 (26%)	9 (18%)	9 (18%)	9 (18%)
Hyperplasia	8 (16%)	11 (22%)	9 (18%)	6 (12%)
Inflammation, chronic active		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Parakeratosis		1 (2%)		
Ulcer		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosclerosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion			1 (2%)	
Hemorrhage		1 (2%)	2 (4%)	
Inflammation, chronic active	5 (10%)	4 (8%)	4 (8%)	4 (8%)
Necrosis			1 (2%)	
Pigmentation			1 (2%)	
Alveolar epithelium, hyperplasia	6 (12%)	3 (6%)	4 (8%)	6 (12%)
Mediastinum, inflammation			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Inflammation		1 (2%)		
Inflammation, chronic active	1 (2%)		2 (4%)	1 (2%)
Thrombosis		3 (6%)	1 (2%)	2 (4%)
Olfactory epithelium, atrophy			1 (2%)	19 (38%)
Olfactory epithelium, metaplasia				47 (94%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Special Senses System				
Eye	(4)	(1)	(3)	(1)
Cataract	4 (100%)	1 (100%)	3 (100%)	1 (100%)
Lens, mineralization	3 (75%)		2 (67%)	
Retina, degeneration	3 (75%)	1 (100%)	3 (100%)	1 (100%)
Zymbal's gland			(1)	
Inflammation, chronic active			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet	2 (4%)		1 (2%)	
Congestion		1 (2%)		
Hydronephrosis				1 (2%)
Inflammation, chronic active	3 (6%)	9 (18%)	5 (10%)	3 (6%)
Necrosis	1 (2%)			
Nephropathy	29 (58%)	27 (54%)	29 (58%)	25 (50%)
Pigmentation	3 (6%)	3 (6%)	2 (4%)	
Renal tubule, hyperplasia		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Inflammation, chronic active	1 (2%)	1 (2%)	1 (2%)	
Transitional epithelium, hyperplasia				1 (2%)

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF METHACRYLONITRILE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Methacrylonitrile[a]

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths				25
Moribund	5	2	3	
Natural deaths	9	5	4	3
Survivors				
Died the last week of the study	1		2	
Terminal sacrifice	34	43	41	22
Missing	1			
Animals examined microscopically	49	50	50	50
Alimentary System				
Intestine large, cecum	(49)	(50)	(50)	(50)
Adenocarcinoma		1 (2%)		
Intestine small, duodenum	(49)	(49)	(50)	(50)
Adenocarcinoma		1 (2%)	1 (2%)	
Adenoma	2 (4%)		2 (4%)	1 (2%)
Intestine small, jejunum	(49)	(50)	(50)	(50)
Adenocarcinoma	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Liver	(49)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland			1 (2%)	
Carcinoma, metastatic, intestine small, duodenum			1 (2%)	
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hepatoblastoma	1 (2%)			
Hepatocellular carcinoma	10 (20%)	7 (14%)	7 (14%)	4 (8%)
Hepatocellular carcinoma, multiple	3 (6%)			
Hepatocellular adenoma	13 (27%)	15 (30%)	16 (32%)	6 (12%)
Hepatocellular adenoma, multiple	4 (8%)	12 (24%)	8 (16%)	6 (12%)
Hepatocholangiocarcinoma	1 (2%)	2 (4%)	1 (2%)	
Sarcoma, metastatic, pancreas		1 (2%)		
Mesentery	(3)	(6)	(6)	(1)
Carcinoma, metastatic, intestine small, duodenum			1 (17%)	
Hemangiosarcoma		1 (17%)		
Hepatocholangiocarcinoma, metastatic, liver		1 (17%)		
Sarcoma, metastatic, pancreas		1 (17%)		
Pancreas	(49)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Sarcoma		1 (2%)		
Salivary glands	(49)	(50)	(50)	(50)
Stomach, forestomach	(49)	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	2 (4%)	1 (2%)	
Stomach, glandular	(49)	(50)	(50)	(50)
Tooth	(6)		(1)	(2)
Odontoma	1 (17%)			
Cardiovascular System				
Heart	(48)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Capsule, adenoma	5 (10%)	4 (8%)	3 (6%)	
Subcapsular, adenoma			1 (2%)	
Adrenal medulla	(49)	(50)	(50)	(50)
Pheochromocytoma benign				1 (2%)
Islets, pancreatic	(49)	(50)	(50)	(50)
Adenoma	2 (4%)		1 (2%)	
Thyroid gland	(49)	(50)	(50)	(50)
C-cell, carcinoma	1 (2%)			
Follicular cell, adenoma			1 (2%)	1 (2%)
Follicular cell, carcinoma	1 (2%)			
General Body System				
None				
Genital System				
Epididymis	(49)	(50)	(50)	(50)
Preputial gland	(49)	(50)	(50)	(49)
Prostate	(49)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			
Sarcoma, metastatic, pancreas		1 (2%)		
Seminal vesicle	(49)	(50)	(50)	(50)
Carcinoma, metastatic, intestine small, duodenum			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Sarcoma, metastatic, pancreas		1 (2%)		
Testes	(49)	(50)	(50)	(50)
Interstitial cell, adenoma		1 (2%)		
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Lymph node	(3)	(5)	(3)	(1)
Bronchial, hepatocholangiocarcinoma, metastatic, liver	1 (33%)			
Mediastinal, carcinoma, metastatic, intestine small, duodenum			1 (33%)	
Mediastinal, hepatocholangiocarcinoma, metastatic, liver		1 (20%)		
Pancreatic, sarcoma, metastatic, pancreas		1 (20%)		
Lymph node, mandibular	(46)	(48)	(50)	(47)
Carcinoma, metastatic, harderian gland			2 (4%)	
Lymph node, mesenteric	(46)	(43)	(49)	(47)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Spleen	(49)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			
Thymus	(40)	(48)	(46)	(49)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Integumentary System				
Skin	(49)	(50)	(50)	(50)
Keratoacanthoma	1 (2%)			
Subcutaneous tissue, hemangioma		1 (2%)		
Subcutaneous tissue, lipoma	1 (2%)	1 (2%)		
Musculoskeletal System				
Skeletal muscle	(1)		(2)	(1)
Carcinoma, metastatic, harderian gland			1 (50%)	
Carcinoma, metastatic, intestine small, duodenum			1 (50%)	
Hepatocholangiocarcinoma, metastatic, liver	1 (100%)			
Nervous System				
None				
Respiratory System				
Lung	(49)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	11 (22%)	7 (14%)	4 (8%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	4 (8%)	2 (4%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Carcinoma, metastatic, harderian gland			2 (4%)	
Carcinoma, metastatic, intestine small, duodenum			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	6 (12%)	2 (4%)	4 (8%)	
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)	1 (2%)	
Mediastinum, carcinoma, metastatic, harderian gland			1 (2%)	
Mediastinum, hepatocholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)		
Serosa, hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Nose	(49)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland			1 (2%)	
Special Senses System				
Harderian gland	(3)	(2)	(7)	(1)
Adenoma	3 (100%)	2 (100%)	5 (71%)	1 (100%)
Carcinoma			2 (29%)	
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)		
Renal tubule, adenoma				1 (2%)
Renal tubule, carcinoma		1 (2%)		
Urinary bladder	(49)	(50)	(50)	(50)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Systemic Lesions				
Multiple organs[b]	(49)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Lymphoma malignant	2 (4%)	3 (6%)	3 (6%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	40	41	39	24
Total primary neoplasms	62	72	64	31
Total animals with benign neoplasms	29	35	33	19
Total benign neoplasms	35	49	46	22
Total animals with malignant neoplasms	24	17	16	8
Total malignant neoplasms	27	23	18	9
Total animals with metastatic neoplasms	7	5	8	
Total metastatic neoplasms	12	17	20	

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	501	513	583	600	638	650	663	670	707	709	744	769	709	720	721	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	01616	04666	02767	00868	01969	02721	02818	02004	01707	02505	02959	03606	03007	02212	02303	02909	03111	03818	04024	03301	03505	04242	04343	04445
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																		X							
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Hepatoblastoma																									
Hepatocellular carcinoma	X		X	X				X										X							
Hepatocellular carcinoma, multiple					X						X		X												
Hepatocellular adenoma	X			X				X																	
Hepatocellular adenoma, multiple			X											X											
Hepatocholangiocarcinoma		X																							
Mesentery								+																	
Oral mucosa		+		+	+	+	+		+	+	+								+	+	+	+			+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver		X																							
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma		X																							
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth							+		+																+
Odontoma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																				X					X
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X	X															
Parathyroid gland	M	M	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, carcinoma							X																		
Follicular cell, carcinoma																X									
General Body System																									
None																									

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 5 0	0 0 1	0 1 0	0 1 2	0 1 4	0 1 5	0 2 0	0 2 2	0 3 3	0 3 3	0 3 7	0 4 0	0 4 4	0 4 8	0 0 2	0 0 6	0 1 3	0 2 5	0 2 6	0 3 0	0 3 4	0 3 8	0 3 9	0 4 1	0 4 7	0 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																		X							X	2
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Hepatoblastoma																		X								1
Hepatocellular carcinoma	X										X				X	X							X			10
Hepatocellular carcinoma, multiple																										3
Hepatocellular adenoma	X		X			X			X	X		X	X							X		X			X	13
Hepatocellular adenoma, multiple																		X					X			4
Hepatocholangiocarcinoma																										1
Mesentery														+									+			3
Oral mucosa		+	+	+	+		+	+	+	+	+	+			+	+			+	+	+	+	+			+	31
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth												+							+					+			6
Odontoma																								X			1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma				X									X						X								5
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																											2
Parathyroid gland	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, carcinoma																											1
Follicular cell, carcinoma																											1
General Body System																										
None																										

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	501	513	583	600	638	650	663	670	677	694	694	694	709	712	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	016	046	027	008	019	021	028	004	017	005	029	036	007	022	003	009	011	018	024	031	035	042	043	045
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis										+														
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+																						
Bronchial, hepatocholangiocarcinoma, metastatic, liver		X																						
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Thymus	+	+	+	+	M	+	M	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																								
Subcutaneous tissue, lipoma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+																						
Hepatocholangiocarcinoma, metastatic, liver		X																						
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X				
Alveolar/bronchiolar carcinoma																					X			X
Hepatocellular carcinoma, metastatic, liver					X						X		X											
Hepatocholangiocarcinoma, metastatic, liver		X																						
Mediastinum, hepatocholangiocarcinoma, metastatic, liver		X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																	+							
Harderian gland																	+							
Adenoma																	X							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	05010	00101	00102	01124	01145	01155	02060	03202	03233	03237	04404	04448	04488	04502	00606	01363	02255	02266	03060	03334	03338	03349	04411	04417	04429	04439	Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Penis																											1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																											1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+				+																						3
Bronchial, hepatocholangiocarcinoma, metastatic, liver																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma				X																							1
Thymus	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+		40
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Keratoacanthoma																	X										1
Subcutaneous tissue, lipoma																		X									1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																											1
Hepatocholangiocarcinoma, metastatic, liver																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																		X									2
Alveolar/bronchiolar carcinoma									X				X														4
Hepatocellular carcinoma, metastatic, liver	X										X				X												6
Hepatocholangiocarcinoma, metastatic, liver																											1
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																											
Eye																											1
Harderian gland															+								+				3
Adenoma															X								X				3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	1	8	0	3	5	6	7	7	9	9	9	0	1	2	2	2	2	2	2	2	2	2	2	2
	1	3	3	0	8	0	3	0	7	4	4	4	9	2	9	9	9	9	9	9	9	9	9	9	9
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	4	2	0	1	2	2	0	1	0	2	3	0	2	0	0	1	1	2	3	3	4	4	4	4
	6	6	7	8	9	1	8	4	7	5	9	6	7	2	3	9	1	8	4	1	5	2	3	5	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocholangiocarcinoma, metastatic, liver		X																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	05010	00101	10100	11202	11404	11505	12000	23302	33303	33707	40004	40404	40808	00202	00606	11303	12205	22606	33000	33404	33808	34209	41401	41707	41909		Total Tissues/ Tumors
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Hepatocholangiocarcinoma, metastatic, liver																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymphoma malignant	X				X																						2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 1.5 mg/kg

Number of Days on Study	563	605	625	625	629	644	714	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730
Carcass ID Number	06565	09657	06622	09644	06633	08681	07713	05753	05754	05755	06764	06766	06768	06769	07090	08666	08768	09191	09292	09963	09966	09968	05787	06677	07772
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																			X						
Intestine small, duodenum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																X									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma			X		X	X	X					X			X										
Hepatocellular adenoma		X		X	X	X				X		X			X	X									
Hepatocellular adenoma, multiple			X								X									X	X				
Hepatocholangiocarcinoma				X																					
Sarcoma, metastatic, pancreas						X																			
Mesentery	+	+		+		+															+				
Hemangiosarcoma																									
Hepatocholangiocarcinoma, metastatic, liver				X																					
Sarcoma, metastatic, pancreas						X																			
Oral mucosa		+	+		+	+	+	+		+	+	+		+			+	+		+	+			+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma						X																			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma									X	X															
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver				X																					
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma						X																			
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 1.5 mg/kg

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 0 7 4	0 0 7 5	0 0 7 6	0 0 7 7	0 0 7 8	0 0 7 9	0 0 8 0	0 0 8 4	0 0 8 5	0 0 8 7	0 0 9 0	0 0 9 5	0 0 9 9	0 1 0 0	0 5 1	0 5 2	0 5 6	0 5 8	0 5 9	0 6 0	0 6 1	0 7 1	0 8 2	0 8 3	0 8 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma				X																						1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma															X											1
Hepatocellular carcinoma														X												7
Hepatocellular adenoma	X		X			X		X					X						X				X			15
Hepatocellular adenoma, multiple					X					X					X					X	X	X		X	X	12
Hepatocholangiocarcinoma			X																							2
Sarcoma, metastatic, pancreas																										1
Mesentery															+											6
Hemangiosarcoma															X											1
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma, metastatic, pancreas																										1
Oral mucosa		+	+	+			+	+	+		+	+		+	+		+		+			+		+		30
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma	X						X											X								4
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	M	+	+	M	+	M	M	M	+	+	M	M	+	+	+	+	M	+	+	M	+	35
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 1.5 mg/kg

Number of Days on Study	5 6 3	6 0 5	6 2 5	6 2 5	6 2 9	6 4 4	7 1 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 6 5	0 9 7	0 6 2	0 9 4	0 6 3	0 8 1	0 7 3	0 5 3	0 5 4	0 5 5	0 6 4	0 6 6	0 6 8	0 6 9	0 7 0	0 8 6	0 8 8	0 9 1	0 9 2	0 9 3	0 9 6	0 9 8	0 5 7	0 6 7	0 7 2
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, pancreas						X																			
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver				X																					
Sarcoma, metastatic, pancreas						X																			
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma														X											
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+		+		+													+				
Mediastinal, hepatocholangiocarcinoma, metastatic, liver				X																					
Pancreatic, sarcoma, metastatic, pancreas						X																			
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	M	M	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+
Hepatocholangiocarcinoma, metastatic, liver				X																					
Histiocytic sarcoma							X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver				X																					
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, lipoma																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X		X									X									
Alveolar/bronchiolar carcinoma	X																								
Alveolar/bronchiolar carcinoma, multiple																									
Alveolar/bronchiolar carcinoma, metastatic, lung	X																								
Hepatocellular carcinoma, metastatic, liver																X									
Hepatocholangiocarcinoma, metastatic, liver				X																					
Mediastinum, hepatocholangiocarcinoma, metastatic, liver				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 1.5 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	00774	00775	00776	00777	00778	00779	00800	00804	00805	00807	00900	00905	00909	00990	01001	00551	00552	00556	00558	00559	00560	00661	00711	00812	00833	00889	Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, pancreas																											1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																											1
Sarcoma, metastatic, pancreas																											1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+																								5
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																											1
Pancreatic, sarcoma, metastatic, pancreas																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	43
Hepatocholangiocarcinoma, metastatic, liver																											1
Histiocytic sarcoma																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocholangiocarcinoma, metastatic, liver																											1
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma			X																								1
Subcutaneous tissue, lipoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X					X					X		X			X			X		X	X					11
Alveolar/bronchiolar carcinoma																X											2
Alveolar/bronchiolar carcinoma, multiple		X																									1
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Hepatocellular carcinoma, metastatic, liver															X												2
Hepatocholangiocarcinoma, metastatic, liver																											1
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 1.5 mg/kg

Number of Days on Study	5 6 3	6 0 5	6 2 5	6 2 5	6 2 9	6 4 4	7 1 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 6 5	0 9 7	0 6 2	0 9 4	0 6 3	0 8 1	0 7 3	0 5 3	0 5 4	0 5 5	0 6 4	0 6 6	0 6 8	0 6 9	0 7 0	0 8 6	0 8 8	0 9 1	0 9 2	0 9 3	0 9 6	0 9 8	0 5 7	0 6 7	0 7 2
Special Senses System																										
Eye											+															
Harderian gland											+															
Adenoma											X															
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver				X																						
Renal tubule, carcinoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																			
Lymphoma malignant								X					X													

