NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 389

TOXICOLOGY AND CARCINOGENESIS STUDIES OF SODIUM AZIDE

(CAS NO. 26628-22-8)

IN F344/N RATS

(GAVAGE STUDIES)

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

FOREWORD

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

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

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the 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. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF SODIUM AZIDE

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IN F344/N RATS

(GAVAGE STUDIES)

NATIONAL TOXICOLOGY PROGRAM
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CONTRIBUTORS

National Toxicology Program

K.M. Abdo, Ph.D.
C.J. Alden, Ph.D.
G.A. Boorman, D.V.M., Ph.D.
D.W. Bristol, Ph.D.
S.L. Eustis, D.V.M., Ph.D.
R.A. Griesemer, D.V.M., Ph.D.
J.K. Haseman, Ph.D.
C.W. Jameson, Ph.D.
M.P. Jokinen, D.V.M.
G.N. Rao, D.V.M., Ph.D.
K.L. Witt, M.S., Oak Ridge Associated Universities

Biotechnical Services, Inc.

Prepared Technical Report

L.G. Cockerham, Ph.D., Principal Investigator
G.F. Corley, D.V.M.
J.L. Elledge, B.A.
J.A. Gregan, M.A.

Microbiological Laboratory Associates

Conducted studies, evaluated tissues

M. Dinowitz, Sc.D., Principal Investigator
K. Kanagalingam, Ph.D.
G.A. Parker, D.V.M.

NTP Pathology Working Group

Evaluated slides, prepared pathology report (21 March 1989)

S. Grumbein, D.V.M., Ph.D., Chair
Pathology Associates, Inc.
R. Cattley, V.M.D., Ph.D.
North Carolina State University
B. Hamilton, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
J.R. Leininger, D.V.M., Ph.D.
National Toxicology Program
M.M. McDonald, D.V.M., Ph.D.
National Toxicology Program
K. Morgan, B.V.Sc., M.R.C.V.S., Ph.D.
Chemical Industry Institute of Toxicology
H. Solleveld, D.V.M., Ph.D.
SmithKline French

Integrated Laboratory Systems

Prepared quality assurance audits

J.C. Bhandari, D.V.M., Ph.D., Principal Investigator

Experimental Pathology Laboratories, Inc.

Prepared pathology quality assessment

J.F. Hardisty, D.V.M., Principal Investigator
B.F. Hamilton, D.V.M., Ph.D.

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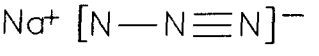
ABSTRACT



SODIUM AZIDE

CAS No. 26628-22-8

Chemical Formula: NaN_3 Molecular Weight: 65.02

Synonyms: Azide, Azium, Smite

Sodium azide is a white crystalline solid used in the manufacture of the explosive lead azide. It is the principal chemical used to generate nitrogen gas in automobile safety airbags and airplane escape chutes and is a broad-spectrum biocide used in both research and agriculture.

Toxicology and carcinogenicity studies were conducted by administering sodium azide (greater than 99% pure) in distilled water by gavage to groups of male and female F344/N rats once daily, 5 days per week for 14 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and Chinese hamster ovary cells.

14-Day Studies
Rats received 0, 5, 10, 20, 40, or 80 mg/kg sodium azide. All male and female rats receiving 40 or 80 mg/kg and two of five female rats receiving 20 mg/kg died during the first week of the studies. Clinical findings of toxicity included lethargy and inactivity. No grossly observable lesions were present in any of the dose groups.

13-Week Studies
Rats received 0, 1.25, 2.5, 5, 10, or 20 mg/kg sodium azide. Seven of 9 males and all 10 females receiving 20 mg/kg died before the end of the studies. Final mean body weights of treated rats were within 10% of those of the controls. Compound-related clinical findings of toxicity in the 20 mg/kg dose groups included lethargy and labored breathing. Histopathologic lesions induced by sodium azide were limited to the brain (necrosis of the cerebrum and thalamus) and lung (congestion, hemorrhage, and edema), and were observed in rats receiving 20 mg/kg that died during the studies.