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 1.5 mg/kg

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 7 4	0 7 5	0 7 6	0 7 7	0 7 8	0 7 9	0 8 0	0 8 4	0 8 5	0 8 7	0 9 0	0 9 5	0 9 9	1 0 0	0 5 1	0 5 2	0 5 6	0 5 8	0 5 9	0 6 0	0 6 1	0 7 1	0 8 2	0 8 3	0 8 9	Total Tissues/ Tumors	
Special Senses System																											
Eye																										1	
Harderian gland																				+						2	
Adenoma																				X						2	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hepatocholangiocarcinoma, metastatic, liver																										1	
Renal tubule, carcinoma								X																		1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																										1	
Lymphoma malignant							X																			3	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	4 2 9	4 3 9	5 0 2	6 1 2	6 5 5	6 9 4	7 0 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 0 3	1 1 0	1 4 5	1 3 7	1 0 9	1 4 0	1 5 0	1 0 7	1 0 8	1 1 2	1 1 3	1 2 0	1 2 3	1 2 5	1 2 6	1 2 7	1 2 8	1 3 0	1 3 1	1 3 4	1 3 6	1 4 1	1 4 3	1 4 6	1 4 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma				X																					
Adenoma											X														
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																	X								
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland																									X
Carcinoma, metastatic, intestine small, duodenum				X																					
Hemangiosarcoma					X																				
Hepatocellular carcinoma						X											X				X				
Hepatocellular adenoma	X	X							X							X					X		X		
Hepatocellular adenoma, multiple				X							X				X										
Hepatocholangiocarcinoma						X																			
Mesentery				+																					
Carcinoma, metastatic, intestine small, duodenum				X																					
Oral mucosa	+		+	+	+	+	+		+					+	+	+	+		+	+	+	+	+		+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma															X		X					X			
Subcapsular, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	10001	10016	10111	11155	11157	11222	12332	13355	13438	13439	11302	11304	11305	11414	11416	11418	11419	12121	12244	12329	13332	14242	14404	14408	14409	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Adenoma																X										2
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma											X															2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Carcinoma, metastatic, intestine small, duodenum																										1
Hemangiosarcoma																										1
Hepatocellular carcinoma	X	X				X		X																		7
Hepatocellular adenoma		X				X					X			X			X				X	X	X	X	X	16
Hepatocellular adenoma, multiple				X	X				X						X				X							8
Hepatocholangiocarcinoma																										1
Mesentery	+	+									+	+					+									6
Carcinoma, metastatic, intestine small, duodenum																										1
Oral mucosa		+	+			+	+	+			+					+	+			+					+	27
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																X										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																				+						1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma																										3
Subcapsular, adenoma																					X					1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				1
Parathyroid gland	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	M	M	+	M	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																				X						1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	4 2 9	4 3 9	5 0 2	6 1 2	6 5 5	6 9 4	7 0 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 0 3	1 1 0	1 4 5	1 3 7	1 0 9	1 4 0	1 5 0	1 0 7	1 0 8	1 1 2	1 1 3	1 2 0	1 2 3	1 2 5	1 2 6	1 2 7	1 2 8	1 3 0	1 3 1	1 3 4	1 3 6	1 4 1	1 4 3	1 4 6	1 4 7
Genital System																											
Coagulating gland							+																				
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small, duodenum				X																							
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+																							
Mediastinal, carcinoma, metastatic, intestine small, duodenum				X																							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland			X																								X
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+																							+
Carcinoma, metastatic, harderian gland																											X
Carcinoma, metastatic, intestine small, duodenum				X																							
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X			
Alveolar/bronchiolar adenoma, multiple				X																							
Alveolar/bronchiolar carcinoma										X																	
Carcinoma, metastatic, harderian gland			X																								X
Carcinoma, metastatic, intestine small, duodenum				X																							
Hepatocellular carcinoma, metastatic, liver																	X										
Hepatocholangiocarcinoma, metastatic, liver						X																					
Mediastinum, carcinoma, metastatic, harderian gland																											X
Serosa, hepatocholangiocarcinoma, metastatic, liver						X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland																											X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 0 0 1	1 0 0 1 6	1 0 1 1	1 1 1 5	1 1 1 7	1 1 2 2	1 2 3 2	1 3 3 5	1 3 3 8	1 3 3 9	1 3 0 2	1 3 0 4	1 3 0 5	1 3 1 4	1 3 1 6	1 3 1 8	1 3 1 9	1 3 2 1	1 3 2 4	1 3 2 9	1 3 3 3	1 3 4 2	1 3 4 4	1 3 4 8	1 3 4 9	Total Tissues/ Tumors
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, intestine small, duodenum																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node												+					+									3
Mediastinal, carcinoma, metastatic, intestine small, duodenum																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Carcinoma, metastatic, harderian gland																										1
Carcinoma, metastatic, intestine small, duodenum																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X		X							X				X					X		X			7
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic, harderian gland																										2
Carcinoma, metastatic, intestine small, duodenum																										1
Hepatocellular carcinoma, metastatic, liver	X	X						X																		4
Hepatocholangiocarcinoma, metastatic, liver																										1
Mediastinum, carcinoma, metastatic, harderian gland																										1
Serosa, hepatocholangiocarcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	4 2 9	4 3 9	5 0 2	6 1 2	6 5 5	6 9 4	7 0 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 0 3	1 1 0	1 4 5	1 3 7	1 0 9	1 4 0	1 5 0	1 0 7	1 0 8	1 1 2	1 1 3	1 2 0	1 2 3	1 2 5	1 2 6	1 2 7	1 2 8	1 3 0	1 3 1	1 3 4	1 3 6	1 4 1	1 4 3	1 4 6	1 4 7
Special Senses System																										
Harderian gland			+						+									+							+
Adenoma									X									X							
Carcinoma			X																						X
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	10001	10006	10011	10015	10017	10022	10023	10025	10038	10039	10302	10044	10045	10054	10114	10116	10118	10119	10121	10124	10129	10213	10233	10244	10248	10249		Total Tissues/ Tumors
Special Senses System																												
Harderian gland	+	+			+																							7
Adenoma	X	X			X																							5
Carcinoma																												2
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant					X								X					X										3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 6 mg/kg

Number of Days on Study	0 0 3	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1
Carcass ID Number	1 6 1	1 6 5	1 6 6	1 6 7	1 6 8	1 6 9	1 7 0	1 7 1	1 7 9	1 8 0	1 8 1	1 8 2	1 8 3	1 8 4	1 8 5	1 8 6	1 8 7	1 8 8	1 8 9	1 9 0	1 9 1	1 9 2	1 9 3	1 9 4	1 9 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma											X														
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X							
Hepatocellular carcinoma												X													
Hepatocellular adenoma							X		X												X				
Hepatocellular adenoma, multiple															X	X									
Mesentery						+																			
Oral mucosa													+		+			+			+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	M	M	+	+	+	+	+	+	+	+	M	+	M	M	M	M	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	I	+	+	+	+	I	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma			X																						
General Body System																									
None																									
Genital System																									
Coagulating gland																									+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 6 mg/kg

Number of Days on Study	621	623	710	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	
Carcass ID Number	16202	16707	16909	15252	15558	15774	15778	15997	16098	16200	15051	15553	15754	15955	15656	15767	16040	16064	16373	16696	16759	16763	16772	16775	16776						Total Tissues/ Tumors
Alimentary System																															
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Adenoma																X															1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Adenocarcinoma			X																												2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+						49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Hemangiosarcoma																															1
Hepatocellular carcinoma	X		X														X														4
Hepatocellular adenoma									X			X													X						6
Hepatocellular adenoma, multiple																	X			X	X								X		6
Mesentery																															1
Oral mucosa										+			+	+					+			+									10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Tooth				+												+															2
Cardiovascular System																															
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Endocrine System																															
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Pheochromocytoma benign										X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M						38
Pituitary gland	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Follicular cell, adenoma																															1
General Body System																															
None																															
Genital System																															
Coagulating gland			+																												2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Preputial gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 6 mg/kg

Number of Days on Study	0 0 3	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1	4 8 1
Carcass ID Number	1 6 1	1 6 5	1 6 6	1 6 7	1 6 8	1 6 9	1 7 0	1 7 1	1 7 9	1 8 0	1 8 1	1 8 2	1 8 3	1 8 4	1 8 5	1 8 6	1 8 7	1 8 8	1 8 9	1 9 0	1 9 1	1 9 2	1 9 3	1 9 4	1 9 5
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	+	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Methacrylonitrile: 6 mg/kg

Number of Days on Study	6 2 1	6 2 3	7 1 0	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 1 6 2	1 1 7 7	1 1 9 9	1 1 5 2	1 1 5 8	1 1 7 4	1 1 7 8	1 1 9 7	1 1 9 8	2 0 0	1 1 5 1	1 1 5 3	1 1 5 4	1 1 5 5	1 1 5 6	1 1 5 7	1 1 6 0	1 1 6 4	1 1 7 3	1 1 9 6	1 1 5 9	1 1 6 3	1 1 7 2	1 1 7 5	1 1 7 6	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node									+																	1
Lymph node, mandibular	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle									+																	1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X	X				X				4
Alveolar/bronchiolar adenoma, multiple																					X					1
Alveolar/bronchiolar carcinoma																						X				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye											+															1
Harderian gland											+															1
Adenoma											X															1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																								X		1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant									X																	1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Adrenal Cortex: Adenoma				
Overall rate[a]	5/49 (10%)	4/50 (8%)	4/50 (8%)	0/50 (0%)
Adjusted rate[b]	11.1%	8.4%	8.5%	0.0%
Terminal rate[c]	5/35 (14%)	3/43 (7%)	4/43 (9%)	0/22 (0%)
First incidence (days)	729 (T)	644	729 (T)	—[e]
Poly-3 test[d]	P=0.083N	P=0.460N	P=0.474N	P=0.078N
Harderian Gland: Adenoma				
Overall rate	3/49 (6%)	2/50 (4%)	5/50 (10%)	1/50 (2%)
Adjusted rate	6.7%	4.2%	10.7%	3.2%
Terminal rate	3/35 (9%)	2/43 (5%)	5/43 (12%)	1/22 (5%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.533N	P=0.474N	P=0.380	P=0.446N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/49 (6%)	2/50 (4%)	7/50 (14%)	1/50 (2%)
Adjusted rate	6.7%	4.2%	14.7%	3.2%
Terminal rate	3/35 (9%)	2/43 (5%)	6/43 (14%)	1/22 (5%)
First incidence (days)	729 (T)	729 (T)	502	729 (T)
Poly-3 test	P=0.463	P=0.474N	P=0.181	P=0.446N
Small Intestine (Duodenum or Jejunum): Adenocarcinoma				
Overall rate	1/49 (2%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	2.2%	4.2%	6.4%	6.3%
Terminal rate	1/35 (3%)	2/43 (5%)	2/43 (5%)	0/22 (0%)
First incidence (days)	729 (T)	729 (T)	612	481
Poly-3 test	P=0.231	P=0.520	P=0.324	P=0.384
Small Intestine (Duodenum or Jejunum): Adenoma or Adenocarcinoma				
Overall rate	3/49 (6%)	2/50 (4%)	5/50 (10%)	3/50 (6%)
Adjusted rate	6.7%	4.2%	10.6%	9.4%
Terminal rate	3/35 (9%)	2/43 (5%)	4/43 (9%)	1/22 (5%)
First incidence (days)	729 (T)	729 (T)	612	481
Poly-3 test	P=0.269	P=0.474N	P=0.385	P=0.497
Liver: Hepatocellular Adenoma				
Overall rate	17/49 (35%)	27/50 (54%)	24/50 (48%)	12/50 (24%)
Adjusted rate	36.3%	54.7%	49.2%	34.7%
Terminal rate	12/35 (34%)	22/43 (51%)	21/43 (49%)	7/22 (32%)
First incidence (days)	501	605	429	481
Poly-3 test	P=0.442N	P=0.053	P=0.143	P=0.531N
Liver: Hepatocellular Carcinoma				
Overall rate	13/49 (27%)	7/50 (14%)	7/50 (14%)	4/50 (8%)
Adjusted rate	27.5%	14.4%	14.9%	12.4%
Terminal rate	6/35 (17%)	3/43 (7%)	6/43 (14%)	1/22 (5%)
First incidence (days)	501	625	694	481
Poly-3 test	P=0.063N	P=0.091N	P=0.106N	P=0.097N
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	14/49 (29%)	7/50 (14%)	7/50 (14%)	4/50 (8%)
Adjusted rate	29.6%	14.4%	14.9%	12.4%
Terminal rate	7/35 (20%)	3/43 (7%)	6/43 (14%)	1/22 (5%)
First incidence (days)	501	625	694	481
Poly-3 test	P=0.040N	P=0.058N	P=0.069N	P=0.067N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	24/49 (49%)	29/50 (58%)	28/50 (56%)	15/50 (30%)
Adjusted rate	50.7%	58.6%	57.2%	41.9%
Terminal rate	16/35 (46%)	23/43 (54%)	24/43 (56%)	7/22 (32%)
First incidence (days)	501	605	429	481
Poly-3 test	P=0.256N	P=0.281	P=0.331	P=0.283N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/49 (4%)	11/50 (22%)	8/50 (16%)	5/50 (10%)
Adjusted rate	4.5%	22.9%	16.9%	15.7%
Terminal rate	2/35 (6%)	9/43 (21%)	7/43 (16%)	4/22 (18%)
First incidence (days)	729 (T)	629	612	481
Poly-3 test	P=0.165	P=0.010	P=0.054	P=0.104
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	4/49 (8%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	8.9%	6.2%	2.1%	3.2%
Terminal rate	4/35 (11%)	2/43 (5%)	1/43 (2%)	1/22 (5%)
First incidence (days)	729 (T)	563	729 (T)	729 (T)
Poly-3 test	P=0.128N	P=0.462N	P=0.166N	P=0.311N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	6/49 (12%)	13/50 (26%)	9/50 (18%)	5/50 (10%)
Adjusted rate	13.4%	26.8%	19.1%	15.7%
Terminal rate	6/35 (17%)	10/43 (23%)	8/43 (19%)	4/22 (18%)
First incidence (days)	729 (T)	563	612	481
Poly-3 test	P=0.534	P=0.087	P=0.325	P=0.515
All Organs: Hemangiosarcoma				
Overall rate	3/49 (6%)	1/50 (2%)	1/50 (2%)	1/50 (2%)
Adjusted rate	6.6%	2.1%	2.1%	3.2%
Terminal rate	2/35 (6%)	1/43 (2%)	0/43 (0%)	0/22 (0%)
First incidence (days)	650	729 (T)	655	481
Poly-3 test	P=0.276N	P=0.287N	P=0.291N	P=0.440N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	3/49 (6%)	2/50 (4%)	1/50 (2%)	1/50 (2%)
Adjusted rate	6.6%	4.2%	2.1%	3.2%
Terminal rate	2/35 (6%)	2/43 (5%)	0/43 (0%)	0/22 (0%)
First incidence (days)	650	729 (T)	655	481
Poly-3 test	P=0.245N	P=0.477N	P=0.291N	P=0.440N
All Organs: Malignant Lymphoma				
Overall rate	2/49 (4%)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted rate	4.5%	6.3%	6.4%	3.2%
Terminal rate	2/35 (6%)	3/43 (7%)	3/43 (7%)	1/22 (5%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.510N	P=0.526	P=0.519	P=0.623N
All Organs: Benign Neoplasms				
Overall rate	29/49 (59%)	35/50 (70%)	33/50 (66%)	19/50 (38%)
Adjusted rate	60.7%	70.8%	67.6%	52.7%
Terminal rate	21/35 (60%)	29/43 (67%)	30/43 (70%)	12/22 (55%)
First incidence (days)	501	605	429	481
Poly-3 test	P=0.250N	P=0.201	P=0.309	P=0.303N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
All Organs: Malignant Neoplasms				
Overall rate	24/49 (49%)	17/50 (34%)	16/50 (32%)	8/50 (16%)
Adjusted rate	49.5%	34.3%	33.1%	23.8%
Terminal rate	14/35 (40%)	11/43 (26%)	12/43 (28%)	3/22 (14%)
First incidence (days)	501	563	502	481
Poly-3 test	P=0.015N	P=0.092N	P=0.075N	P=0.016N
All Organs: Benign or Malignant Neoplasms				
Overall rate	40/49 (82%)	41/50 (82%)	39/50 (78%)	24/50 (48%)
Adjusted rate	81.9%	82.0%	78.2%	62.1%
Terminal rate	27/35 (77%)	34/43 (79%)	33/43 (77%)	12/22 (55%)
First incidence (days)	501	563	429	481
Poly-3 test	P=0.018N	P=0.596	P=0.418N	P=0.027N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, and lung; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Methacrylonitrile[a]

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths				25
Moribund	5	2	3	
Natural deaths	9	5	4	3
Survivors				
Died the last week of the study	1		2	
Terminal sacrifice	34	43	41	22
Missing	1			
Animals examined microscopically	49	50	50	50
Alimentary System				
Esophagus	(49)	(50)	(50)	(50)
Inflammation, chronic active				1 (2%)
Periesophageal tissue, inflammation, chronic active		1 (2%)		
Intestine small, duodenum	(49)	(49)	(50)	(50)
Ectasia			1 (2%)	
Hyperplasia		3 (6%)	1 (2%)	1 (2%)
Intestine small, jejunum	(49)	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)		
Peyer's patch, hyperplasia, lymphoid			1 (2%)	1 (2%)
Intestine small, ileum	(49)	(50)	(50)	(49)
Inflammation, chronic active	1 (2%)	1 (2%)		
Liver	(49)	(50)	(50)	(50)
Angiectasis	1 (2%)		1 (2%)	
Basophilic focus		4 (8%)	6 (12%)	2 (4%)
Clear cell focus	7 (14%)	10 (20%)	10 (20%)	4 (8%)
Eosinophilic focus	16 (33%)	10 (20%)	12 (24%)	3 (6%)
Fibrosis			1 (2%)	
Hematopoietic cell proliferation			3 (6%)	1 (2%)
Hepatodiaphragmatic nodule	1 (2%)			
Infiltration cellular, mast cell	1 (2%)			
Infiltration cellular, mononuclear cell	9 (18%)	11 (22%)	7 (14%)	6 (12%)
Inflammation, chronic active	22 (45%)	21 (42%)	19 (38%)	21 (42%)
Inflammation, granulomatous			1 (2%)	
Malformation	1 (2%)			
Mineralization			1 (2%)	
Mixed cell focus		11 (22%)	11 (22%)	2 (4%)
Necrosis	6 (12%)	5 (10%)	1 (2%)	
Pigmentation	3 (6%)		2 (4%)	3 (6%)
Tension lipidosis	1 (2%)		1 (2%)	
Bile duct, cyst			1 (2%)	1 (2%)
Bile duct, hyperplasia				1 (2%)
Hepatocyte, vacuolization cytoplasmic	6 (12%)	10 (20%)	9 (18%)	16 (32%)
Hepatocyte, portal, hypertrophy			1 (2%)	
Hepatocyte, centrilobular, degeneration			1 (2%)	

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

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Alimentary System (continued)				
Mesentery	(3)	(6)	(6)	(1)
Fibrosis	1 (33%)	1 (17%)		
Inflammation, chronic active	1 (33%)	1 (17%)	1 (17%)	1 (100%)
Inflammation, granulomatous			2 (33%)	
Mineralization		1 (17%)	1 (17%)	
Thrombosis	1 (33%)			
Fat, necrosis	1 (33%)	2 (33%)	1 (17%)	
Oral mucosa	(31)	(30)	(27)	(10)
Gingival, foreign body	27 (87%)	29 (97%)	26 (96%)	10 (100%)
Gingival, inflammation, acute	9 (29%)	3 (10%)	10 (37%)	6 (60%)
Gingival, inflammation, chronic		1 (3%)		
Gingival, inflammation, chronic active	19 (61%)	26 (87%)	16 (59%)	2 (20%)
Pancreas	(49)	(50)	(50)	(50)
Infiltration cellular, mononuclear cell	1 (2%)	1 (2%)		1 (2%)
Artery, mineralization				1 (2%)
Salivary glands	(49)	(50)	(50)	(50)
Granuloma	1 (2%)			
Infiltration cellular, mononuclear cell	22 (45%)	35 (70%)	36 (72%)	29 (58%)
Inflammation, chronic	1 (2%)			
Inflammation, chronic active			1 (2%)	
Mineralization	1 (2%)	1 (2%)	1 (2%)	
Stomach, forestomach	(49)	(50)	(50)	(50)
Cyst, squamous			1 (2%)	
Epithelium, hyperplasia	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Epithelium, inflammation, chronic active	2 (4%)	1 (2%)	2 (4%)	
Epithelium, ulcer	1 (2%)	1 (2%)		
Stomach, glandular	(49)	(50)	(50)	(50)
Hyperplasia		1 (2%)		
Mineralization		1 (2%)		2 (4%)
Ulcer	1 (2%)			
Epithelium, erosion	1 (2%)			
Epithelium, hyperplasia		1 (2%)	1 (2%)	
Epithelium, inflammation, chronic active	1 (2%)	1 (2%)	1 (2%)	
Glands, ectasia	17 (35%)	10 (20%)	20 (40%)	5 (10%)
Serosa, inflammation, granulomatous			1 (2%)	
Tooth	(6)		(1)	(2)
Malformation	6 (100%)		1 (100%)	2 (100%)
Cardiovascular System				
Heart	(48)	(50)	(50)	(50)
Inflammation, chronic active	2 (4%)	1 (2%)		1 (2%)
Mineralization	2 (4%)		1 (2%)	1 (2%)
Artery, inflammation, chronic active		1 (2%)		
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Degeneration, fatty	1 (2%)			
Hematopoietic cell proliferation			1 (2%)	
Hyperplasia	14 (29%)	12 (24%)	16 (32%)	7 (14%)
Hypertrophy	26 (53%)	34 (68%)	28 (56%)	15 (30%)
Inflammation, suppurative		1 (2%)		
Metaplasia, osseous	1 (2%)			
Capsule, hyperplasia	41 (84%)	41 (82%)	40 (80%)	45 (90%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Endocrine System (continued)				
Adrenal medulla	(49)	(50)	(50)	(50)
Hematopoietic cell proliferation			1 (2%)	
Hyperplasia	1 (2%)			
Islets, pancreatic	(49)	(50)	(50)	(50)
Hyperplasia	47 (96%)	43 (86%)	48 (96%)	46 (92%)
Parathyroid gland	(42)	(35)	(39)	(38)
Cyst	1 (2%)	2 (6%)	1 (3%)	1 (3%)
Pituitary gland	(48)	(49)	(49)	(46)
Atypia cellular				1 (2%)
Pars distalis, cyst	1 (2%)	2 (4%)	5 (10%)	3 (7%)
Pars distalis, hyperplasia	2 (4%)	2 (4%)		
Thyroid gland	(49)	(50)	(50)	(50)
Follicle, cyst	2 (4%)	2 (4%)	2 (4%)	
General Body System				
None				
Genital System				
Coagulating gland			(1)	(2)
Inflammation, suppurative			1 (100%)	
Epididymis	(49)	(50)	(50)	(50)
Atrophy	1 (2%)			
Granuloma sperm	2 (4%)		1 (2%)	
Infiltration cellular, mononuclear cell	17 (35%)	26 (52%)	30 (60%)	21 (42%)
Inflammation, chronic active	1 (2%)	1 (2%)		1 (2%)
Mineralization	2 (4%)		1 (2%)	
Penis	(1)			
Hemorrhage	1 (100%)			
Preputial gland	(49)	(50)	(50)	(49)
Atrophy	1 (2%)			
Infiltration cellular, mononuclear cell	21 (43%)	25 (50%)	27 (54%)	26 (53%)
Inflammation, chronic active	13 (27%)	6 (12%)	7 (14%)	3 (6%)
Duct, cyst	18 (37%)	20 (40%)	18 (36%)	16 (33%)
Prostate	(49)	(50)	(50)	(50)
Atrophy	1 (2%)			
Infiltration cellular, mononuclear cell	25 (51%)	31 (62%)	34 (68%)	32 (64%)
Inflammation, suppurative			1 (2%)	
Artery, inflammation, chronic active		1 (2%)		
Seminal vesicle	(49)	(50)	(50)	(50)
Atrophy	1 (2%)			
Dilatation		1 (2%)		
Infiltration cellular, mononuclear cell		2 (4%)	2 (4%)	
Testes	(49)	(50)	(50)	(50)
Atrophy			1 (2%)	
Inflammation, chronic active		1 (2%)		
Mineralization	2 (4%)	2 (4%)	1 (2%)	
Germinal epithelium, atrophy	1 (2%)	2 (4%)	2 (4%)	

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Hyperplasia			4 (8%)	
Lymph node	(3)	(5)	(3)	(1)
Inguinal, hyperplasia, plasma cell		1 (20%)		
Lumbar, hyperplasia, plasma cell		1 (20%)		
Mediastinal, hyperplasia, plasma cell		1 (20%)		
Pancreatic, hyperplasia, lymphoid		1 (20%)		
Renal, hyperplasia, plasma cell		1 (20%)		
Renal, inflammation, suppurative		1 (20%)		
Lymph node, mandibular	(46)	(48)	(50)	(47)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		
Hyperplasia, plasma cell		1 (2%)	1 (2%)	
Infiltration cellular, polymorphonuclear			1 (2%)	
Lymph node, mesenteric	(46)	(43)	(49)	(47)
Hematopoietic cell proliferation	1 (2%)			
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, plasma cell	1 (2%)	1 (2%)		
Inflammation, chronic active			1 (2%)	1 (2%)
Inflammation, granulomatous	1 (2%)			
Inflammation, suppurative		1 (2%)		
Spleen	(49)	(50)	(50)	(50)
Hematopoietic cell proliferation	12 (24%)	13 (26%)	14 (28%)	4 (8%)
Hyperplasia, lymphoid	1 (2%)	4 (8%)	1 (2%)	
Thymus	(40)	(48)	(46)	(49)
Atypia cellular			1 (2%)	
Cyst	16 (40%)	19 (40%)	18 (39%)	17 (35%)
Ectopic parathyroid gland	3 (8%)	1 (2%)	3 (7%)	1 (2%)
Ectopic thyroid	1 (3%)			
Mineralization		1 (2%)		
Thymocyte, necrosis			1 (2%)	
Integumentary System				
Skin	(49)	(50)	(50)	(50)
Infiltration cellular, mononuclear cell			1 (2%)	
Inflammation, chronic active		2 (4%)	3 (6%)	
Epidermis, hyperkeratosis			1 (2%)	
Epidermis, hyperplasia		2 (4%)	2 (4%)	
Epidermis, ulcer		2 (4%)	2 (4%)	
Epidermis, pinna, hyperplasia			1 (2%)	
Epidermis, pinna, ulcer			1 (2%)	
Pinna, inflammation, chronic active			1 (2%)	
Subcutaneous tissue, fibrosis		1 (2%)		
Musculoskeletal System				
None				
Nervous System				
None				

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Respiratory System				
Lung	(49)	(50)	(50)	(50)
Hemorrhage		1 (2%)	1 (2%)	
Infiltration cellular, mononuclear cell	1 (2%)	1 (2%)		
Inflammation, chronic		1 (2%)		
Inflammation, chronic active	2 (4%)	2 (4%)		4 (8%)
Mineralization	3 (6%)	1 (2%)		2 (4%)
Thrombosis	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	3 (6%)	6 (12%)	5 (10%)	4 (8%)
Alveolus, infiltration cellular, histiocyte	4 (8%)	8 (16%)	3 (6%)	3 (6%)
Bronchiole, foreign body	1 (2%)			
Mediastinum, inflammation, chronic active				1 (2%)
Mediastinum, inflammation, suppurative		1 (2%)		
Pleura, inflammation, chronic active				1 (2%)
Nose	(49)	(50)	(50)	(50)
Foreign body	3 (6%)	3 (6%)	4 (8%)	1 (2%)
Inflammation, chronic active	2 (4%)		3 (6%)	
Nasolacrimal duct, inflammation, suppurative	4 (8%)		1 (2%)	
Special Senses System				
Eye	(1)	(1)		(1)
Cornea, inflammation, chronic active		1 (100%)		
Cornea, inflammation, suppurative	1 (100%)			
Cornea, metaplasia, squamous		1 (100%)		
Harderian gland	(3)	(2)	(7)	(1)
Infiltration cellular, mononuclear cell	1 (33%)			
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Infarct	2 (4%)	2 (4%)	1 (2%)	
Infiltration cellular, mononuclear cell	27 (55%)	37 (74%)	39 (78%)	22 (44%)
Inflammation, chronic active	1 (2%)		1 (2%)	
Inflammation, suppurative			1 (2%)	
Metaplasia, osseous	2 (4%)	1 (2%)		
Mineralization	43 (88%)	49 (98%)	47 (94%)	36 (72%)
Nephropathy	43 (88%)	48 (96%)	47 (94%)	39 (78%)
Artery, inflammation, chronic active		1 (2%)		
Cortex, cyst	11 (22%)	12 (24%)	8 (16%)	9 (18%)
Renal tubule, hyperplasia	9 (18%)	8 (16%)	9 (18%)	2 (4%)
Renal tubule, necrosis	1 (2%)			
Urinary bladder	(49)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
Infiltration cellular, mononuclear cell	12 (24%)	17 (34%)	9 (18%)	10 (20%)
Inflammation, suppurative			1 (2%)	

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF METHACRYLONITRILE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Methacrylonitrile[a]

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths				15
Moribund	1	2	3	3
Natural deaths	14	13	4	7
Survivors				
Died the last week of the study	1			
Terminal sacrifice	34	35	43	25
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Periesophageal tissue, fibrous histiocytoma, metastatic, mesentery			1 (2%)	
Periesophageal tissue, leiomyosarcoma, metastatic, intestine small, ileum				1 (2%)
Intestine large, cecum	(50)	(50)	(50)	(50)
Adenocarcinoma		1 (2%)		
Leiomyoma	3 (6%)	1 (2%)		
Intestine small, duodenum	(49)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)	(50)
Sarcoma NOS, metastatic, uncertain primary site	1 (2%)			
Intestine small, ileum	(50)	(50)	(50)	(50)
Adenocarcinoma			1 (2%)	
Leiomyosarcoma				1 (2%)
Liver	(50)	(50)	(49)	(50)
Hemangiosarcoma		1 (2%)		1 (2%)
Hepatocellular carcinoma	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Hepatocellular carcinoma, multiple		1 (2%)	1 (2%)	
Hepatocellular adenoma	6 (12%)	9 (18%)	11 (22%)	4 (8%)
Hepatocellular adenoma, multiple	3 (6%)		1 (2%)	1 (2%)
Histiocytic sarcoma		1 (2%)		1 (2%)
Leiomyosarcoma, metastatic, intestine small, ileum				1 (2%)
Mesentery	(16)	(11)	(15)	(4)
Fibrosarcoma, metastatic, skin			1 (7%)	
Fibrous histiocytoma			1 (7%)	
Hepatocellular carcinoma, metastatic, liver			1 (7%)	
Leiomyosarcoma, metastatic, uterus	1 (6%)			
Leiomyosarcoma, metastatic, intestine small, ileum				1 (25%)
Lipoma			1 (7%)	
Sarcoma NOS	1 (6%)			
Sarcoma NOS, metastatic, uncertain primary site	1 (6%)			
Schwannoma malignant, metastatic, skin	1 (6%)			
Oral mucosa	(3)	(5)	(2)	(1)
Squamous cell carcinoma				1 (100%)
Pharyngeal, squamous cell papilloma	1 (33%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Alimentary System (continued)				
Pancreas	(50)	(50)	(50)	(48)
Fibrosarcoma, metastatic, skin			1 (2%)	
Fibrous histiocytoma, metastatic, mesentery			1 (2%)	
Leiomyosarcoma, metastatic, intestine small, ileum				1 (2%)
Salivary glands	(48)	(50)	(50)	(49)
Fibrosarcoma, metastatic, skin			1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Leiomyosarcoma, metastatic, intestine small, ileum				1 (2%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Leiomyosarcoma, metastatic, intestine small, ileum				1 (2%)
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Adrenal medulla	(49)	(50)	(50)	(50)
Pheochromocytoma benign			1 (2%)	
Pituitary gland	(49)	(49)	(49)	(49)
Pars distalis, adenoma	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Pars intermedia, adenoma	2 (4%)			1 (2%)
Thyroid gland	(49)	(50)	(50)	(50)
Follicular cell, adenoma			1 (2%)	
Follicular cell, carcinoma		2 (4%)		
General Body System				
Peritoneum				(1)
Leiomyosarcoma, metastatic, intestine small, ileum				1 (100%)
Genital System				
Clitoral gland	(50)	(50)	(50)	(49)
Ovary	(50)	(50)	(50)	(49)
Adenocarcinoma				1 (2%)
Cystadenoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Fibrous histiocytoma, metastatic, mesentery			1 (2%)	
Hemangioma	2 (4%)			
Leiomyosarcoma, metastatic, intestine small, ileum				1 (2%)
Luteoma			1 (2%)	
Teratoma benign	1 (2%)			
Thecoma malignant			1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Genital System (continued)				
Uterus	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, mesentery			1 (2%)	
Hemangiosarcoma		1 (2%)		
Leiomyoma	1 (2%)			
Leiomyosarcoma	1 (2%)			
Leiomyosarcoma, metastatic, intestine small, ileum				1 (2%)
Polyp stromal		1 (2%)	1 (2%)	1 (2%)
Cervix, hemangiosarcoma		1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin			1 (2%)	
Hemangiosarcoma				1 (2%)
Lymph node	(9)	(6)	(8)	(5)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			1 (13%)	
Mediastinal, fibrosarcoma, metastatic, skin			1 (13%)	
Mediastinal, sarcoma, metastatic, bone				1 (20%)
Renal, leiomyosarcoma, metastatic, intestine small, ileum				1 (20%)
Lymph node, mandibular	(48)	(49)	(46)	(47)
Carcinoma, metastatic, harderian gland	1 (2%)			
Lymph node, mesenteric	(47)	(48)	(47)	(46)
Histiocytic sarcoma		1 (2%)		1 (2%)
Sarcoma NOS, metastatic, uncertain primary site	1 (2%)			
Spleen	(50)	(50)	(49)	(49)
Hemangiosarcoma	1 (2%)			1 (2%)
Hemangiosarcoma, metastatic, bone marrow				1 (2%)
Histiocytic sarcoma		1 (2%)		
Leiomyosarcoma, metastatic, intestine small, ileum				1 (2%)
Thymus	(47)	(43)	(46)	(48)
Sarcoma, metastatic, bone				1 (2%)
Integumentary System				
Mammary gland	(49)	(50)	(49)	(49)
Adenoacanthoma			1 (2%)	
Carcinoma				2 (4%)
Schwannoma malignant, metastatic, skin	1 (2%)			
Duct, adenoma		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibrosarcoma	2 (4%)	1 (2%)	5 (10%)	1 (2%)
Subcutaneous tissue, liposarcoma		1 (2%)		
Subcutaneous tissue, sarcoma		1 (2%)		
Subcutaneous tissue, sarcoma NOS, metastatic, uncertain primary site	1 (2%)			
Subcutaneous tissue, schwannoma malignant	2 (4%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin			2 (4%)	
Cranium, carcinoma, metastatic, harderian gland	1 (2%)			
Rib, periosteum, sarcoma				1 (2%)
Vertebra, schwannoma malignant, metastatic, skin	1 (2%)			
Skeletal muscle	(4)	(1)	(2)	
Fibrosarcoma, metastatic, skin			2 (100%)	
Leiomyosarcoma, metastatic, uterus	1 (25%)			
Liposarcoma, metastatic, skin		1 (100%)		
Schwannoma malignant, metastatic, skin	2 (50%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hamartoma			1 (2%)	
Spinal cord	(1)		(2)	
Fibrosarcoma, metastatic, skin			2 (100%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	6 (12%)	3 (6%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)		1 (2%)	3 (6%)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Carcinoma, metastatic, harderian gland	2 (4%)			
Carcinoma, metastatic, thyroid gland		1 (2%)		
Fibrosarcoma, metastatic, skin			3 (6%)	
Hepatocellular carcinoma, metastatic, liver	2 (4%)		3 (6%)	
Leiomyosarcoma, metastatic, intestine small, ileum				1 (2%)
Liposarcoma, metastatic, skin		1 (2%)		
Sarcoma, metastatic, bone				1 (2%)
Artery, schwannoma malignant, metastatic, skin	1 (2%)			
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Mediastinum, fibrosarcoma, metastatic, skin			1 (2%)	
Mediastinum, leiomyosarcoma, metastatic, uterus	1 (2%)			
Mediastinum, leiomyosarcoma, metastatic, intestine small, ileum				1 (2%)
Mediastinum, sarcoma, metastatic, bone				1 (2%)
Nose	(50)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland	1 (2%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Special Senses System				
Eye	(2)	(1)		(4)
Carcinoma, metastatic, harderian gland	1 (50%)			
Harderian gland	(4)	(2)	(2)	(2)
Adenoma	2 (50%)	1 (50%)	2 (100%)	2 (100%)
Carcinoma	2 (50%)			
Bilateral, adenoma		1 (50%)		
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)			
Leiomyosarcoma, metastatic, uterus	1 (2%)			
Leiomyosarcoma, metastatic, intestine small, ileum				1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			
Hemangiosarcoma, metastatic, bone marrow				1 (2%)
Leiomyosarcoma, metastatic, intestine small, ileum				1 (2%)
Sarcoma NOS, metastatic, uncertain primary site	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		1 (2%)
Lymphoma malignant	9 (18%)	7 (14%)	7 (14%)	2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	33	28	29	21
Total primary neoplasms	55	39	46	31
Total animals with benign neoplasms	24	15	20	13
Total benign neoplasms	32	20	25	14
Total animals with malignant neoplasms	19	17	17	14
Total malignant neoplasms	23	19	21	17
Total animals with metastatic neoplasms	8	2	9	4
Total metastatic neoplasms	23	3	26	22
Total animals with malignant neoplasms of uncertain primary site	1			