Body Weights, Feed Consumption, and Survival in the 2-Year Studies
Because compound-related deaths were observed in the groups receiving 20 mg/kg in the 13-week studies, lower dose levels were used in the 2-year studies. Two-year studies were conducted by administering 0, 5, or 10 mg/kg sodium azide to groups of 60 male and 60 female rats. Dose-related depression in mean body weight was observed throughout the study period. Mean feed consumption values in low- and high-dose groups were lower than control values. Survival of high-dose rats of each sex was significantly ($P<0.05$) lower than controls (males-control, 24/60; low-dose, 27/60; high-dose, 9/60; females-37/60; 43/60; 21/59). The reduced survival was attributed to brain necrosis and cardiovascular collapse induced by sodium azide.

Neoplastic and Nonneoplastic Effects in the 2-Year Studies
There were no compound-related increases in incidences of neoplasms in rats. Significantly decreased incidences were observed for certain neoplasms, including mononuclear cell leukemia in male rats (control, 33/60; low-dose, 28/60; high-

dose, 14/60), adrenal gland pheochromocytoma in male rats (26/55; 16/56; 6/54), mammary gland fibroadenoma in female rats (20/60; 11/60; 8/59), and pituitary gland neoplasms in female rats (37/60; 28/60; 17/59). These decreases reflected to some extent, but could not be attributed solely to, the reduced survival of the high-dose groups. Compound-related nonneoplastic brain lesions (necrosis of the cerebrum and thalamus) were observed at significantly ($P<0.001$) increased incidences in high-dose male and female rats. The increased incidence of lung congestion observed in this dose group was considered due to cardiovascular collapse secondary to brain necrosis.

Genetic Toxicology

Sodium azide was mutagenic in *Salmonella typhimurium* strains TA100 and TA1535, with or without exogenous metabolic activation (S9); it was not mutagenic in strain TA1537 or TA98. In cytogenetic tests with Chinese hamster ovary cells, sodium azide induced sister chromatid exchanges, but not chromosomal aberrations, in the presence and the absence of S9.

Conclusions

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of sodium azide in male or female F344/N rats administered 5 or 10 mg/kg.

Sodium azide induced necrosis in the cerebrum and the thalamus of the brain in both male and female rats.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 7. A summary of peer review comments and public discussion on this Technical Report appears on page 9.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Sodium Azide

Variable	Male F344/N Rats	Female F344/N Rats
Doses	0, 5, or 10 mg/kg in water by gavage, 5 days per week	0, 5, or 10 mg/kg in water by gavage, 5 days per week
Body weights	Dosed groups lower than controls	Dosed groups lower than controls
2-Year survival rates	24/60, 27/60, 9/60	37/60, 43/60, 21/59
Nonneoplastic effects	Brain: cerebral necrosis (0/60, 1/60, 24/60); thalamic necrosis (0/60, 1/60, 25/60); Lung: pulmonary congestion (6/60, 4/60, 30/60); pulmony hemorrhage (4/60, 5/60, 17/60)	Brain: cerebral necrosis (0/60, 1/60, 33/58); thalamic necrosis (0/60, 0/60, 21/58); Lung: pulmonary congestion (6/60, 3/60, 21/59)
Neoplastic effects	None attributed to sodium azide	None attributed to sodium azide
Level of evidence of carcinogenic activity	No evidence	No evidence
Genetic toxicology		
Salmonella typhimurium gene mutation:	Positive with or without S9 in strains TA100 and TA1535; negative with or without S9 in strains TA1537 or TA98	
Sister chromatid exchanges Chinese hamster ovary cells *in vitro*:	Positive with or without S9	
Chromosomal aberrations Chinese hamster ovary cells *in vitro*:	Negative with or without S9	

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 chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. 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.

TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on sodium azide on April 25, 1990, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members have five major responsibilities in reviewing NTP studies:

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

Michael A. Gallo, Ph.D., Chair
Department of Environmental and Community Medicine
UMDNJ-Rutgers Medical School
Piscataway, NJ

John Ashby, Ph.D., Principal Reviewer
Central Toxicology Laboratory
Imperial Chemical Industries, PLC
Alderly Park, England

Gary P. Carlson, Ph.D., Principal Reviewer
Department of Pharmacology and Toxicology
Purdue University
West Lafayette, IN

Harold Davis, D.V.M., Ph.D., Principal Reviewer
School of Aerospace Medicine
Brooks Air Force Base, TX

Robert H. Garman, D.V.M.
Consultants in Veterinary Pathology
Murrysville, PA

Lois Swirsky Gold, Ph.D.
Lawrence Berkeley Laboratory
University of California
Berkeley, CA

Jay I. Goodman, Ph.D.
Department of Pharmacology and Toxicology
Michigan State University
East Lansing, MI

David W. Hayden, D.V.M., Ph.D.
Department of Veterinary Pathobiology
College of Veterinary Medicine
University of Minnesota
St. Paul, MN

Curtis D. Klaassen, Ph.D.*
Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City, KS

Daniel S. Longnecker, M.D.
Department of Pathology
Dartmouth Medical School
Hanover, NH

Barbara McKnight, Ph.D.
Department of Biostatistics
University of Washington
Seattle, WA

Ellen K. Silbergeld, Ph.D.*
University of Maryland Medical School
Baltimore, MD
Environmental Defense Fund
Washington, DC

Lauren Zeise, Ph.D.
California Department of Health Services/RCHAS
Berkeley, CA

* did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On April 25, 1990, the draft Technical Report on the toxicology and carcinogenesis studies of sodium azide received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Committee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle, Park, NC.

Dr. K.M. Abdo, NIEHS, introduced the toxicology and carcinogenesis studies of sodium azide by discussing chemical uses and describing the experimental design, survival and body weight changes, and the only compound-related lesions, nonneoplastic brain lesions in male and female rats. The proposed conclusions were *no evidence of carcinogenic activity* in male or female rats.

Dr. Ashby, a principal reviewer, agreed with the conclusions. However, he questioned why only rats were studied, and thought the use of only one species along with the poor survival in high-dose groups made this a less useful reference non-carcinogen than most. Dr. Abdo said NTP made the decision to use rats only in the 2-year studies after 14-day and 13-week studies in mice showed minimal tissue pathology. Dr. Ashby said that the low dose probably was the maximum tolerated dose (MTD) and this probably compensated for the poor survival at the high dose.

Dr. Davis, the second principal reviewer, agreed with the conclusions. His major concern was the difficulty in assessing carcinogenic activity because the MTD was exceeded in the high-dose groups and there were few lesions in the low-dose groups. He commented on the observation that the severity of brain lesions ranged from acute to chronic. Dr. M. Jokinen, NIEHS, said that both acute and chronic lesions were often seen in the same animal. Dr. Carlson noted that in other studies with chemicals that produce similar types of brain lesions, no animals had both acute and chronic lesions. Usually, those animals with acute lesions died from the lesions.

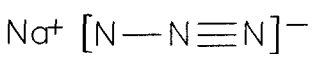
Dr. Carlson, the third principal reviewer, agreed with the conclusions. He thought the doses chosen appeared to have been appropriate and concluded that the study was adequate because the survival at 90 weeks in the high-dose groups was 60% or higher and the low dose was probably close to the MTD. Dr. Carlson asked for a more detailed explanation of the comment that decreased incidences of some neoplasms "reflected to some extent, but could not be solely attributed to, the reduced survival of the high-dose group."