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	3 6 2	4 9 2	5 9 3	6 0 7	6 0 3	6 2 5	6 2 5	6 4 5	6 5 3	6 6 2	6 6 8	6 7 1	6 8 7	7 0 4	7 0 9	7 2 7	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	2 4 5	2 4 8	2 0 1	2 0 0 7	2 0 0 9	2 0 2 4	2 0 4 3	2 0 1 2	2 1 2 6	2 2 4 6	2 4 6 6	2 3 3 2	2 2 2 9	2 1 0 0	2 0 0 8	2 0 3 6	2 0 0 2	2 0 0 4	2 1 1 4	2 1 1 5	2 1 1 9	2 2 0 0	2 2 2 2	2 2 2 3	2 2 3 8	2 3 3 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Intestine small, duodenum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma NOS, metastatic, uncertain primary site										X															
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma									X						X										
Hepatocellular adenoma								X							X		X								
Hepatocellular adenoma, multiple																									
Mesentery				+	+			+		+					+	+			+		+				
Leiomyosarcoma, metastatic, uterus																									
Sarcoma NOS																					X				
Sarcoma NOS, metastatic, uncertain primary site										X															
Schwannoma malignant, metastatic, skin				X																					
Oral mucosa										+															
Pharyngeal, squamous cell papilloma										X															
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	M	M	M	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																						X			
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 3 5	2 3 8	2 3 9	2 4 9	2 5 0	2 0 5	2 0 6	2 1 1	2 1 3	2 1 6	2 1 7	2 1 8	2 2 1	2 2 5	2 2 7	2 3 0	2 3 3	2 3 4	2 3 7	2 4 0	2 4 1	2 4 2	2 4 3	2 4 4	2 4 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma			X					X									X									3
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																				X						1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma NOS, metastatic, uncertain primary site																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										2
Hepatocellular adenoma	X																	X					X			6
Hepatocellular adenoma, multiple								X							X	X										3
Mesentery	+	+									+	+					+			+	+			+		16
Leiomyosarcoma, metastatic, uterus	X																									1
Sarcoma NOS																										1
Sarcoma NOS, metastatic, uncertain primary site																										1
Schwannoma malignant, metastatic, skin																										1
Oral mucosa							+							+												3
Pharyngeal, squamous cell papilloma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	+	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																						X				2
Pars intermedia, adenoma																	X						X			2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	3 6 2	4 9 2	5 9 3	6 0 7	6 2 3	6 2 5	6 4 5	6 5 3	6 6 2	6 6 8	6 7 1	6 8 7	7 0 4	7 0 9	7 2 7	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	2 4 5	2 4 8	2 0 1	2 0 7	2 0 9	2 2 4	2 0 3	2 1 2	2 2 6	2 4 6	2 3 2	2 2 9	2 1 0	2 0 8	2 3 6	2 0 2	2 0 4	2 1 4	2 1 5	2 1 9	2 2 0	2 2 2	2 2 3	2 2 8	2 3 1
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																								
Hemangioma																								
Teratoma benign	X																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																								
Leiomyosarcoma																								
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+			+		+										+				
Lymph node, mandibular	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland																				X				
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma NOS, metastatic, uncertain primary site										X														
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X											
Thymus	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma											X													
Subcutaneous tissue, sarcoma NOS, metastatic, uncertain primary site										X														
Subcutaneous tissue, schwannoma malignant				X																				
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, carcinoma, metastatic, harderian gland																					X			
Vertebra, schwannoma malignant, metastatic, skin																								
Skeletal muscle				+																		+		
Leiomyosarcoma, metastatic, uterus																								
Schwannoma malignant, metastatic, skin				X																				
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve						+																		
Spinal cord						+																		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 3 5	2 3 8	2 3 9	2 4 9	2 5 0	2 0 5	2 0 6	2 1 1	2 1 3	2 1 6	2 1 7	2 1 8	2 2 1	2 2 5	2 2 7	2 3 0	2 3 3	2 3 4	2 3 7	2 4 0	2 4 1	2 4 2	2 4 3	2 4 4	2 4 7	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma					X		X																			2
Hemangioma		X							X																	2
Teratoma benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																							X			1
Leiomyosarcoma	X																									1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+														+					+			+		9
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, harderian gland																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Sarcoma NOS, metastatic, uncertain primary site																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant, metastatic, skin																						X				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma											X															2
Subcutaneous tissue, sarcoma NOS, metastatic, uncertain primary site																										1
Subcutaneous tissue, schwannoma malignant																						X				2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, carcinoma, metastatic, harderian gland																										1
Vertebra, schwannoma malignant, metastatic, skin																						X				1
Skeletal muscle	+																					+				4
Leiomyosarcoma, metastatic, uterus	X																									1
Schwannoma malignant, metastatic, skin																						X				2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	3 6 2	4 9 2	5 9 3	6 0 7	6 0 3	6 2 5	6 4 5	6 5 3	6 6 2	6 6 8	6 7 1	6 8 7	7 0 4	7 0 9	7 2 7	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	2 4 5	2 4 8	2 0 1	2 0 7	2 0 9	2 2 4	2 0 3	2 1 2	2 2 6	2 4 6	2 3 2	2 2 9	2 1 0	2 0 8	2 3 6	2 0 2	2 0 4	2 1 4	2 1 5	2 1 9	2 2 0	2 2 2	2 2 3	2 2 8	2 3 1
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X								X		X
Alveolar/bronchiolar carcinoma																						X		
Carcinoma, metastatic, harderian gland																					X			
Hepatocellular carcinoma, metastatic, liver									X					X										
Artery, schwannoma malignant, metastatic, skin																								
Mediastinum, leiomyosarcoma, metastatic, uterus																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland																					X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																					+			
Carcinoma, metastatic, harderian gland																					X			
Harderian gland																	+				+			
Adenoma																	X							
Carcinoma																					X			
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X											
Leiomyosarcoma, metastatic, uterus																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Sarcoma NOS, metastatic, uncertain primary site										X														
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant					X			X		X			X					X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: Vehicle Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 3 5	2 3 8	2 3 9	2 4 9	2 5 0	2 0 5	2 0 6	2 1 1	2 1 3	2 1 6	2 1 7	2 1 8	2 2 1	2 2 5	2 2 7	2 3 0	2 3 3	2 3 4	2 3 7	2 4 0	2 4 1	2 4 2	2 4 3	2 4 4	2 4 7	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X				X													X							6
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic, harderian gland																			X							2
Hepatocellular carcinoma, metastatic, liver																										2
Artery, schwannoma malignant, metastatic, skin																						X				1
Mediastinum, leiomyosarcoma, metastatic, uterus	X																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye											+															2
Carcinoma, metastatic, harderian gland																										1
Harderian gland																		+	+							4
Adenoma																		X								2
Carcinoma																			X							2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Leiomyosarcoma, metastatic, uterus	X																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma											X															1
Sarcoma NOS, metastatic, uncertain primary site																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant							X									X					X			X		9

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 1.5 mg/kg

Number of Days on Study	289	374	405	422	476	521	556	568	638	644	666	709	711	721	722	730	730	730	730	730	730	731	731	731
Carcass ID Number	289	280	288	293	257	259	277	281	255	265	256	263	285	272	286	251	254	271	275	297	299	252	258	264
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																								
Leiomyoma																								
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X																					
Hepatocellular carcinoma																								
Hepatocellular carcinoma, multiple																								
Hepatocellular adenoma									X							X		X		X				
Histiocytic sarcoma														X										
Mesentery	+								+							+		+				+		
Oral mucosa																				+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, carcinoma										X													X	
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X											
Polyp stromal																								
Cervix, hemangiosarcoma																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 1.5 mg/kg

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 6 6 8	2 7 7 3	2 7 7 4	2 7 7 6	2 8 8 2	2 8 8 4	2 8 8 7	2 9 9 0	2 9 9 1	2 9 9 4	2 9 9 6	2 9 9 8	2 5 3 3	2 6 6 1	2 6 6 2	2 6 6 6	2 6 6 7	2 6 6 9	2 7 7 0	2 7 7 8	2 7 7 9	2 8 8 3	2 8 9 2	2 9 9 5	3 0 0 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																	X									1
Leiomyoma								X																		1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma																	X									1
Hepatocellular carcinoma, multiple										X																1
Hepatocellular adenoma					X		X	X						X							X					9
Histiocytic sarcoma																										1
Mesentery				+	+		+	+								+				+						11
Oral mucosa		+						+									+				+					5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																						X				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, carcinoma																										2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																	X									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Polyp stromal															X											1
Cervix, hemangiosarcoma																						X				1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 1.5 mg/kg

Number of Days on Study	289	374	405	422	476	521	556	568	638	644	667	709	711	721	722	730	730	730	730	730	730	731	731	731	731
Carcass ID Number	289	280	288	293	257	259	277	281	255	265	256	263	285	272	286	251	254	271	275	297	299	252	258	260	264
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+											+					+					+			
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	I	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Thymus	+	+	M	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Duct, adenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma						X																			
Subcutaneous tissue, liposarcoma				X																					
Subcutaneous tissue, sarcoma										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+																					
Liposarcoma, metastatic, skin				X																					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, thyroid gland										X															
Liposarcoma, metastatic, skin				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye														+											
Harderian gland									+																
Adenoma									X																
Bilateral, adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Lymphoma malignant	X											X					X					X			X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 1.5 mg/kg

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	26838	27733	27744	27766	28022	28844	28877	29090	29101	29394	29966	29988	30553	31161	31262	31666	31767	31969	32070	32278	32479	32833	32922	32955	33060	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node													+							+						6
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Duct, adenoma									X																	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, liposarcoma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Liposarcoma, metastatic, skin																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X										X	X					3
Carcinoma, metastatic, thyroid gland																										1
Liposarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland																	+									2
Adenoma																										1
Bilateral, adenoma																	X									1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant													X							X						7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	5 3 3	5 8 9	5 8 9	6 0 2	6 5 3	7 0 1	7 1 6	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	3 1 3	3 1 2	3 2 6	3 1 7	3 1 1	3 4 4	3 2 2	3 0 2	3 1 8	3 2 8	3 3 8	3 3 9	3 4 2	3 4 5	3 4 6	3 0 1	3 0 5	3 0 9	3 1 0	3 1 5	3 2 0	3 2 1	3 2 4	3 2 5	3 2 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Periesophageal tissue, fibrous histiocytoma, metastatic, mesentery							X																		
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma		X																							
Liver	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma														X											
Hepatocellular carcinoma, multiple					X																				
Hepatocellular adenoma								X												X			X		
Hepatocellular adenoma, multiple																									
Mesentery		+			+	+	+	+			+				+		+			+					
Fibrosarcoma, metastatic, skin		X																							
Fibrous histiocytoma							X																		
Hepatocellular carcinoma, metastatic, liver					X																				
Lipoma																									
Oral mucosa																	+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin		X																							
Fibrous histiocytoma, metastatic, mesentery							X																		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung														X											
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																	X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	M	M	+	+	+	+	+	+	+	+	M	M	+	M	+	M	+	+	M	+	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 3 0	3 3 3	3 3 5	3 3 6	3 3 7	3 4 1	3 4 7	3 0 3	3 0 4	3 0 6	3 0 7	3 0 8	3 1 4	3 1 6	3 1 9	3 2 3	3 2 9	3 3 1	3 3 2	3 3 4	3 4 0	3 4 3	3 4 8	3 4 9	3 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Periesophageal tissue, fibrous histiocytoma, metastatic, mesentery																										1
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma		X																		X						3
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X	X						X				X	X				X							X	X	11
Hepatocellular adenoma, multiple																				X						1
Mesentery	+						+								+	+		+			+					15
Fibrosarcoma, metastatic, skin																										1
Fibrous histiocytoma																										1
Hepatocellular carcinoma, metastatic, liver																										1
Lipoma																X										1
Oral mucosa						+																				2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Fibrous histiocytoma, metastatic, mesentery																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																X										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																									X	1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	M	M	M	M	+	+	M	M	+	M	+	+	+	+	+	+	+	+	M	34
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X					X																				2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma											X															1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	5 3 3	5 8 9	5 8 9	6 0 2	6 5 3	7 0 1	7 1 6	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	3 1 3	3 1 2	3 2 6	3 1 7	3 1 1	3 4 4	3 2 2	3 0 2	3 1 8	3 2 8	3 3 8	3 3 9	3 4 2	3 4 5	3 4 6	3 0 1	3 0 5	3 0 9	3 1 0	3 1 5	3 2 0	3 2 1	3 2 4	3 2 5	3 2 7
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma								X																	
Fibrous histiocytoma, metastatic, mesentery							X																		
Luteoma									X																
Thecoma malignant			X																						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, mesentery							X																		
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin			X																						
Lymph node		+											+	+					+						
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung														X											
Mediastinal, fibrosarcoma, metastatic, skin		X																							
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma		X	X	X		X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin			X			X																			
Skeletal muscle			+			+																			
Fibrosarcoma, metastatic, skin			X			X																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hamartoma																									
Peripheral nerve						+																			
Spinal cord			+			+																			
Fibrosarcoma, metastatic, skin			X			X																			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 3 0	3 3 3	3 3 5	3 3 6	3 3 7	3 4 1	3 4 7	3 0 3	3 0 4	3 0 6	3 0 7	3 0 8	3 1 4	3 1 6	3 1 9	3 2 3	3 2 9	3 3 1	3 3 2	3 3 4	3 4 0	3 4 3	3 4 8	3 4 9	3 5 0	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										1
Fibrous histiocytoma, metastatic, mesentery																										1
Luteoma																										1
Thecoma malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery																										1
Polyp stromal																			X							1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Lymph node	+										+		+				+									8
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinal, fibrosarcoma, metastatic, skin																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoacanthoma						X																				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																X										5
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										2
Skeletal muscle																										2
Fibrosarcoma, metastatic, skin																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hamartoma																								X		1
Peripheral nerve																										1
Spinal cord																										2
Fibrosarcoma, metastatic, skin																										2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	5 3 3	5 8 9	5 8 9	6 0 2	6 5 3	7 0 1	7 1 6	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	3 1 3	3 1 2	3 2 6	3 1 7	3 1 1	3 4 4	3 2 2	3 0 2	3 1 8	3 2 8	3 3 8	3 3 9	3 4 2	4 4 5	4 4 6	3 0 1	3 0 5	3 0 9	3 1 0	3 1 5	3 2 0	3 2 1	3 2 4	3 2 5	3 2 7
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma														X											
Fibrosarcoma, metastatic, skin		X	X	X																					
Hepatocellular carcinoma, metastatic, liver					X									X											
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung														X											
Mediastinum, fibrosarcoma, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland			+																						
Adenoma			X																						
Urinary System																									
Kidney	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																			X		X	X	X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 3 mg/kg

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 3 0	3 3 3	3 3 5	3 3 6	3 3 7	3 4 1	3 4 7	3 0 3	3 0 4	3 0 6	3 0 7	3 0 8	3 1 4	3 1 6	3 1 9	3 2 3	3 2 9	3 3 1	3 3 2	3 3 4	3 4 0	3 4 3	3 4 8	3 4 9	3 5 0	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			1
Alveolar/bronchiolar carcinoma																										1
Fibrosarcoma, metastatic, skin																										3
Hepatocellular carcinoma, metastatic, liver																				X						3
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinum, fibrosarcoma, metastatic, skin																X										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																						+				2
Adenoma																						X				2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant											X		X							X						7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 6 mg/kg

Number of Days on Study	21	30	34	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48
	12	28	33	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	11	11	13	34	33	34
Carcass ID Number	398	361	400	351	352	353	354	355	356	357	358	359	360	371	372	373	374	375	369	363	368	388	397	393	390
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Periesophageal tissue, leiomyosarcoma, metastatic, intestine small, ileum																						X			
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																						X			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma																									
Hepatocellular adenoma							X																		
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma																									
Leiomyosarcoma, metastatic, intestine small, ileum																						X			
Mesentery																						+			
Leiomyosarcoma, metastatic, intestine small, ileum																						X			
Oral mucosa																								+	
Squamous cell carcinoma																								X	
Pancreas	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Leiomyosarcoma, metastatic, intestine small, ileum																						X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, intestine small, ileum																						X			
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, intestine small, ileum																						X			
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Parathyroid gland	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+
Pars distalis, adenoma																				X					
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Peritoneum																						+			
Leiomyosarcoma, metastatic, intestine small, ileum																						X			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 6 mg/kg

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 7 7 9	3 8 5	3 9 1	3 6 2	3 6 4	3 7 0	3 7 8	3 8 1	3 8 3	3 8 4	3 8 7	3 9 2	3 9 4	3 9 6	3 9 9	3 6 5	3 6 6	3 6 7	3 7 6	3 7 7	3 8 0	3 8 2	3 8 6	3 8 9	3 9 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Periesophageal tissue, leiomyosarcoma, metastatic, intestine small, ileum																										1
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X																							1
Hepatocellular carcinoma															X											1
Hepatocellular adenoma			X			X																			X	4
Hepatocellular adenoma, multiple																X										1
Histiocytic sarcoma												X														1
Leiomyosarcoma, metastatic, intestine small, ileum																										1
Mesentery			+	+																			+			4
Leiomyosarcoma, metastatic, intestine small, ileum																										1
Oral mucosa																										1
Squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyosarcoma, metastatic, intestine small, ileum																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, intestine small, ileum																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, intestine small, ileum																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	M	+	+	+	+	M	+	M	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma									X																	2
Pars intermedia, adenoma															X											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
Peritoneum																										1
Leiomyosarcoma, metastatic, intestine small, ileum																										1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 6 mg/kg

Number of Days on Study	2 1 2	3 0 8	3 4 3	4 8 0	4 8 0	4 8 0	4 8 0	4 8 0	4 8 0	4 8 0	4 8 0	4 8 0	4 8 0	4 8 0	4 8 0	4 8 0	4 8 0	4 8 0	5 8 1	6 4 1	6 4 1	6 7 3	6 9 4	7 0 3	7 1 4
Carcass ID Number	3 9 8	3 6 1	4 0 0	3 5 1	3 5 2	3 5 3	3 5 4	3 5 5	3 5 6	3 5 7	3 5 8	3 5 9	3 6 0	3 7 1	3 7 2	3 7 3	3 7 4	3 7 5	3 6 9	3 6 3	3 6 8	3 8 8	3 9 7	3 9 3	3 9 0
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Adenocarcinoma																									
Cystadenoma																									
Leiomyosarcoma, metastatic, intestine small, ileum																						X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, intestine small, ileum																						X			
Polyp stromal																									
Vagina																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node																						+		+	+
Mediastinal, sarcoma, metastatic, bone																									X
Renal, leiomyosarcoma, metastatic, intestine small, ileum																						X			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, bone marrow																									
Leiomyosarcoma, metastatic, intestine small, ileum																						X			
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Sarcoma, metastatic, bone																									X
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Carcinoma																			X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rib, periosteum, sarcoma																									X
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 6 mg/kg

Number of Days on Study	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	379	385	391	362	364	370	378	381	383	384	387	392	394	396	399	365	366	367	376	377	380	382	386	389	395	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma				X																						1
Cystadenoma																						X				1
Leiomyosarcoma, metastatic, intestine small, ileum																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, intestine small, ileum																										1
Polyp stromal										X																1
Vagina						+																				1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X																	1
Lymph node		+													+											5
Mediastinal, sarcoma, metastatic, bone																										1
Renal, leiomyosarcoma, metastatic, intestine small, ileum																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma												X														1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																				X						1
Hemangiosarcoma, metastatic, bone marrow									X																	1
Leiomyosarcoma, metastatic, intestine small, ileum																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, metastatic, bone																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma													X													2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma								X																		1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rib, periosteum, sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 6 mg/kg

Number of Days on Study	21	30	34	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	51	64	64	67	67	70	71
	12	28	33	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	11	11	11	33	44	33	44
Carcass ID Number	398	361	400	501	552	553	554	555	556	557	558	559	560	671	772	773	774	775	776	596	663	668	688	697	693	690
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X			
Alveolar/bronchiolar carcinoma																					X			X		
Alveolar/bronchiolar carcinoma, metastatic, lung																								X		
Leiomyosarcoma, metastatic, intestine small, ileum																							X			
Sarcoma, metastatic, bone																										X
Mediastinum, leiomyosarcoma, metastatic, intestine small, ileum																							X			
Mediastinum, sarcoma, metastatic, bone																										X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye							+																			
Harderian gland																										
Adenoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, intestine small, ileum																							X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, bone marrow																										
Leiomyosarcoma, metastatic, intestine small, ileum																							X			
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Lymphoma malignant																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Methacrylonitrile: 6 mg/kg

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 7 9	3 8 5	3 9 1	3 6 2	3 6 4	3 7 0	3 7 8	3 8 1	3 8 3	3 8 4	3 8 7	3 9 2	3 9 4	3 9 6	3 9 9	3 6 5	3 6 6	3 6 7	3 7 6	3 7 7	3 8 0	3 8 2	3 8 6	3 8 9	3 9 5	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X																			2
Alveolar/bronchiolar carcinoma												X														3
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Leiomyosarcoma, metastatic, intestine small, ileum																										1
Sarcoma, metastatic, bone																										1
Mediastinum, leiomyosarcoma, metastatic, intestine small, ileum																										1
Mediastinum, sarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye						+		+															+			4
Harderian gland						+		+																		2
Adenoma						X		X																		2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, intestine small, ileum																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, bone marrow									X																	1
Leiomyosarcoma, metastatic, intestine small, ileum																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma												X														1
Lymphoma malignant									X						X											2