Dr. Silbergeld also had submitted a written review which Dr. L. Hart, NIEHS, read in her absence. Dr. Silbergeld did not agree with the conclusions. Rather, she thought the correct interpretation was that of an *inadequate study of carcinogenic activity* based primarily on a very high rate of mortality in all animal groups and a high incidence of tumors, particularly leukemias, in controls. Dr. Abdo responded that in his judgment there were sufficient numbers of surviving animals in dose groups at 90 weeks to detect a carcinogenic effect had there been one. Further, he commented that there has been a general trend for reduced survival in NTP control animals over the past several years and the survival in the sodium azide study animals was within the range of survival for control animals in contemporary NTP feed or water gavage studies. Dr. J. Haseman, NIEHS, noted that higher rates of leukemia in the more recent control groups were partly responsible for the lower survival rates.

There was considerable discussion about the gavage deaths in the high-dose groups and whether they were due to accidents or at least in part whether they may have been secondary to the brain toxicity. Dr. Gold wondered about the adequacy of the study for detecting an effect when there was such poor survival compounded by the gavage deaths in high-dose groups. Dr. McKnight requested a parallel survival analysis included which does not censor the gavage deaths but rather counts them as true deaths. Dr. Haseman said a revised survival curve would be added. Dr. S. Eustis, NIEHS, stated that the acceptable survival rates of high-dose groups at 90 weeks and the absence of carcinogenic activity in low-dose groups supported the adequacy of the studies.

Dr. Ashby moved that the Technical Report on sodium azide be accepted with the revisions discussed and the conclusions as written for male and female rats, *no evidence of carcinogenic activity.* Dr. Carlson seconded the motion, which was accepted by nine votes to one (Dr. Gold).

INTRODUCTION



SODIUM AZIDE

CAS No. 26628-22-8

Chemical Formula: NaN_3 Molecular Weight: 65.02

Synonyms: Azide, Azium, Smite

PHYSICAL AND CHEMICAL PROPERTIES, PRODUCTION, AND USE

Sodium azide, a white crystalline solid, is prepared by reacting sodium metal and liquid ammonia in the presence of ferric chloride as catalyst and treating the resulting amide with nitrous oxide under pressure (*Herbicide Handbook*, 1979). Sodium azide crystals have a density of 1.845 and decompose upon heating to sodium and nitrogen. Sodium azide is highly soluble in water, alcohol, and liquid ammonia and is insoluble in ether (*The Merck Index*, 1983).

No information was available on the commercial production of sodium azide in the United States. However, in 1966 approximately 45,000 kg of this chemical was consumed in the U.S. (Reichle, 1966), and in 1977 nearly 9,000 kg was imported into the U.S. No recent import data were available (NLM Toxnet System, 1989).

Sodium azide is used in the preparation of hydrazoic acid, lead azide, and pure sodium (*The Merck Index*, 1983). It is the principal chemical used to generate nitrogen gas in automobile safety airbags and airplane escape chutes (Sax, 1975; *The Merck Index*, 1976). Sodium azide is also used as a retardant in the manufacture of sponge rubber and is used to prevent the coagulation of styrene and butadiene latexes stored in contact with metals and to decompose nitrites in the presence of nitrates (Sittig, 1985). Because of its broad-spectrum biocidal activity, sodium azide is used as an herbicide, insecticide, nematocide, fungicide, and bactericide (*Farm Chemical Handbook*, 1981). This biocidal activity also makes it useful as a preservative for some products, such as seeds and wine. In the Japanese beer industry, sodium azide is used to prevent growth of fungus, which darkens the brew (Sittig, 1985). Sodium azide is also used to stabilize human aqueous prealbumin fractions during storage, to prepare human blood samples for ethanol and acetaldehyde determinations, and to preserve diagnostic medicinals (Mackie *et al.*, 1982; Demaster *et al.*, 1983; Sax and Lewis, 1987). This compound is also used as a reagent for the determination of tocopherols in erythrocyte membranes and of dissolved oxygen in polluted water (*Handbook of Reactive Chemical Hazards*, 1979; Feo, 1982). Because of its potent peripheral vasodilator activity, sodium azide has been used therapeutically to control hypertension (NRC, 1981).