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Harderian Gland: Adenoma or Carcinoma				
Overall rate[a]	4/50 (8%)	2/50 (4%)	2/50 (4%)	2/50 (4%)
Adjusted rate[b]	8.9%	4.6%	4.2%	5.7%
Terminal rate[c]	4/35 (11%)	1/35 (3%)	1/43 (2%)	2/25 (8%)
First incidence (days)	730 (T)	638	589	730 (T)
Poly-3 test[d]	P=0.344N	P=0.356N	P=0.309N	P=0.462N
Large Intestine (Cecum): Leiomyoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rate	6.6%	2.3%	0.0%	0.0%
Terminal rate	3/35 (9%)	1/35 (3%)	0/43 (0%)	0/25 (0%)
First incidence (days)	730 (T)	730 (T)	—[e]	—
Poly-3 test	P=0.040N	P=0.323N	P=0.110N	P=0.172N
Liver: Hepatocellular Adenoma				
Overall rate	9/50 (18%)	9/50 (18%)	12/49 (24%)	5/50 (10%)
Adjusted rate	19.8%	20.8%	25.5%	14.1%
Terminal rate	7/35 (20%)	8/35 (23%)	12/43 (28%)	4/25 (16%)
First incidence (days)	653	638	730 (T)	480
Poly-3 test	P=0.380N	P=0.559	P=0.341	P=0.355N
Liver: Hepatocellular Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	4/49 (8%)	1/50 (2%)
Adjusted rate	4.4%	4.7%	8.5%	2.9%
Terminal rate	0/35 (0%)	2/35 (6%)	3/43 (7%)	1/25 (4%)
First incidence (days)	662	730 (T)	653	730 (T)
Poly-3 test	P=0.565N	P=0.674	P=0.356	P=0.591N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	10/50 (20%)	11/50 (22%)	14/49 (29%)	6/50 (12%)
Adjusted rate	21.9%	25.4%	29.6%	16.9%
Terminal rate	7/35 (20%)	10/35 (29%)	13/43 (30%)	5/25 (20%)
First incidence (days)	653	638	653	480
Poly-3 test	P=0.410N	P=0.444	P=0.269	P=0.392N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	6/50 (12%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rate	13.3%	7.0%	2.1%	5.7%
Terminal rate	5/35 (14%)	3/35 (9%)	1/43 (2%)	1/25 (4%)
First incidence (days)	709	730 (T)	730 (T)	673
Poly-3 test	P=0.092N	P=0.267N	P=0.048N	P=0.231N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.2%	0.0%	2.1%	8.5%
Terminal rate	1/35 (3%)	0/35 (0%)	1/43 (2%)	1/25 (4%)
First incidence (days)	730 (T)	—	730 (T)	641
Poly-3 test	P=0.077	P=0.510N	P=0.749N	P=0.224

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	6/50 (12%)	3/50 (6%)	2/50 (4%)	5/50 (10%)
Adjusted rate	13.3%	7.0%	4.2%	14.1%
Terminal rate	5/35 (14%)	3/35 (9%)	2/43 (5%)	2/25 (8%)
First incidence (days)	709	730 (T)	730 (T)	641
Poly-3 test	P=0.547N	P=0.267N	P=0.117N	P=0.586
Skin: Fibrosarcoma				
Overall rate	2/50 (4%)	1/50 (2%)	5/50 (10%)	1/50 (2%)
Adjusted rate	4.4%	2.3%	10.2%	2.9%
Terminal rate	1/35 (3%)	0/35 (0%)	1/43 (2%)	1/25 (4%)
First incidence (days)	671	521	589	730 (T)
Poly-3 test	P=0.477	P=0.513N	P=0.250	P=0.590N
Skin: Fibrosarcoma or Sarcoma				
Overall rate	2/50 (4%)	2/50 (4%)	5/50 (10%)	1/50 (2%)
Adjusted rate	4.4%	4.6%	10.2%	2.9%
Terminal rate	1/35 (3%)	0/35 (0%)	1/43 (2%)	1/25 (4%)
First incidence (days)	671	521	589	730 (T)
Poly-3 test	P=0.528	P=0.683	P=0.250	P=0.590N
All Organs: Hemangiosarcoma				
Overall rate	2/50 (4%)	3/50 (6%)	0/50 (0%)	3/50 (6%)
Adjusted rate	4.4%	6.8%	0.0%	8.6%
Terminal rate	1/35 (3%)	1/35 (3%)	0/43 (0%)	3/25 (12%)
First incidence (days)	704	405	—	730 (T)
Poly-3 test	P=0.444	P=0.487	P=0.226N	P=0.383
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/50 (8%)	3/50 (6%)	0/50 (0%)	3/50 (6%)
Adjusted rate	8.8%	6.8%	0.0%	8.6%
Terminal rate	3/35 (9%)	1/35 (3%)	0/43 (0%)	3/25 (12%)
First incidence (days)	704	405	—	730 (T)
Poly-3 test	P=0.385N	P=0.516N	P=0.054N	P=0.639N
All Organs: Malignant Lymphoma				
Overall rate	9/50 (18%)	7/50 (14%)	7/50 (14%)	2/50 (4%)
Adjusted rate	19.5%	15.9%	14.7%	5.7%
Terminal rate	5/35 (14%)	5/35 (14%)	7/43 (16%)	2/25 (8%)
First incidence (days)	623	289	730 (T)	730 (T)
Poly-3 test	P=0.065N	P=0.432N	P=0.367N	P=0.073N
All Organs: Benign Neoplasms				
Overall rate	24/50 (48%)	15/50 (30%)	20/50 (40%)	13/50 (26%)
Adjusted rate	51.5%	34.6%	41.6%	36.1%
Terminal rate	20/35 (57%)	14/35 (40%)	19/43 (44%)	10/25 (40%)
First incidence (days)	362	638	589	480
Poly-3 test	P=0.143N	P=0.076N	P=0.223N	P=0.116N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
All Organs: Malignant Neoplasms				
Overall rate	19/50 (38%)	17/50 (34%)	17/50 (34%)	14/50 (28%)
Adjusted rate	40.3%	36.4%	34.4%	38.7%
Terminal rate	11/35 (31%)	9/35 (26%)	11/43 (26%)	8/25 (32%)
First incidence (days)	607	289	589	581
Poly-3 test	P=0.452N	P=0.428N	P=0.349N	P=0.531N
All Organs: Benign or Malignant Neoplasms				
Overall rate	33/50 (66%)	28/50 (56%)	29/50 (58%)	21/50 (42%)
Adjusted rate	68.8%	59.5%	58.7%	57.0%
Terminal rate	24/35 (69%)	19/35 (54%)	23/43 (54%)	14/25 (56%)
First incidence (days)	362	289	589	480
Poly-3 test	P=0.164N	P=0.230N	P=0.204N	P=0.180N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver and lung; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Methacrylonitrile[a]

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths				15
Moribund	1	2	3	3
Natural deaths	14	13	4	7
Survivors				
Died the last week of the study	1			
Terminal sacrifice	34	35	43	25
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Periesophageal tissue, inflammation, chronic active	1 (2%)			
Gallbladder	(50)	(50)	(50)	(48)
Cyst	1 (2%)			
Infiltration cellular, mononuclear cell			1 (2%)	
Intestine small, duodenum	(49)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)			
Metaplasia, squamous			1 (2%)	
Epithelium, ulcer	1 (2%)			
Intestine small, jejunum	(50)	(50)	(50)	(50)
Ulcer		1 (2%)		
Epithelium, inflammation, suppurative		1 (2%)		
Peyer's patch, hyperplasia, lymphoid				2 (4%)
Liver	(50)	(50)	(49)	(50)
Angiectasis		1 (2%)	1 (2%)	
Basophilic focus	1 (2%)	7 (14%)	2 (4%)	2 (4%)
Clear cell focus	3 (6%)	6 (12%)	6 (12%)	1 (2%)
Eosinophilic focus	9 (18%)	3 (6%)	11 (22%)	3 (6%)
Hematopoietic cell proliferation	2 (4%)	2 (4%)	6 (12%)	2 (4%)
Hepatodiaphragmatic nodule		1 (2%)		
Infiltration cellular, mononuclear cell	30 (60%)	36 (72%)	40 (82%)	30 (60%)
Inflammation, chronic active	32 (64%)	36 (72%)	41 (84%)	38 (76%)
Mineralization			1 (2%)	1 (2%)
Mixed cell focus	3 (6%)	1 (2%)	3 (6%)	
Necrosis	3 (6%)	2 (4%)	2 (4%)	1 (2%)
Pigmentation	18 (36%)	12 (24%)	17 (35%)	7 (14%)
Tension lipidosis	2 (4%)	3 (6%)		
Hepatocyte, vacuolization cytoplasmic	7 (14%)	9 (18%)	3 (6%)	18 (36%)
Mesentery	(16)	(11)	(15)	(4)
Fibrosis	8 (50%)	7 (64%)	10 (67%)	2 (50%)
Hemorrhage		1 (9%)		
Inflammation, chronic active	5 (31%)	6 (55%)	8 (53%)	
Mineralization	5 (31%)	7 (64%)	12 (80%)	1 (25%)
Pigmentation			1 (7%)	
Thrombosis			1 (7%)	
Fat, necrosis	8 (50%)	7 (64%)	11 (73%)	3 (75%)

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

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Alimentary System (continued)				
Oral mucosa	(3)	(5)	(2)	(1)
Gingival, foreign body	2 (67%)	5 (100%)	1 (50%)	
Gingival, inflammation, chronic active	2 (67%)	5 (100%)	2 (100%)	
Pharyngeal, foreign body	1 (33%)			
Pancreas	(50)	(50)	(50)	(48)
Cyst			1 (2%)	
Infiltration cellular, mononuclear cell				2 (4%)
Acinus, atrophy	1 (2%)			
Acinus, hyperplasia				1 (2%)
Salivary glands	(48)	(50)	(50)	(49)
Infiltration cellular, mononuclear cell	27 (56%)	29 (58%)	32 (64%)	27 (55%)
Inflammation, chronic active			2 (4%)	1 (2%)
Mineralization			1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Diverticulum	1 (2%)			
Hyperkeratosis		1 (2%)		
Epithelium, hyperplasia	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Epithelium, inflammation, chronic active	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Epithelium, ulcer	1 (2%)	1 (2%)	1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Ectopic tissue		1 (2%)		
Mineralization	1 (2%)	1 (2%)		1 (2%)
Epithelium, dysplasia		1 (2%)		
Epithelium, erosion	1 (2%)			
Glands, ectasia	16 (32%)	9 (18%)	10 (20%)	3 (6%)
Cardiovascular System				
Blood vessel	(49)	(50)	(50)	(50)
Aorta, mineralization	1 (2%)			
Heart	(50)	(50)	(50)	(50)
Inflammation, suppurative				1 (2%)
Mineralization	1 (2%)			
Artery, mineralization	1 (2%)			
Valve, inflammation, chronic active		1 (2%)		
Valve, inflammation, suppurative	1 (2%)			
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Accessory adrenal cortical nodule				2 (4%)
Hematopoietic cell proliferation		1 (2%)		1 (2%)
Hypertrophy	1 (2%)		1 (2%)	
Infiltration cellular, mononuclear cell		1 (2%)		
Capsule, hyperplasia	48 (98%)	48 (96%)	50 (100%)	50 (100%)
Zona reticularis, hyperplasia			1 (2%)	
Adrenal medulla	(49)	(50)	(50)	(50)
Hyperplasia	1 (2%)			1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Hyperplasia	41 (82%)	37 (74%)	40 (80%)	33 (67%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Endocrine System (continued)				
Pituitary gland	(49)	(49)	(49)	(49)
Pars distalis, angiectasis	2 (4%)	3 (6%)	6 (12%)	2 (4%)
Pars distalis, cyst	1 (2%)		2 (4%)	2 (4%)
Pars distalis, hemorrhage		1 (2%)		
Pars distalis, hyperplasia	9 (18%)	12 (24%)	10 (20%)	11 (22%)
Pars distalis, pigmentation			1 (2%)	
Thyroid gland	(49)	(50)	(50)	(50)
Ectopic thymus			1 (2%)	
Infiltration cellular, mononuclear cell	1 (2%)			1 (2%)
Inflammation, chronic active	1 (2%)			
C-cell, hyperplasia		1 (2%)		
Follicle, cyst	5 (10%)	3 (6%)	3 (6%)	4 (8%)
Follicular cell, hyperplasia	1 (2%)			
General Body System				
None				
Genital System				
Clitoral gland	(50)	(50)	(50)	(49)
Infiltration cellular, mononuclear cell	4 (8%)	2 (4%)	3 (6%)	1 (2%)
Inflammation, chronic active	2 (4%)	1 (2%)		1 (2%)
Pigmentation		1 (2%)		
Duct, cyst			2 (4%)	2 (4%)
Ovary	(50)	(50)	(50)	(49)
Angiectasis		1 (2%)		
Cyst	17 (34%)	14 (28%)	18 (36%)	10 (20%)
Hemorrhage		1 (2%)	4 (8%)	1 (2%)
Inflammation, suppurative				1 (2%)
Mineralization	2 (4%)	3 (6%)	2 (4%)	1 (2%)
Pigmentation	7 (14%)	16 (32%)	11 (22%)	6 (12%)
Thrombosis		1 (2%)	3 (6%)	
Uterus	(50)	(50)	(50)	(50)
Angiectasis				1 (2%)
Hemorrhage				1 (2%)
Hydrometra	23 (46%)	28 (56%)	31 (62%)	20 (40%)
Inflammation, chronic active	1 (2%)			
Inflammation, suppurative		1 (2%)		
Pigmentation		1 (2%)		
Thrombosis	1 (2%)			
Endometrium, hyperplasia	1 (2%)			
Endometrium, hyperplasia, cystic	27 (54%)	24 (48%)	24 (48%)	32 (64%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)	2 (4%)	4 (8%)	1 (2%)
Myelofibrosis	2 (4%)	3 (6%)		

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Hematopoietic System (continued)				
Lymph node	(9)	(6)	(8)	(5)
Lumbar, ectasia		1 (17%)		1 (20%)
Lumbar, hyperplasia, lymphoid			1 (13%)	
Mediastinal, hyperplasia, lymphoid	1 (11%)		2 (25%)	
Mediastinal, infiltration cellular, histiocyte	1 (11%)			
Mediastinal, inflammation				1 (20%)
Pancreatic, fibrosis	1 (11%)			
Pancreatic, hyperplasia, lymphoid	1 (11%)			
Pancreatic, pigmentation	1 (11%)			
Lymph node, mandibular	(48)	(49)	(46)	(47)
Hyperplasia, lymphoid	5 (10%)	4 (8%)	3 (7%)	1 (2%)
Infiltration cellular, plasma cell	1 (2%)			
Pigmentation	3 (6%)	16 (33%)	9 (20%)	4 (9%)
Lymph node, mesenteric	(47)	(48)	(47)	(46)
Ectasia	2 (4%)			
Hemorrhage	2 (4%)	1 (2%)		
Hyperplasia, lymphoid	2 (4%)		1 (2%)	1 (2%)
Inflammation, chronic active		1 (2%)		
Pigmentation	1 (2%)			
Spleen	(50)	(50)	(49)	(49)
Hematopoietic cell proliferation	18 (36%)	22 (44%)	15 (31%)	10 (20%)
Hyperplasia, lymphoid	1 (2%)	3 (6%)	1 (2%)	
Mineralization			1 (2%)	
Necrosis		1 (2%)		
Pigmentation			1 (2%)	
Thymus	(47)	(43)	(46)	(48)
Cyst	20 (43%)	17 (40%)	23 (50%)	19 (40%)
Ectopic parathyroid gland	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, lymphoid			2 (4%)	
Thymocyte, necrosis		1 (2%)		1 (2%)
Integumentary System				
Mammary gland	(49)	(50)	(49)	(49)
Hyperplasia, cystic	3 (6%)	1 (2%)		
Skin	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)			
Epidermis, ulcer	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosclerosis	1 (2%)			
Skeletal muscle	(4)	(1)	(2)	
Infiltration cellular, mononuclear cell	1 (25%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Infiltration cellular, mononuclear cell	2 (4%)			
Inflammation, chronic active		1 (2%)		
Meninges, hemorrhage		1 (2%)		

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Nervous System (continued)				
Peripheral nerve	(1)		(1)	
Sciatic, axon, degeneration	1 (100%)			
Spinal cord	(1)		(2)	
Demyelination	1 (100%)		1 (50%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Inflammation, chronic active	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Mineralization	5 (10%)	1 (2%)	2 (4%)	2 (4%)
Necrosis				1 (2%)
Pigmentation	1 (2%)			
Thrombosis		1 (2%)	1 (2%)	
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)	1 (2%)	
Alveolus, infiltration cellular, histiocyte	1 (2%)			2 (4%)
Artery, mediastinum, mineralization	1 (2%)			
Mediastinum, mineralization		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)			
Special Senses System				
Eye	(2)	(1)		(4)
Atrophy	1 (50%)	1 (100%)		1 (25%)
Anterior chamber, infiltration cellular, polymorphonuclear				1 (25%)
Cornea, inflammation, chronic active				1 (25%)
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Accumulation, hyaline droplet	2 (4%)	1 (2%)		
Hydronephrosis			1 (2%)	
Infarct, multiple	1 (2%)			
Infiltration cellular, mononuclear cell	35 (70%)	42 (84%)	44 (90%)	35 (70%)
Inflammation, chronic active	1 (2%)	1 (2%)		
Mineralization	5 (10%)	5 (10%)	5 (10%)	6 (12%)
Nephropathy	15 (30%)	19 (38%)	22 (45%)	9 (18%)
Pigmentation			1 (2%)	
Capsule, mineralization	1 (2%)			
Cortex, cyst	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Papilla, inflammation, acute	1 (2%)			
Renal tubule, casts protein			1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)
Infiltration cellular, mononuclear cell	28 (56%)	31 (62%)	29 (58%)	22 (44%)
Inflammation, chronic active	1 (2%)			
Pigmentation	1 (2%)			

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

Salmonella Typhimurium Mutagenicity Test Protocol

Testing was performed as reported by Zeiger *et al*. (1987). Methacrylonitrile was sent to the laboratories as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

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

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

Drosophila Melanogaster Test Protocol

The assay for induction of sex-linked recessive lethal (SLRL) mutations was performed with larvae as described by Zimmering *et al.* (1989). Methacrylonitrile was supplied as a coded aliquot by Radian Corporation. Canton-S males and females were mated, and eggs were exposed in vials with standard cornmeal feed containing methacrylonitrile in solvent (5% ethanol) or solvent alone (Valencia *et al*., 1989). Adult emergent males were mated at approximately 24 hours of age with two successive harems of three to five *Basc* females to establish two single-day broods (sample sperm from successive matings were treated at successively earlier postmeiotic stages). F_1 heterozygous females were mated with their siblings and then placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as vials containing fewer than 5% of the expected number of wild-type males after 17 days; these were retested to confirm the response.

SLRL data were analyzed by simultaneous comparison with the concurrent and historical controls (Mason *et al*., 1992) using a normal approximation to the binomial test (Margolin *et al*., 1983). A test result was considered positive if the P value was less than or equal to 0.01 and the mutation frequency in the treatment group was greater than 0.10% or if the P value was less than or equal to 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if the P value was between 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15% or if the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 0.10%. A test was considered negative if the P value was greater than 0.10 or if the frequency in the treatment group was less than 0.10%.

Rat and Mouse Bone Marrow Micronucleus Test Protocol

Preliminary range-finding studies were performed because of the lack of adequate toxicity data in the literature. Factors affecting dose selection included chemical solubility and toxicity and the extent of cell cycle delay induced by methacrylonitrile exposure. The standard three-exposure protocol is described in detail by Shelby *et al*. (1993). Male rats and mice (five per group) were injected intraperitoneally three times at 24-hour intervals with methacrylonitrile dissolved in corn oil. Solvent control animals were injected with corn oil only. The positive control animals received injections of cyclophosphamide. The animals were killed 24 hours after the third injection, and slides were prepared from bone marrow cells obtained from the

femurs. Air-dried smears were fixed and stained with acridine orange; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in up to five animals per dose group.