HUMAN EXPOSURE

The National Occupational Hazard Survey lists 5,954 workers as potentially exposed to sodium azide (NIOSH, 1978). However, the diverse uses of this chemical suggest that there is a potential for more widespread human exposure. According to a National Occupational Exposure Survey conducted from 1981 to 1983, NIOSH has estimated that a total of 48,815 workers have been occupationally

exposed to sodium azide. Over 70% of those potentially exposed were health services employees (NIOSH, 1990). The American Conference of Governmental Industrial Hygienists has adopted a threshold limit value of 0.1 ppm for this compound in the workplace air (ACGIH, 1989).

ABSORPTION, DISTRIBUTION, AND METABOLISM

Sodium azide given orally at nonlethal doses is absorbed and metabolized rapidly in the rat. In one study, the compound was detected in the plasma of rats 5 minutes after the administration of a single oral dose of 40 mg/kg. No azide was detected in plasma or tissues 24 hours after administration. During the same period, no azide was exhaled in the air or excreted in the feces, and only 7.9 μg was excreted in the urine. In a separate study, no azide was detected in the blood of rats given a daily dose of 23 mg/kg in drinking water for up to 147 days. The results of *in vitro* studies with tissue homogenates indicate that the liver is the organ responsible for the deactivation of sodium azide (Lee, 1982).

BIOCHEMICAL EFFECTS

Among the biochemical effects of sodium azide is the inhibition of cellular cytochrome oxidases (Gauze and Fatkullina, 1972). As a consequence of this inhibition, hepatic hexokinase activity is increased, suggesting stimulation of the glycolytic pathway, and lactate dehydrogenase activity is decreased, reflecting an increase in membrane permeability (Serban and Serban, 1980). Other effects of the compound include the activation of guanylate cyclase, resulting in increased levels of cyclic GMP in the brain and liver (Kimura *et al.*, 1975), the inhibition of calcium release in canine cardiac preparations (Entman *et al.*, 1973), and the inhibition of erythrocyte ATPase (Ivashchenko and Ryskulova, 1976).

TOXICITY

Human Toxicity

Accidental poisoning of five laboratory technicians due to ingestion of 10 to 20 mg sodium azide caused dizziness, pounding of the heart, faintness, and myocardial ischemia (Edmonds and Bourne, 1982). Altered mental status, pronounced acidosis, cardiac arrhythmia, decreased cardiac output, hypotension, and noncardiogenic pulmonary edema preceded the death of a male chemist who ingested 10 to 20 g of the chemical (Albertson *et al.*, 1986). Sodium azide lowered the blood pressure of hypertensive individuals, but had little effect on normotensives when administered orally at therapeutic dosages of 0.6 to 3.9 mg in divided doses for up to 2.5 years. Clinical examinations of these individuals revealed no damage to the kidney, heart, or liver (Frederick and Babish, 1982).

Animal Toxicity

The reported oral LD_{50} values for sodium azide are 45 mg/kg for rats and 27 to 40 mg/kg for mice (Kleinhofs *et al.*, 1978a; NRC, 1981). Acute toxic effects of this compound include respiratory stimulation and convulsions, followed by respiratory depression and death. Sodium azide given orally to rats or intravenously to dogs resulted in hypotension (Kleinhofs *et al.*, 1978a). A dose of 8 to 10 mg/kg given intramuscularly to monkeys resulted in convulsion, unconsciousness, apnea, and death; ataxia developed in survivors as a result of cerebellar cortical destruction. Repeated administration of sodium azide to monkeys produced necrosis or demyelination of the optic nerves and tracts and necrosis of the caudate nucleus and putamen of the lenticular nucleus. These lesions may have resulted from hypotension, impairment of ventilation, and inhibition of the activity of oxidative enzymes (Mettler and Sax, 1972).