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

Mouse Peripheral Blood Micronucleus Test Protocol

A detailed discussion of this assay is presented by MacGregor *et al*. (1990). At the end of the 13-week toxicity study, peripheral blood samples were obtained from male and female mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with acridine orange and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 normochromatic erythrocytes (NCEs) in up to ten animals per dose group. In addition, the percentage of PCEs among the total erythrocyte population in the peripheral blood was scored for each dose group as a measure of toxicity.

The results for NCEs were tabulated as described for PCEs in the bone marrow micronucleus test. Results of the 13-week studies were accepted without repeat tests, because additional test data could not be obtained.

Evaluation Protocol

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and different results were obtained among aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the *in vitro* assays have another variable that must be considered in arriving at an overall test result. *In vitro* assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgement of the overall evidence for activity of the chemical in an assay.

Results

Methacrylonitrile (100 to 10,000 µg/plate) did not induce mutations in *S. typhimurium* strain TA97, TA98, TA100, TA1535, or TA1537 (Table E1; Zeiger *et al*., 1987). All tests were performed with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9. No induction of sex-linked recessive lethal mutations was observed in germ cells of male *D. melanogaster* treated during the larval stage by feeding on medium containing approximately 6,000 ppm methacrylonitrile (Table E2; Zimmering *et al*., 1989). In a male rat bone marrow micronucleus test, an initial trial showed a significant induction of micronuclei in the 25 mg/kg group; however, a second trial showed no induction of micronuclei in bone marrow PCEs and the test was determined to be negative overall (Table E3). Also, no increase in the frequency of micronucleated PCEs was observed in the bone marrow of male mice treated with 6.25 to 25 mg/kg methacrylonitrile (Table E4). Consistent with the negative

results seen with the short-term bone marrow tests in rats and mice, the results of a 13-week peripheral blood micronucleus test in male and female mice showed no evidence of methacrylonitrile-induced genetic damage (Table E5). In conclusion, this battery of short-term *in vitro* and *in vivo* tests showed no evidence of genotoxicity of methacrylonitrile.

TABLE E1
Mutagenicity of Methacrylonitrile in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/Plate[b] -S9 Trial 1	-S9 Trial 2	+ hamster S9 10%	+ hamster S9 30%	+ hamster S9 30%	+ rat S9 10%	+ rat S9 30%
Study performed at SRI International								
TA100	0	164 ± 8.7	135 ± 0.6	126 ± 4.6	138 ± 2.7	126 ± 7.5	150 ± 4.9	150 ± 10.5
	100	151 ± 7.9	131 ± 10.4	147 ± 9.3	132 ± 15.2		149 ± 13.3	153 ± 9.3
	333	136 ± 13.5	129 ± 3.4	140 ± 8.1	137 ± 5.1	138 ± 10.8	144 ± 15.9	139 ± 6.5
	1,000	138 ± 18.7	144 ± 5.0	123 ± 5.6	139 ± 15.4	131 ± 10.4	135 ± 4.5	136 ± 13.6
	3,333	126 ± 19.9	130 ± 5.0	138 ± 7.4	84 ± 19.2	109 ± 9.0	144 ± 13.5	134 ± 3.2
	6,666					116 ± 10.7		
	10,000	155 ± 7.8	125 ± 6.5	113 ± 7.6	0 ± 0.0[c]	81 ± 31.2[c]	126 ± 19.9	140 ± 5.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		612 ± 25.2	591 ± 4.8	1,936 ± 40.2	698 ± 28.2	497 ± 12.2	512 ± 7.3	273 ± 19.5
TA1535	0	23 ± 3.0	29 ± 4.9	9 ± 2.1	12 ± 1.2	22 ± 0.9	13 ± 1.5	18 ± 1.5
	100	23 ± 1.7	33 ± 2.3	11 ± 1.5	8 ± 0.3		8 ± 0.3	20 ± 4.8
	333	23 ± 3.9	24 ± 3.5	10 ± 2.6	11 ± 1.5	28 ± 4.4	7 ± 1.3	22 ± 1.9
	1,000	18 ± 2.6	24 ± 1.3	10 ± 1.2	8 ± 1.9	30 ± 2.7	10 ± 2.3	23 ± 3.8
	3,333	24 ± 3.0	25 ± 3.8	11 ± 0.7	8 ± 2.8	18 ± 4.2	8 ± 2.1	10 ± 0.3
	6,666					17 ± 4.1		
	10,000	20 ± 3.7	18 ± 1.2	10 ± 1.0	0 ± 0.0[c]	7 ± 3.7[c]	11 ± 2.7	15 ± 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control		326 ± 18.0	360 ± 23.5	304 ± 19.2	357 ± 32.5	246 ± 21.4	196 ± 5.9	112 ± 9.0
TA97	0	147 ± 11.0	149 ± 10.5	167 ± 9.3	161 ± 11.3	130 ± 2.7	186 ± 1.2	195 ± 4.7
	100	188 ± 9.0	158 ± 4.3	171 ± 16.6	165 ± 7.4		175 ± 5.8	192 ± 1.8
	333	159 ± 6.2	154 ± 5.7	171 ± 12.3	166 ± 2.1	136 ± 11.4	185 ± 7.9	192 ± 2.8
	1,000	167 ± 4.0	155 ± 7.9	181 ± 11.8	144 ± 24.5	150 ± 11.6	183 ± 7.2	186 ± 4.0
	3,333	182 ± 11.0	153 ± 3.9	175 ± 10.8	146 ± 15.8	152 ± 6.9	174 ± 7.2	194 ±5.2
	6,666					148 ± 6.1		
	10,000	173 ± 4.7	134 ± 4.9	179 ± 10.6	0 ± 0.0[c]	146 ± 10.4[c]	173 ± 15.0	186 ± 4.6
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,206 ± 39.9	719 ± 26.4	1,420 ± 25.2	1,185 ± 82.6	619 ± 57.2	887 ± 25.8	550 ± 21.7
TA98	0	23 ± 4.5	26 ± 4.7	43 ± 3.6	35 ± 5.1	44 ± 6.2	40 ± 3.0	40 ± 4.2
	100	23 ± 2.5	25 ± 3.6	33 ± 2.8	33 ± 5.4		36 ± 2.4	35 ± 2.4
	333	24 ± 2.0	23 ± 1.0	34 ± 1.5	30 ± 1.5	39 ± 1.8	32 ± 2.0	35 ±3.2
	1,000	25 ± 3.5	23 ± 3.8	33 ± 1.3	31 ± 5.9	37 ± 2.3	37 ± 3.7	30 ± 0.0
	3,333	21 ± 2.3	20 ± 2.6	32 ± 0.3	11 ± 2.0	31 ± 4.6	33 ± 2.6	35 ± 1.7
	6,666					18 ± 1.0		
	10,000	23 ± 3.7	15 ± 1.2	37 ± 0.3	0 ± 0.0[c]	12 ± 4.0[c]	29 ± 2.6	33 ± 3.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control		495 ± 67.4	1,099 ± 37.6	1,419 ± 19.9	366 ± 30.2	229 ± 4.5	287 ± 9.1	104 ± 6.2

TABLE E1
Mutagenicity of Methacrylonitrile in *Salmonella typhimurium*

Strain	Dose (µg/plate)	Revertants/Plate -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% hamster S9 Trial 3	+10% rat S9 Trial 1	+10% rat S9 Trial 2	+10% rat S9 Trial 3
Study performed at Case Western Reserve University									
TA100	0	127 ± 0.9	83 ± 6.6	147 ± 17.1	116 ± 21.4	226 ± 29.5	132 ± 2.6	82 ± 8.3	202 ± 7.3
	100	173 ± 2.9	82 ± 3.5	130 ± 12.4	109 ± 3.5	175 ± 3.5	151 ± 17.9	94 ± 2.3	200 ± 11.2
	333	166 ± 4.5	92 ± 2.0	158 ± 7.4	140 ± 13.5	226 ± 5.4	126 ± 5.9	123 ± 16.3	183 ± 7.5
	1,000	158 ± 4.5	72 ± 0.0	164 ± 12.8	122 ± 15.4	200 ± 6.5	160 ± 3.2	109 ± 4.6	194 ± 6.9
	3,333	158 ± 9.4	81 ± 4.6	165 ± 11.2	152 ± 6.2	236 ± 16.8	150 ± 15.5	115 ± 9.3	223 ± 16.9
	10,000	126 ± 9.3	Toxic	173 ± 16.3	128 ± 8.7	211 ± 12.9	145 ± 16.2	123 ± 4.7	196 ± 18.8
Trial summary		Equivocal	Negative	Negative	Equivocal	Negative	Negative	Equivocal	Negative
Positive control		1,322 ± 11.1	910 ± 28.7	2,165 ± 35.1	2,419 ± 125.4	2,288 ± 2.7	2,952 ± 72.8	635 ± 27.7	1,539 ± 143.6
TA1535	0	16 ± 0.9	10 ± 2.0	14 ± 2.8	11 ± 0.7		14 ± 0.6	11 ± 1.7	
	100	16 ± 0.6	11 ± 2.9	13 ± 2.1	11 ± 1.2		11 ± 2.9	11 ± 0.6	
	333	13 ± 1.8	5 ± 1.2	16 ± 2.0	9 ± 1.7		20 ± 2.4	7 ± 0.3	
	1,000	16 ± 0.9	5 ± 0.3	9 ± 2.0	6 ± 1.5		13 ± 1.3	6 ± 1.2	
	3,333	13 ± 4.3	7 ± 1.2	16 ± 1.2	6 ± 0.3		16 ± 1.9	5 ± 2.2	
	10,000	15 ± 0.6	6 ± 0.7	16 ± 3.0	10 ± 2.3		15 ± 2.3	7 ± 1.0	
Trial summary		Negative	Negative	Negative	Negative		Negative	Negative	
Positive control		834 ± 45.0	874 ± 44.9	280 ± 45.7	65 ± 11.1		354 ± 19.2	188 ± 7.5	
TA98	0	35 ± 5.8	13 ± 1.2	31 ± 4.4	12 ± 2.1	26 ± 0.3	28 ± 3.2	17 ± 4.4	17 ± 2.9
	100	23 ± 2.3	13 ± 2.0	37 ± 1.9	17 ± 3.2	35 ± 2.5	27 ± 1.5	18 ± 3.6	16 ± 0.9
	333	29 ± 6.7	16 ± 2.1	34 ± 5.8	18 ± 3.5	33 ± 6.9	37 ± 5.1	19 ± 4.2	20 ± 1.2
	1,000	23 ± 2.4	11 ± 1.0	32 ± 8.0	22 ± 3.2	29 ± 5.5	27 ± 4.4	17 ± 0.9	27 ± 6.4
	3,333	28 ± 1.7	9 ± 0.3	29 ± 4.8	19 ± 4.9	26 ± 2.4	35 ± 5.2	14 ± 1.0	19 ± 0.7
	10,000	23 ± 3.3	10 ± 3.2	29 ± 0.7	13 ± 1.5	21 ± 3.5	36 ± 3.2	20 ± 1.7	22 ± 2.3
Trial summary		Negative	Negative	Negative	Equivocal	Negative	Negative	Negative	Negative
Positive control		212 ± 4.1	183 ± 43.5	962 ± 54.6	1,003 ± 55.2	1,632 ± 32.0	1,537 ± 48.4	482 ± 42.2	737 ± 160.2

TABLE E1
Mutagenicity of Methacrylonitrile in *Salmonella typhimurium*

Strain	Dose (µg/plate)	Revertants/Plate -S9 Trial 1	-S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2	+10% rat S9 Trial 3	+10% rat S9 Trial 4
Study performed at Case Western Reserve University (continued)							
TA1537	0	7 ± 1.5	10 ± 0.9	14 ± 1.0	10 ± 2.3	10 ± 1.8	9 ± 2.5
	100	9 ± 1.2	6 ± 2.3	17 ± 3.2	21 ± 2.6	11 ± 2.0	9 ± 3.3
	333	8 ± 1.2	5 ± 1.2	15 ± 1.0	11 ± 1.0	16 ± 2.0	8 ± 1.2
	1,000	7 ± 0.7	6 ± 1.2	17 ± 4.0	11 ± 1.2	10 ± 2.0	8 ± 1.5
	3,333	8 ± 0.9	6 ± 1.7	18 ± 2.7	10 ± 2.3	12 ± 0.3	8 ± 0.9
	10,000	9 ± 1.5	2 ± 0.9	23 ± 1.5	13 ± 0.7	13 ± 1.5	Toxic
Trial summary		Negative	Negative	Negative	Equivocal	Negative	Negative
Positive control		195 ± 29.3	813 ± 65.0	75 ± 20.2	191 ± 12.9	198 ± 20.2	37 ± 2.3

TA1537 (continued)

Dose (µg/plate)	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% hamster S9 Trial 3
0	18 ± 2.0	9 ± 0.7	9 ± 0.9
100	11 ± 2.4	10 ± 2.1	9 ± 0.9
333	13 ± 0.0	9 ± 0.3	11 ± 0.9
1,000	17 ± 3.7	11 ± 2.0	11 ± 2.3
3,333	20 ± 0.9	12 ± 1.2	13 ± 1.5
10,000	12 ± 0.3	5 ± 0.7	13 ± 0.3
Trial summary	Negative	Negative	Negative
Positive control	135 ± 17.8	98 ± 27.4	119 ± 9.7

[a] The detailed protocol and these data are presented by Zeiger *et al*. (1987). 0 µg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97 and TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by Methacrylonitrile[a]

Route of Exposure	Dose (ppm)	Incidence of Death (%)	Incidence of Sterility (%)	No. of Lethals/No. of X Chromosomes Tested Mating 1	Mating 2	Total[b]	
Feed	0			2/1,341	0/1,332	2/2,673	(0.07%)
	5,950	15	6	1/1,379	2/1,332	3/2,711	(0.11%)
Feed	0			1/1,281	0/1,234	1/2,515	(0.04%)
	6,077	16	2	1/1,360	0/1,317	1/2,677	(0.04%)

[a] Study was performed at Brown University. The detailed protocol and these data are presented by Zimmering *et al.* (1989). Results were negative (Margolin *et al*., 1983; Mason *et al*., 1992).
[b] Total number of lethal mutations/number of X chromosomes tested for three mating trials

TABLE E3
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Rats Treated with Methacrylonitrile by Intraperitoneal Injection[a]

Compound	Dose (mg/kg)	Number of Rats with Erythrocytes Scored	Micronucleated PCEs/ 1,000 PCEs[b]	P Value[c]
Trial 1				
Corn oil[d]		4	0.25 ± 0.14	
Methacrylonitrile	25	5	1.40 ± 0.37	0.0050
	50	3	0.83 ± 0.44	0.0633
	100	2[e]	0.50 ± 0.50	
	200		Lethal	
			P=0.086[g]	
Cyclophosphamide[f]	25	4	6.00 ± 0.98	0.0000
Trial 2				
Corn oil		5	1.80 ± 0.46	
Methacrylonitrile	12	5	1.10 ± 0.37	0.9033
	25	5	1.60 ± 0.29	0.6343
	50		Lethal	
			P=0.643	
Cyclophosphamide	25	3	4.00 ± 0.29	0.0042

[a] Study was performed at Integrated Laboratory Systems, Inc. The detailed protocol is presented by Shelby *et al*. (1993). PCE=polychromatic erythrocyte
[b] Mean ± standard error
[c] Pairwise comparison with the vehicle control. Dosed group values are significant at P≤0.013; positive control values are significant at P≤0.05 (ILS, 1990)
[d] Vehicle control
[e] Omitted from statistical analysis; invalid data point due to poor survival
[f] Positive control
[g] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test, significant at P≤0.025 (ILS, 1990)

TABLE E4
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Mice Treated with Methacrylonitrile by Intraperitoneal Injection[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/ 1,000 PCEs[b]
Corn oil[c]		5	1.00 ± 0.16
Methacrylonitrile	6.25	5	1.60 ± 0.62
	12.5	5	1.60 ± 1.23
	25	3	1.17 ± 1.17
			P=0.450[d]
Cyclophosphamide[e]	25	5	3.30 ± 0.60

[a] Study was performed at Integrated Laboratory Systems, Inc. The detailed protocol is presented by Shelby *et al.* (1993). PCE=polychromatic erythrocyte
[b] Mean ± standard error
[c] Vehicle control
[d] Significance of micronucleated PCEs/1,000 PCEs tested by a one-tailed trend test, significant at P≤0.025 (ILS, 1990)
[e] Positive control

TABLE E5
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Treatment with Methacrylonitrile by Gavage for 13 Weeks[a]

	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/ 1,000 NCEs[b]	P Value[c]	PCEs (%)
Male					
Corn oil[d]		10	0.45 ± 0.15		1.3
Methacrylonitrile	0.75	10	0.50 ± 0.16	0.4093	1.7
	1.5	10	0.60 ± 0.12	0.2563	1.8
	3	10	0.70 ± 0.13	0.1485	1.6
	6	10	0.55 ± 0.11	0.3273	1.7
	12	10	0.60 ± 0.17	0.2563	1.4
			P=0.340[e]		
Female					
Corn oil		10	0.55 ± 0.18		1.6
Methacrylonitrile	0.75	10	0.50 ± 0.07	0.5864	1.7
	1.5	10	0.35 ± 0.10	0.8272	1.8
	3	10	0.40 ± 0.15	0.7544	1.4
	6	10	0.35 ± 0.16	0.8272	1.6
	12	8	0.31 ± 0.09	0.8560	1.5
			P=0.855		

[a] Study was performed at SITEK Research Laboratories, Inc. The detailed protocol is presented by MacGregor *et al*. (1990). NCE=normochromatic erythrocyte; PCE=polychromatic erythrocyte
[b] Mean ± standard error
[c] Pairwise comparison with the vehicle control; significant at P≤0.005 (ILS, 1990)
[d] Vehicle control
[e] Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)

APPENDIX F
URINALYSIS AND
URINARY METABOLITE ANALYSES

TABLE F1
Urinalysis and Urinary Metabolite Data for Rats in the 2-Year Gavage Study of Methacrylonitrile[a]

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Male				
n				
Week 2	5	5	5	5
Month 3	5	5	4	5
Month 12	5	5	5	5
Month 18	5	5	5	5
Volume (mL/24 hours)				
Week 2	7.3 ± 0.6	6.7 ± 0.8	5.9 ± 0.6	6.5 ± 0.2
Month 3	8.0 ± 0.8	6.7 ± 0.7	8.2 ± 0.8	7.4 ± 1.0
Month 12	8.3 ± 1.5	8.9 ± 0.8	10.7 ± 0.6	11.4 ± 1.4
Month 18	9.3 ± 1.3	8.5 ± 2.0	11.2 ± 1.4	11.0 ± 1.0
Creatinine (mg/dL)				
Week 2	86.72 ± 3.98	103.64 ± 14.29	100.24 ± 8.47	91.12 ± 4.53
Month 3	135.24 ± 11.25	140.52 ± 8.54	116.30 ± 15.81	132.82 ± 13.82
Month 12	182.00 ± 38.11	150.62 ± 7.21	141.44 ± 4.87	131.76 ± 20.51
Month 18	154.18 ± 15.73	177.62 ± 29.64	105.90 ± 2.51*	117.42 ± 8.08
N-Acetyl-S-(2-cyanopropyl)-L-cysteine (µmol/24 hours)				
Week 2	0.000 ± 0.000	0.007 ± 0.001**	0.060 ± 0.018**	0.651 ± 0.084**
Month 3	0.000 ± 0.000	0.137 ± 0.005**	0.896 ± 0.163**	4.521 ± 0.736**
Month 12	0.000 ± 0.000	0.153 ± 0.008**	1.141 ± 0.093**	11.999 ± 0.714**
Month 18	0.000 ± 0.000	0.280 ± 0.033**	1.702 ± 0.258**	10.019 ± 1.022**
N-Acetyl-S-(2-cyanopropyl)-L-cysteine (µmol/mg creatinine)				
Week 2	0.000 ± 0.000	0.001 ± 0.000**	0.010 ± 0.003**	0.111 ± 0.014**
Month 3	0.000 ± 0.000	0.015 ± 0.001**	0.097 ± 0.016**	0.474 ± 0.037**
Month 12	0.000 ± 0.000	0.012 ± 0.001**	0.076 ± 0.007**	0.866 ± 0.064**
Month 18	0.000 ± 0.000	0.026 ± 0.006**	0.143 ± 0.015**	0.776 ± 0.030**
N-Acetyl-S-(2-hydroxypropyl)-L-cysteine (µmol/24 hours)				
Week 2	0.005 ± 0.002	0.312 ± 0.025**	0.962 ± 0.118**	2.563 ± 0.298**
Month 3	0.020 ± 0.009	1.561 ± 0.095**	3.033 ± 0.101**	7.162 ± 1.366**
Month 12	0.002 ± 0.002	0.857 ± 0.075**	3.365 ± 0.095**	10.673 ± 0.634**
Month 18	0.000 ± 0.000	1.438 ± 0.160**	3.347 ± 0.631**	7.870 ± 0.710**
N-Acetyl-S-(2-hydroxypropyl)-L-cysteine (µmol/mg creatinine)				
Week 2	0.001 ± 0.000	0.048 ± 0.004**	0.165 ± 0.013**	0.436 ± 0.046**
Month 3	0.002 ± 0.001	0.173 ± 0.015**	0.334 ± 0.022**	0.745 ± 0.080**
Month 12	0.000 ± 0.000	0.066 ± 0.007**	0.223 ± 0.006**	0.769 ± 0.052**
Month 18	0.000 ± 0.000	0.122 ± 0.018**	0.271 ± 0.039**	0.619 ± 0.043**

TABLE F1
Urinalysis and Urinary Metabolite Data for Rats in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	3 mg/kg	10 mg/kg	30 mg/kg
Female				
n				
Week 2	5	5	5	4
Month 3	5	5	5	5
Month 12	5	5	5	5
Month 18	5	5	5	5
Volume (mL/24 hours)				
Week 2	6.1 ± 0.8	5.9 ± 0.6	6.2 ± 0.3	6.1 ± 1.0
Month 3	6.3 ± 0.3	4.7 ± 0.7	5.8 ± 0.8	5.8 ± 1.5
Month 12	6.6 ± 0.4	6.0 ± 0.4	7.4 ± 0.9	5.6 ± 0.5
Month 18	6.4 ± 1.3	7.8 ± 0.6	9.8 ± 1.0*	8.5 ± 0.4
Creatinine (mg/dL)				
Week 2	71.60 ± 4.37	74.12 ± 8.78	69.28 ± 3.91	65.85 ± 7.95
Month 3	93.02 ± 6.37	104.32 ± 3.20	99.86 ± 9.40	123.10 ± 23.14
Month 12	103.56 ± 8.95	112.08 ± 5.04	104.92 ± 16.77	123.66 ± 9.88
Month 18	126.90 ± 22.33	96.16 ± 5.27	93.20 ± 5.56	94.18 ± 3.06
N-Acetyl-S-(2-cyanopropyl)-L-cysteine (µmol/24 hours)				
Week 2	0.000 ± 0.000	0.000 ± 0.000	0.049 ± 0.016**	0.351 ± 0.055**
Month 3	0.003 ± 0.003	0.030 ± 0.002**	0.224 ± 0.021**	1.488 ± 0.359**
Month 12	0.000 ± 0.000	0.037 ± 0.006**	0.298 ± 0.014**	2.453 ± 0.456**
Month 18	0.000 ± 0.000	0.089 ± 0.012**	0.659 ± 0.053**	3.680 ± 0.155**
N-Acetyl-S-(2-cyanopropyl)-L-cysteine (µmol/mg creatinine)				
Week 2	0.000 ± 0.000	0.000 ± 0.000	0.011 ± 0.004**	0.095 ± 0.015**
Month 3	0.001 ± 0.001	0.007 ± 0.002**	0.041 ± 0.004**	0.253 ± 0.058**
Month 12	0.000 ± 0.000	0.005 ± 0.001**	0.041 ± 0.001**	0.367 ± 0.078**
Month 18	0.000 ± 0.000	0.012 ± 0.002**	0.075 ± 0.008**	0.462 ± 0.016**
N-Acetyl-S-(2-hydroxypropyl)-L-cysteine (µmol/24 hours)				
Week 2	0.002 ± 0.001	0.244 ± 0.028**	0.792 ± 0.076**	2.059 ± 0.233**
Month 3	0.021 ± 0.010	0.824 ± 0.058**	1.728 ± 0.177**	3.477 ± 0.125**
Month 12	0.000 ± 0.000	0.481 ± 0.070**	1.752 ± 0.162**	5.048 ± 0.310**
Month 18	0.000 ± 0.000	0.899 ± 0.101**	3.196 ± 0.294**	5.506 ± 0.241**
N-Acetyl-S-(2-hydroxypropyl)-L-cysteine (µmol/mg creatinine)				
Week 2	0.001 ± 0.000	0.059 ± 0.007**	0.187 ± 0.015**	0.552 ± 0.048**
Month 3	0.004 ± 0.002	0.188 ± 0.042**	0.314 ± 0.028**	0.597 ± 0.030**
Month 12	0.000 ± 0.000	0.073 ± 0.012**	0.242 ± 0.020**	0.749 ± 0.054**
Month 18	0.000 ± 0.000	0.120 ± 0.012**	0.359 ± 0.029**	0.690 ± 0.017**

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

TABLE F2
Urinalysis and Urinary Metabolite Data for Mice in the 2-Year Gavage Study of Methacrylonitrile[a]

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Male				
n				
Week 2	3	5	5	5
Month 3	5	5	5	4
Month 12	4	5	4	5
Month 18	3	5	4	4
Volume (mL/24 hours)				
Week 2	0.6 ± 0.2	0.9 ± 0.2	1.2 ± 0.2	0.5 ± 0.3
Month 3	1.7 ± 0.5	0.8 ± 0.4	0.9 ± 0.2	0.7 ± 0.2
Month 12	2.6 ± 0.5	2.2 ± 0.4	2.3 ± 0.2	1.4 ± 0.2
Month 18	1.8 ± 0.8[b]	1.7 ± 0.4	2.1 ± 0.4	2.0 ± 0.4
Creatinine (mg/dL)				
Week 2	41.10 ± 7.91	37.88 ± 2.03	34.96 ± 4.64	52.24 ± 6.72
Month 3	46.88 ± 7.24	35.58 ± 7.71	38.84 ± 7.31	50.30 ± 8.65
Month 12	27.00 ± 3.60	34.94 ± 4.17	31.00 ± 2.47	39.46 ± 4.09
Month 18	31.93 ± 9.21[b]	32.84 ± 7.15	40.10 ± 11.32	29.98 ± 4.31
N-Acetyl-S-(2-cyanopropyl)-L-cysteine (µmol/24 hours)				
Week 2	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Month 3	0.000 ± 0.000	0.001 ± 0.001	0.002 ± 0.001**	0.004 ± 0.002**
Month 12	0.000 ± 0.000	0.000 ± 0.000	0.002 ± 0.000**	0.005 ± 0.001**
Month 18	0.000 ± 0.000	0.004 ± 0.001*	0.010 ± 0.001**	0.022 ± 0.003**
N-Acetyl-S-(2-cyanopropyl)-L-cysteine (µmol/mg creatinine)				
Week 2	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Month 3	0.000 ± 0.000	0.004 ± 0.002	0.008 ± 0.001**	0.012 ± 0.004**
Month 12	0.000 ± 0.000	0.000 ± 0.000	0.003 ± 0.000**	0.009 ± 0.002**
Month 18	0.000 ± 0.000	0.007 ± 0.001*	0.015 ± 0.002**	0.040 ± 0.001**
N-Acetyl-S-(2-hydroxypropyl)-L-cysteine (µmol/24 hours)				
Week 2	0.001 ± 0.001	0.053 ± 0.008	0.096 ± 0.014**	0.086 ± 0.031
Month 3	0.002 ± 0.001	0.060 ± 0.029*	0.184 ± 0.067**	0.344 ± 0.130**
Month 12	0.000 ± 0.000	0.253 ± 0.039*	0.604 ± 0.014**	0.586 ± 0.064**
Month 18	0.000 ± 0.000	0.206 ± 0.059*	0.665 ± 0.068**	1.147 ± 0.177**
N-Acetyl-S-(2-hydroxypropyl)-L-cysteine (µmol/mg creatinine)				
Week 2	0.006 ± 0.002	0.177 ± 0.024*	0.264 ± 0.043**	0.508 ± 0.142**
Month 3	0.003 ± 0.001	0.206 ± 0.074**	0.546 ± 0.116**	1.040 ± 0.240**
Month 12	0.000 ± 0.000	0.361 ± 0.061*	0.883 ± 0.087**	1.132 ± 0.119**
Month 18	0.001 ± 0.001	0.398 ± 0.075*	0.929 ± 0.138**	2.216 ± 0.361**

TABLE F2
Urinalysis and Urinary Metabolite Data for Mice in the 2-Year Gavage Study of Methacrylonitrile

	Vehicle Control	1.5 mg/kg	3 mg/kg	6 mg/kg
Female				
n				
Week 2	4	3	5	4
Month 3	4	4	2	5
Month 12	5	5	5	5
Month 18	5	4	4	5
Volume (mL/24 hours)				
Week 2	1.3 ± 0.2	1.9 ± 0.5	1.5 ± 0.2	1.5 ± 0.4
Month 3	2.4 ± 0.5	1.4 ± 0.1*	1.7 ± 0.3	1.6 ± 0.2
Month 12	2.1 ± 0.2	1.5 ± 0.3	2.2 ± 0.4	1.6 ± 0.3
Month 18	2.1 ± 0.5	2.1 ± 0.2	2.2 ± 0.2	1.8 ± 0.4
Creatinine (mg/dL)				
Week 2	43.53 ± 0.39	36.53 ± 6.17	42.22 ± 1.32	36.88 ± 3.81
Month 3	32.20 ± 7.19	48.05 ± 3.29	39.50 ± 7.90	46.92 ± 4.41
Month 12	23.22 ± 2.86	25.48 ± 3.50	21.38 ± 2.22	24.42 ± 3.36
Month 18	19.88 ± 1.22	22.70 ± 0.83	20.68 ± 1.20	23.84 ± 3.27
N-Acetyl-S-(2-cyanopropyl)-L-cysteine (µmol/24 hours)				
Week 2	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.001 ± 0.000
Month 3	0.000 ± 0.000	0.003 ± 0.000*	0.005 ± 0.000**	0.013 ± 0.002**
Month 12	0.000 ± 0.000	0.001 ± 0.001*	0.005 ± 0.000**	0.017 ± 0.003**
Month 18	0.000 ± 0.000	0.008 ± 0.001**	0.014 ± 0.001**	0.028 ± 0.005**
N-Acetyl-S-(2-cyanopropyl)-L-cysteine (µmol/mg creatinine)				
Week 2	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.001 ± 0.001
Month 3	0.000 ± 0.000	0.005 ± 0.001*	0.008 ± 0.000**	0.018 ± 0.003**
Month 12	0.000 ± 0.000	0.004 ± 0.001*	0.015 ± 0.005**	0.046 ± 0.008**
Month 18	0.000 ± 0.000	0.017 ± 0.001**	0.032 ± 0.004**	0.071 ± 0.007**
N-Acetyl-S-(2-hydroxypropyl)-L-cysteine (µmol/24 hours)				
Week 2	0.003 ± 0.001	0.064 ± 0.020*	0.124 ± 0.020**	0.220 ± 0.023**
Month 3	0.008 ± 0.005	0.230 ± 0.031*	0.309 ± 0.024*	0.705 ± 0.082**
Month 12	0.000 ± 0.000	0.155 ± 0.021**	0.457 ± 0.082**	0.702 ± 0.119**
Month 18	0.000 ± 0.000	0.330 ± 0.014**	0.691 ± 0.019**	0.944 ± 0.123**
N-Acetyl-S-(2-hydroxypropyl)-L-cysteine (µmol/mg creatinine)				
Week 2	0.006 ± 0.001	0.096 ± 0.020*	0.188 ± 0.018**	0.425 ± 0.034**
Month 3	0.012 ± 0.006	0.363 ± 0.070*	0.479 ± 0.049*	0.973 ± 0.085**
Month 12	0.000 ± 0.000	0.450 ± 0.046**	1.072 ± 0.151**	1.920 ± 0.253**
Month 18	0.000 ± 0.000	0.726 ± 0.061**	1.567 ± 0.046**	2.480 ± 0.248**

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=4

APPENDIX G
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

Procurement and Characterization of Methacrylonitrile

Methacrylonitrile was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (00427ET) and used during the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory (Radian Corporation, Austin, TX) and the study laboratory. Reports on analyses performed in support of the methacrylonitrile studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a colorless liquid, was identified as methacrylonitrile by the analytical chemistry laboratory using infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy and gas chromatography/mass spectrometry (system A, Table G1) and confirmed by the study laboratory using infrared spectroscopy. All spectra were consistent with the literature spectra (*Sadtler Standard Spectra*; API, 1974; *NBS75K Spectral Library*) and with the structure of methacrylonitrile. The infrared and nuclear magnetic resonance spectra are presented in Figures G1 and G2.

The purity of lot 00427ET was determined by the analytical chemistry laboratory using Karl Fischer water analysis and gas chromatography with systems B and C. The study laboratory used gas chromatography with system D and *n*-butanol added as an internal standard to compare samples of lot 00427ET with a frozen reference sample received from the analytical chemistry laboratory.

Karl Fischer water analysis indicated 0.19% water. Gas chromatography indicated one major peak and one impurity with an area of 0.03% (system B) or 0.04% (system C) of the total area. Results obtained by the study laboratory indicated that the samples of lot 00427ET had a purity of 100.4% relative to the frozen reference sample. The overall purity was determined to be greater than 99%.

Accelerated stability studies of the bulk chemical were conducted by the analytical chemistry laboratory using gas chromatography (system B) to evaluate the potential for degradation during storage over the course of the study. No degradation of the bulk chemical was observed after storage for 14 days at 60° C. The bulk chemical was stored at room temperature, protected from light, in amber glass bottles in metal cans. Stability was monitored during the 2-year studies with gas chromatography (system D). No degradation of the bulk chemical was detected during the studies.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared every 4 weeks through 3 January 1996 and every 2 weeks thereafter by mixing methacrylonitrile with deionized water (Table G2). The dose formulations were stored initially at room temperature in amber glass bottles with Teflon-lined lids for up to 35 days. After 17 November 1995, dose formulations were stored at approximately 5° C in amber glass bottles with Teflon-lined septa that were sealed with metal crimp tops for up to 35 days.

Stability studies of a 0.15 mg/mL dose formulation were performed by the study laboratory using gas chromatography. Stability of dose formulations was confirmed for at least 35 days. However, the individual values obtained in these analyses had a higher-than-normal variability, and it was determined that the ethyl acetate internal standard decomposed under the conditions of the analysis.

Periodic analyses of the dose formulations of methacrylonitrile were conducted approximately every 8 to 12 weeks by the study laboratory using gas chromatography with system D or E (Table G3). All 36 dose formulations analyzed for rats were within 10% of the target concentrations; 5 of 12 animal room samples were within 10% of the target concentrations. For mice, 35 of 36 dose formulations analyzed were within 10% of the target concentrations; one dose formulation that was 112% of the target concentration was mistakenly used for dosing. One of twelve animal room samples for mice was within 10% of the target concentration. Analysis of postadministration dosing solutions showed declines in methacrylonitrile concentrations that were attributed to volatilization. Typically, losses were greater in mouse dosing solutions than in rat dosing solutions. Efforts to minimize headspace in dosing bottles as well as the use of crimp-top dosing bottles with septa decreased losses but did not eliminate them completely.