Reproductive Effects

Female Fischer 344/N rats given sodium azide by gavage at doses of 5 or 10 mg/kg per day, five days per week for 1 year, showed no significant alteration in average estrous cycle length or relative frequency of estrous stages. However, the frequency of stages classified as unclear was higher in the treated females (data on file at NIEHS). Sodium azide induced sterility in *Musca domestica* (Thakur and Mann, 1981).

Carcinogenicity

No information regarding the carcinogenicity of sodium azide in humans was available, and few

animal studies have been reported in the literature. Sodium azide was reported not to be carcinogenic when given in the diet or by gavage at the maximum or half the maximum tolerated dose for 18 months followed by 6 months of observation, but the dose levels and test species were not specified (Ulland *et al.*, 1973). Sodium azide was not carcinogenic in male Charles River rats given 100 or 200 ppm in the diet for 18 months followed by 6 months of observation. Female rats treated similarly showed a significant increase in the incidence of pituitary chromophobe adenoma at the 100 ppm dose level. However, because too few rats survived the sodium azide treatment, this study was considered to be inadequate for evaluating the carcinogenic potential of this chemical (Weisburger *et al.*, 1981).

Genetic Toxicity

The mutagenicity of sodium azide has recently been reviewed (Arenaz *et al.*, 1989). Sodium azide has been shown to induce DNA damage in *Escherichia coli* (Mamber *et al.*, 1983), but negative results have also been reported (Suter and Jaeger, 1982; De Flora *et al.*, 1984). Tests for the induction of single-strand DNA breaks were positive in plants (Veleminsky *et al.*, 1977) and negative in Chinese hamster V79 cells. No unscheduled DNA synthesis was observed in plants (Jackson and Linskens, 1980) or mammalian cells treated with sodium azide (Martin *et al.*, 1978; Slamenova and Gabelova, 1980; Probst *et al.*, 1981). Although these tests for the induction of primary DNA damage by sodium azide yielded mixed results, the chemical is a confirmed bacterial mutagen in strains that respond to base pair substitution mutations, independent of S9 activation (Kleinhofs and Smith, 1976; De Flora *et al.*, 1979; Dunkel, 1979; Probst *et al.*, 1981; Owais *et al.*, 1983; Zeiger *et al.*, 1987). The mutagenic activity of sodium azide in eukaryotic systems has also been extensively investigated, and the results have generally been positive. For example, sodium azide induced gene mutations in yeast (Šilhánkova *et al.*, 1979) and in higher plants such as barley, rice, and corn (Nilan *et al.*, 1973; Kleinhofs *et al.*, 1978b; Sander *et al.*, 1978; Sarma *et al.*, 1979; Hasegawa and Inoue, 1983). Weakly positive results were reported for the induction of sex-linked recessive lethal mutations in male *Drosophila melanogaster* fed 0.1 mM sodium azide at pH 4.6 for 3 days (Kamra and Gollapudi, 1979). Sodium azide was weakly mutagenic at the $TK^{+/-}$ locus of mouse L5178Y cells (Clive *et al.*, 1979), and weakly positive responses were reported for induction of 8-azaguanine or ouabain resistance, or both, in rat epithelial cells and Chinese hamster cells (Jones *et al.*, 1980).

Tests for clastogenic effects in eukaryotic cells were almost uniformly negative. Sodium azide did not induce chromosomal aberrations in barley (Nilan *et al.*, 1973; Choudhary and Kaul, 1976; Prina and Favret, 1983), *Vicia faba* (Kihlman and Sturelid, 1975), human lymphocytes (Sander *et al.*, 1978), or Chinese hamster ovary cells (Arenaz and Nilan, 1981; Appendix C, Table C4). NTP studies demonstrated increases in sister chromatid exchanges in Chinese hamster ovary cells treated with sodium azide (Appendix C, Tables C2 and C3); however, Arenaz and Nilan (1981) reported negative results and azide-induced cellular toxicity in a similar assay using shorter treatment times.