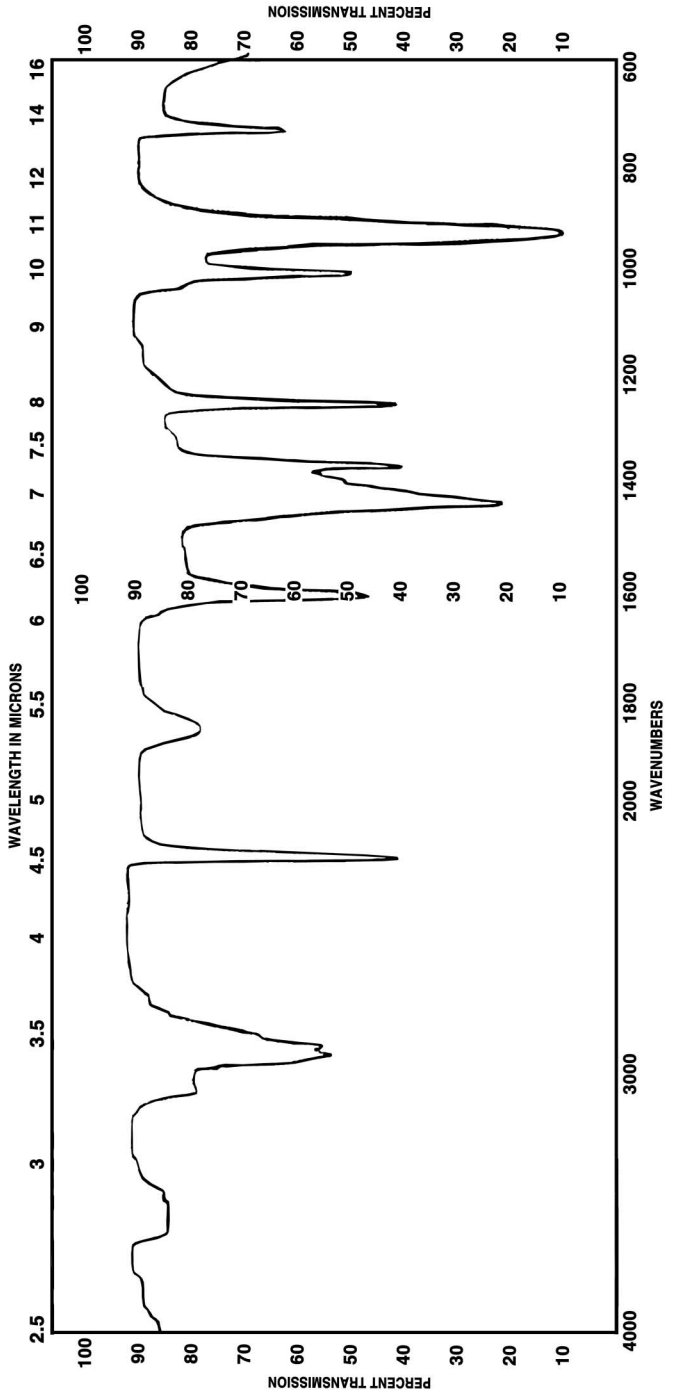

Figure G1
Infrared Absorption Spectrum of Methacrylonitrile

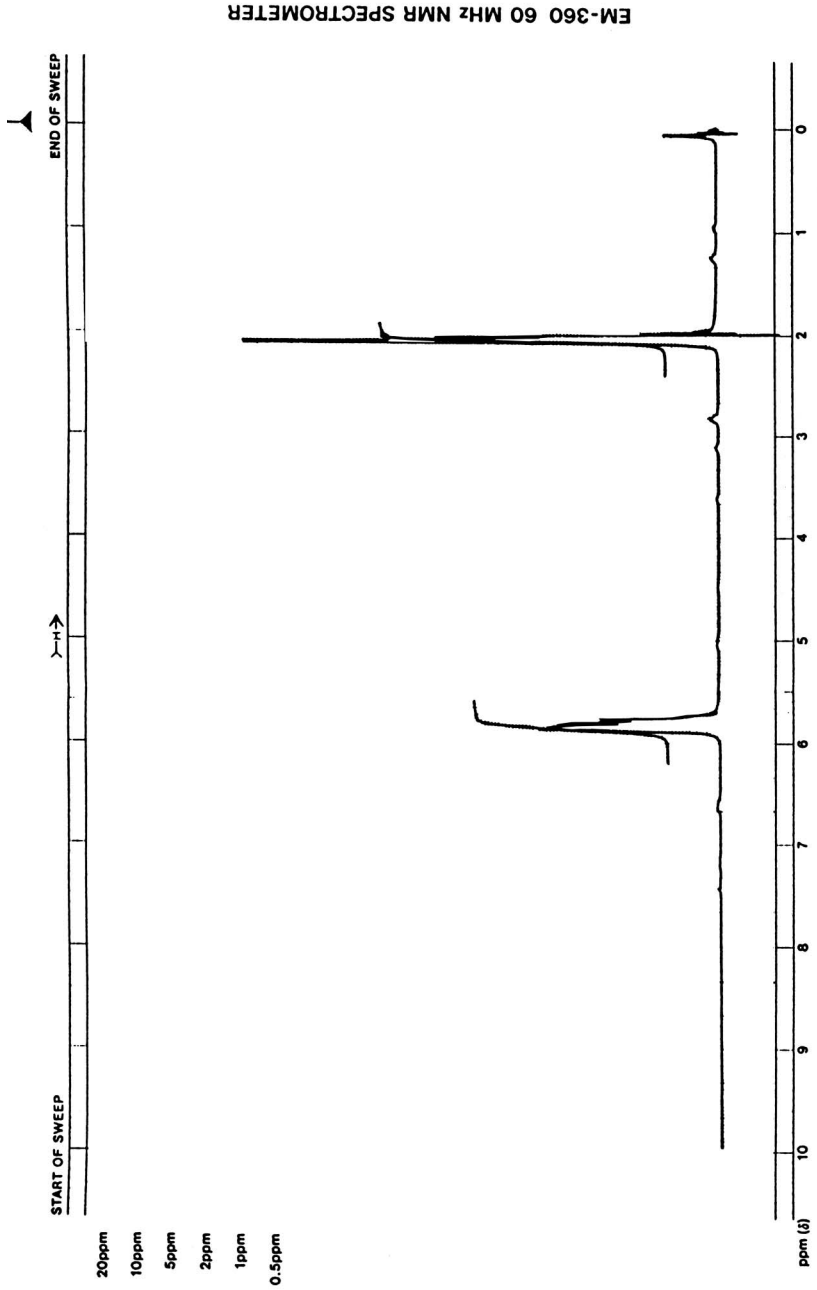

FIGURE G2
Nuclear Magnetic Resonance Spectrum of Methacrylonitrile

TABLE G1
Gas Chromatography Systems Used in the 2-Year Gavage Studies of Methacrylonitrile[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A			
Mass spectrometry	DB-1, 60 m × 0.32 mm (J&W Scientific)	Helium at 1 mL/minute	10° C for 3 minutes, then 10° C/minute to 300° C
System B			
Flame ionization	DB-17, 30 m × 0.53 mm (J&W Scientific)	Helium at 3.33 mL/minute	40° C for 5 minutes, then 10° C/minute to 90° C
System C			
Flame ionization	DB-624, 30 m × 0.53 mm (J&W Scientific)	Helium at 4.0 mL/minute	40° C for 3 minutes, then 10° C/minute to 90° C, held 2 minutes
System D			
Flame ionization	1% SP1000 on 60/80 Carbopack B, 2.4 m × 2 mm	Helium at 10 mL/minute	Isothermal at 150° C
System E			
Flame ionization	1% SP1000 on 60/80 Carbopack B, 2.4 m × 2 mm	Nitrogen at 20 mL/minute	Isothermal at 150° C

[a] Gas chromatographs were manufactured by Hewlett Packard (Palo Alto, CA) (system A) and Varian, Inc. (Palo Alto, CA) (systems B and C).

TABLE G2
Preparation and Storage of Dose Formulations in the 2-Year Gavage Studies of Methacrylonitrile

Preparation
Methacrylonitrile was added to deionized water and mixed by shaking or stirring. The doses were prepared every 4 weeks through 3 January 1996 and every 2 weeks thereafter.

Chemical Lot Number
00427ET

Maximum Storage Time
35 days

Storage Conditions
Initially stored in amber glass bottles with Teflon-lined lids at room temperature; after 17 November 1995, stored at approximately 5° C in amber glass bottles with Teflon-lined septa sealed with metal crimp tops

Study Laboratory
Battelle Columbus Operations
(Columbus, OH)

TABLE G3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Methacrylonitrile

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats				
13 October 1995	14 October 1995	0.6	0.6029	0
		2	2.114	+6
		6	6.422	+7
	16-17 November 1995[b]	0.6	0.5331	–11
		2	1.040	–48
		6	3.939	–34
5 December 1995	5 December 1995	0.6	0.5884	–2
		2	1.809	–10
		6	5.500	–8
30 January 1996	31 January 1996	0.6	0.5541	–8
		2	1.814	–9
		6	5.821	–3
23 April 1996	25 April 1996	0.6	0.6152	+3
		2	1.954	–2
		6	6.085	+1
	15 May 1995[b]	0.6	0.5651	–6
		2	1.824	–9
		6	5.512	–8
18 June 1996	19-20 June 1996	0.6	0.5778	–4
		2	2.002	0
		6	5.785	–4
13 August 1996	14 August 1996	0.6	0.5843	–3
		2	2.015	+1
		6	5.957	–1
5 November 1996	7-8 November 1996	0.6	0.5927	–1
		2	2.044	+2
		6	6.105	+2
	25 November 1996[b]	0.6	0.5000	–17
		2	1.822	–9
		6	5.481	–9
30 December 1996	2 January 1997	0.6	0.6060	+1
		2	2.018	+1
		6	5.964	–1
25 February 1997	25-26 February 1997	0.6	0.5894	–2
		2	2.057	+3
		6	6.129	+2

TABLE G3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Methacrylonitrile

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Rats (continued)				
20 May 1997	22 May 1997	0.6	0.5500	–8
		2	1.901	–5
		6	5.943	–1
	12-13 June 1997[b]	0.6	0.4805	–20
		2	1.665	–17
		6	5.179	–14
15 July 1997	16 July 1997	0.6	0.6430	+7
		2	1.944	–3
		6	5.960	–1
9 September 1997	12 September 1997	0.6	0.6311	+5
		2	1.928	–4
		6	5.799	–3
Mice				
13 October 1995	14 October 1995	0.15	0.1517	+1
		0.3	0.3216	+7
		0.6	0.6191	+3
	16-17 November 1995[b]	0.15	0.0810	–46
		0.3	0.1417	–53
		0.6	0.2413	–60
5 December 1995	5 December 1995	0.15	0.1581	+5
		0.3	0.2834	–6
		0.6	0.5820	–3
30 January 1996	31 January 1996	0.15	0.1373	–8
		0.3	0.06223[c]	–79
		0.6	0.5507	–8
1 February 1996	1 February 1996	0.3	0.2797[d]	–7
23 April 1996	25 April 1996	0.15	0.1446	–4
		0.3	0.3201	+7
		0.6	0.6201	+3
	15 May 1996[b]	0.15	0.1099	–27
		0.3	0.2487	–17
		0.6	0.4814	–20

TABLE G3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Methacrylonitrile

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)				
18 June 1996	19-20 June 1996	0.15	0.1561	+4
		0.3	0.3084	+3
		0.6	0.6096	+2
13 August 1996	14 August 1996	0.15	0.1682	+12
		0.3	0.3235	+8
		0.6	0.6376	+6
5 November 1996	7-8 November 1996	0.15	0.1523	+2
		0.3	0.3012	0
		0.6	0.6110	+2
	25 November 1996[b]	0.15	0.1144	–24
		0.3	0.2380	–21
		0.6	0.5599	–7
30 December 1996	2 January 1997	0.15	0.1486	–1
		0.3	0.3087	+3
		0.6	0.6217	+4
25 February 1997	25-26 February 1997	0.15	0.1488	–1
		0.3	0.2959	–1
		0.6	0.6186	+3
20 May 1997	22 May 1997	0.15	0.1428	–5
		0.3	0.2944	–2
		0.6	0.5874	–2
	12-13 June 1997[b]	0.15	0.06215	–59
		0.3	0.1877	–37
		0.6	0.3237	–46
15 July 1997	16 July 1997	0.15	0.1493	0
		0.3	0.3024	+1
		0.6	0.6000	0
9 September 1997	12 September 1997	0.15	0.1484	–1
		0.3	0.2890	–4
		0.6	0.6033	+1

[a] Results of duplicate analyses. Dosing volume for rats=5 mL/kg; 0.6 mg/mL=3 mg/kg, 2 mg/mL=10 mg/kg, 6 mg/mL=30 mg/kg. Dosing volume for mice=10 mL/kg; 0.15 mg/mL=1.5 mg/kg, 0.3 mg/mL=3 mg/kg, 0.6 mg/mL=6 mg/kg
[b] Animal room samples
[c] Remixed; not used in study
[d] Results of remix

APPENDIX H
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NTP-2000 RAT AND MOUSE RATION

TABLE H1
Ingredients of NTP-2000 Rat and Mouse Ration

Ingredients	Percent by Weight
Ground hard winter wheat	22.26
Ground #2 yellow shelled corn	22.18
Wheat middlings	15.0
Oat hulls	8.5
Alfalfa meal (dehydrated, 17% protein)	7.5
Purified cellulose	5.5
Soybean meal (49% protein)	5.0
Fish meal (60% protein)	4.0
Corn oil (without preservatives)	3.0
Soy oil (without preservatives)	3.0
Dried brewer's yeast	1.0
Calcium carbonate (USP)	0.9
Vitamin premix[a]	0.5
Mineral premix[b]	0.5
Calcium phosphate, dibasic (USP)	0.4
Sodium chloride	0.3
Choline chloride (70% choline)	0.26
Methionine	0.2

[a] Wheat middlings as carrier
[b] Calcium carbonate as carrier

TABLE H2
Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	4,000 IU	Stabilized vitamin A palmitate or acetate
D	1,000 IU	D-activated animal sterol
K	1.0 mg	Menadione sodium bisulfite complex
α-Tocopheryl acetate	100 IU	
Niacin	23 mg	
Folic acid	1.1 mg	
d-Pantothenic acid	10 mg	*d*-Calcium pantothenate
Riboflavin	3.3 mg	
Thiamine	4 mg	Thiamine mononitrate
B_{12}	52 µg	
Pyridoxine	6.3 mg	Pyridoxine hydrochloride
Biotin	0.2 mg	*d*-Biotin
Minerals		
Magnesium	514 mg	Magnesium oxide
Iron	35 mg	Iron sulfate
Zinc	12 mg	Zinc oxide
Manganese	10 mg	Manganese oxide
Copper	2.0 mg	Copper sulfate
Iodine	0.2 mg	Calcium iodate
Chromium	0.2 mg	Chromium acetate

[a] Per kg of finished product

TABLE H3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	13.7 ± 0.70	12.7 – 16.2	23
Crude fat (% by weight)	8.1 ± 0.32	7.5 – 8.7	23
Crude fiber (% by weight)	9.5 ± 0.60	7.8 – 10.3	23
Ash (% by weight)	5.0 ± 0.16	4.8 – 5.4	23
Amino Acids (% of total diet)			
Arginine	0.732 ± 0.050	0.670 – 0.800	6
Cystine	0.220 ± 0.011	0.210 – 0.240	6
Glycine	0.683 ± 0.048	0.620 – 0.740	6
Histidine	0.333 ± 0.020	0.310 – 0.350	6
Isoleucine	0.522 ± 0.054	0.430 – 0.590	6
Leucine	1.065 ± 0.070	0.960 – 1.130	6
Lysine	0.705 ± 0.066	0.620 – 0.790	6
Methionine	0.402 ± 0.042	0.350 – 0.460	6
Phenylalanine	0.600 ± 0.042	0.540 – 0.640	6
Threonine	0.512 ± 0.056	0.430 – 0.590	6
Tryptophan	0.125 ± 0.015	0.110 – 0.150	6
Tyrosine	0.410 ± 0.037	0.360 – 0.460	6
Valine	0.628 ± 0.052	0.550 – 0.690	6
Essential Fatty Acids (% of total diet)			
Linoleic	3.98 ± 0.325	3.59 – 4.54	6
Linolenic	0.30 ± 0.048	0.21 – 0.35	6
Vitamins			
Vitamin A (IU/kg)	4,761 ± 1,411	2,780 – 8,140	23
Vitamin D (IU/kg)	1,000[a]		
α -Tocopherol (ppm)	77.2 ± 10.94	62.2 – 87.1	6
Thiamine (ppm)[b]	8.8 ± 2.07	6.0 – 15.0	23
Riboflavin (ppm)	5.6 ± 1.24	4.20 – 7.70	6
Niacin (ppm)	73.1 ± 4.13	66.4 – 78.8	6
Pantothenic acid (ppm)	24.2 ± 2.92	21.4 – 29.1	6
Pyridoxine (ppm)[b]	9.37 ± 2.50	6.7 – 12.4	6
Folic acid (ppm)	1.70 ± 0.43	1.26 – 2.32	6
Biotin (ppm)	0.349 ± 0.18	0.225 – 0.704	6
Vitamin B_{12} (ppb)	83.4 ± 67.1	30.0 – 174.0	6
Choline (ppm)	3,082 ± 232	2,700 – 3,400	6
Minerals			
Calcium (%)	0.961 ± 0.046	0.858 – 1.050	23
Phosphorus (%)	0.575 ± 0.023	0.547 – 0.640	23
Potassium (%)	6.660 ± 0.026	0.627 – 0.691	6
Chloride (%)	0.356 ± 0.031	0.300 – 0.392	6
Sodium (%)	0.193 ± 0.020	0.160 – 0.212	6
Magnesium (%)	0.197 ± 0.010	0.185 – 0.213	6
Sulfur (%)	0.182 ± 0.023	0.153 – 0.209	6
Iron (ppm)	158 ± 15.2	135 – 173	6
Manganese (ppm)	51.8 ± 4.05	46.2 – 56.0	6
Zinc (ppm)	53.2 ± 5.68	45.0 – 61.1	6
Copper (ppm)	6.49 ± 0.786	5.38 – 7.59	6
Iodine (ppm)	0.487 ± 0.204	0.233 – 0.843	6
Chromium (ppm)	0.763 ± 0.620	0.330 – 2.000	6
Cobalt (ppm)	0.53 ± 0.720	0.20 – 2.0	6

[a] From formulation
[b] As hydrochloride

TABLE H4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.26 ± 0.12	0.10 – 0.50	23
Cadmium (ppm)	0.05 ± 0.01	0.04 – 0.10	23
Lead (ppm)	0.13 ± 0.10	0.06 – 0.40	23
Mercury (ppm)	<0.02		23
Selenium (ppm)	0.17 ± 0.04	0.10 – 0.26	23
Aflatoxins (ppb)	<5.00		23
Nitrate nitrogen (ppm)[c]	14.2 ± 5.84	6.5 – 31.9	23
Nitrite nitrogen (ppm)[c]	0.84 ± 0.66	0.30 – 3.20	23
BHA (ppm)[d]	1.2 ± 0.67	0.01 – 3.50	23
BHT (ppm)[d]	1.0 ± 0.48	0.01 – 2.29	23
Aerobic plate count (CFU/g)[e]	116,380 ± 294,032	15,000 – 1,000,000	8
Coliform (MPN/g)[e]	11 ± 8	3 – 30	8
Escherichia coli (MPN/g)	<10		23
Salmonella (MPN/g)	Negative		23
Total nitrosoamines (ppb)[f]	5.9 ± 4.05	2.1 – 20.9	23
N-Nitrosodimethylamine (ppb)[f]	3.0 ± 2.17	1.0 – 7.2	23
N-Nitrosopyrrolidine (ppb)[f]	2.9 ± 2.73	1.0 – 14.5	23
Pesticides (ppm)			
α -BHC	<0.01		23
β -BHC	<0.02		23
γ -BHC	<0.01		23
δ -BHC	<0.01		23
Heptachlor	<0.01		23
Aldrin	<0.01		23
Heptachlor epoxide	<0.01		23
DDE	<0.01		23
DDD	<0.01		23
DDT	<0.01		23
HCB	<0.01		23
Mirex	<0.01		23
Methoxychlor	<0.05		23
Dieldrin	<0.01		23
Endrin	<0.01		23
Telodrin	<0.01		23
Chlordane	<0.05		23
Toxaphene	<0.10		23
Estimated PCBs	<0.20		23
Ronnel	<0.01		23
Ethion	<0.02		23
Trithion	<0.05		23
Diazinon	<0.10		23
Methyl chlorpyrifos	0.058 ± 0.054	0.010 – 0.200	22
Methyl parathion	<0.02		23
Ethyl parathion	<0.02		23
Malathion	0.161 ± 0.201	0.020 – 0.830	23
Endosulfan I	<0.01		23
Endosulfan II	<0.01		23
Endosulfan sulfate	<0.03		23

[a] CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] Fifteen of 23 lots produced from May 1996 to August 1997 were irradiated; microbial counts for irradiated lots were below the detection limit. Remaining lots were not irradiated.
[f] All values were corrected for percent recovery.

APPENDIX I
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

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

Method and Test	Time of Analysis
RATS	
ELISA	
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	1, 6, 12, and 18 months, study termination
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
Mycoplasma arthritidis	Study termination
Parvovirus	12 months and study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	1, 6, 12, and 18 months
KRV (Kilham rat virus)	1, 6, 12, and 18 months
MICE	
ELISA	
Ectromelia virus	1, 6, 12, and 18 months, study termination
EDIM (epizootic diarrhea of infant mice)	1, 6, 12, and 18 months, study termination
GDVII (mouse encephalomyelitis virus)	1, 6, 12, and 18 months, study termination
LCM (lymphocytic choriomeningitis virus)	1, 6, 12, and 18 months, study termination
Mouse adenoma virus-FL	1, 6, 12, and 18 months, study termination
MHV (mouse hepatitis virus)	1, 6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	1, 6, 12, and 18 months, study termination
Reovirus 3	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination

Method and Test	Time of Analysis
MICE (continued)	
Immunofluorescence Assay	
LCM	12 months
MCMV (mouse cytomegalovirus)	Study termination
M. arthritidis	Study termination
Parvovirus	Study termination
Reovirus 3	6 months
Hemagglutination Inhibition	
K (papovavirus)	1, 6, 12, and 18 months
MVM (minute virus of mice)	1, 6, 12, and 18 months
Polyoma virus	1, 6, 12, and 18 months

RESULTS

All test results were negative.