Sodium azide is metabolized in barley and *Salmonella typhimurium* to a stable mutagenic intermediate, azidoalanine, in a reaction mediated by the enzyme O-acetylserine(thio)-lyase (Owais *et al.*, 1979, 1983). Azidoalanine, when tested directly, was mutagenic without S9 activation in *S. typhimurium* strains TA1530 and TA100 (Owais *et al.*, 1983).

Study Rationale

Sodium azide was nominated by the National Cancer Institute for carcinogenic evaluation because of the high potential for human exposure and the lack of adequate carcinogenicity studies. The gavage route of administration was chosen because sodium azide was unstable in feed formulations.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF SODIUM AZIDE

Sodium azide was obtained from Fairmont Chemical Co. (Newark, NJ) in one lot (lot no. 32880). Purity, identity, and stability analyses were conducted at Midwest Research Institute, Kansas City, MO (Appendix E). The study chemical, a white, microcrystalline powder, was identified as sodium azide by infrared, ultraviolet-visible, and nuclear magnetic resonance spectroscopy. The purity was determined to be greater than 99% by oxidation-reduction titration, elemental analyses, Karl Fischer water analysis, and spark source mass spectrometry. Sodium azide was stable as a bulk chemical for at least 2 weeks at temperatures up to 60° C when protected from light, as determined by a titration method.

Based on the results of the stability studies, the bulk chemical was stored at room temperature in the dark at the testing laboratory throughout the study period. The stability of the bulk chemical was monitored periodically during all phases of the studies by infrared spectroscopy and by titration. No change in the study material was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing appropriate amounts of sodium azide and distilled water (Appendix E, Table E1). Stability studies showed no decrease in sodium azide concentration after storage of the solutions for 3 weeks in the dark at 25° C or under simulated animal dosing conditions (open to air and light for 3 hours). During the studies, the dose formulations were stored at 5° C for no longer than 3 weeks.

The study laboratory conducted periodic analyses of the sodium azide dose formulations using a titrimetric procedure as described in Appendix E. During the 2-year studies, the dose formulations were analyzed at approximately 8-week intervals and were within ± 10% of the target concentrations 100% of the time (Table E4). Results of periodic referee analyses by the analytical chemistry laboratory agreed with the results from the study laboratory (Table E5).

14-DAY STUDIES

Male and female F344/N rats were obtained from Harlan Industries (Indianapolis, IN) and were quarantined for 19 days before the studies began. The rats were 7 weeks old at the beginning of the studies.

Groups of five rats of each sex were administered 0, 5, 10, 20, 40, or 80 mg/kg sodium azide in deionized water by gavage 5 days per week (excluding weekends) for a total of 12 dose days. Animals were housed five per cage. Water and feed were available *ad libitum*.

Animals were weighed prior to initiation of chemical administration, weekly, and at the end of the study. Observations were made daily throughout the studies. All animals were necropsied. Organ weights were obtained for liver, right kidney, brain, heart, thymus, and lungs for all surviving animals. Histopathologic examinations were performed on selected tissues and animals. Further experimental details are presented in Table 1.

13-WEEK STUDIES

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

Male and female F344/N rats were obtained from Frederick Cancer Research Center (Frederick, MD). Animals were observed for 18 days, distributed to weight classes, and assigned to groups according to tables of random numbers. The rats were 7 weeks old at the beginning of the studies. Further experimental details are provided in Table 1.

Groups of 10 rats of each sex were administered 0, 1.25, 2.5, 5, 10, or 20 mg/kg sodium azide in distilled water by gavage, 5 days per week for 13 weeks. Rats were housed five per cage. Feed and water were available *ad libitum*. Animals were observed twice daily for morbidity and mortality and were given physical examinations weekly, or as necessary. Moribund animals were killed and necropsied. Individual animal weights were recorded weekly.

After 13 weeks, organ weights were determined for the liver, right kidney, brain, heart, thymus, and lungs of all surviving rats. All rats were necropsied and a complete histopathologic examination was performed on all rats in the control, 10 mg/kg, and 20 mg/kg dose groups. Tissues and groups examined are listed in Table 1.

2-YEAR STUDIES

Study Design

Groups of 60 rats of each sex were administered 0, 5, or 10 mg/kg sodium azide in distilled water by gavage at a dose volume of 5 mL/kg for 5 days per week for 103 weeks. Ten rats per group were originally scheduled for interim evaluations. However, due to the high early mortality in the high-dose groups, there were no interim evaluations.

Source and Specification of Animals

The male and female F344/N rats used in the 2-year studies were produced under strict barrier conditions at Charles River Breeding Laboratories (Kingston, NY). Rats were shipped to the study laboratory at 4 to 5 weeks of age and were quarantined for 19 days. During this time, animals were checked daily. To assess the health status of the rats, five animals of each sex were killed for gross examination of abdominal and thoracic viscera, histopathologic examination of abnormal tissues, and determination of pathogen burden. Pathogens evaluated included ectoparasites (mites, fleas, lice), intestinal parasites, bacteria, and viruses. The rats were 48 to 55 days of age at the beginning of the studies. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix G).

Animal Maintenance

Rats were housed five per cage. Feed and water were available *ad libitum*. Cages within groups were rotated once every 2 weeks. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed twice daily, and clinical findings were recorded once per week. Body weights by cage were recorded once per week for the first 13 weeks of the studies, during weeks 17 and 19, and from weeks 21 to 31, and every 2 to 5 weeks thereafter. Mean body weights were calculated for each group.

Animals found moribund and those surviving to the end of the studies were killed. All animals were necropsied. During necropsy all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin and routinely processed for microscopic examination (embedded in paraffin, sectioned, and stained with hematoxylin and eosin). A complete histopathologic evaluation inclusive of gross lesions was performed on all animals. Tissues examined microscopically are listed in Table 1.

Upon completion of the microscopic evaluation by the laboratory pathologist, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide-block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slide and tissue counts were verified, and histotechnique was evaluated. All tissues with a diagnosis of neoplasia, brains from male and female rats, adrenal glands from males, and tissues from a randomly selected 10% of the control and high-dose rats were re-evaluated microscopically by a quality assessment pathologist.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who microscopically reviewed the above tissues and any other tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists.

Representative examples of potential chemical-related neoplasms and nonneoplastic lesions, including differences in diagnosis between the study pathologist and reviewing pathologist, were selected by the chair for review by the PWG. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicology. This group examined the tissues without knowledge of dose groups or previously rendered diagnoses. When the consensus opinion of the PWG differed from that of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used Cox's method (1972) 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

Tables A1 and B1 in the appendixes to this report present the incidence of neoplastic lesions in male and female rats, respectively. Tables A5 and B5 summarize the incidence of nonneoplastic lesions in male and female rats. The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary gland) prior to histologic sampling, or when lesions had multiple potential sites of occurrence (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence

The majority of tumors in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was a logistic regression analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, tumor prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When tumors are incidental, this comparison of the time-specific tumor prevalences also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

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

Tests of significance included pairwise comparisons of each dosed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. (For further discussion of these statistical methods, see Haseman, 1984.)

Historical Control Data

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

Analysis of Continuous Variables

The nonparametric multiple comparison procedures of Dunn (1964) or Shirley (1977) were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of organ weight data. Jonckheere's test (Jonckheere, 1954) was used to evaluate the significance of dose-response trends and to determine whether Dunn's or Shirley's test was more appropriate for pairwise comparisons.

Quality Assurance Methods

The 13-week and 2-year studies were conducted in compliance with FDA Good Laboratory Practice Regulations (21 CFR Part 58). In addition, as study records were submitted to the NTP Archives, they were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and draft of the NTP Technical Report were conducted. Audit procedures are presented in the audit reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by NTP staff so that all discrepancies had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICITY

The genetic toxicity of sodium azide was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and to induce sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells. The protocols for these studies and tabular presentations of their findings are given in Appendix C.

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Sodium Azide

14-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory Microbiological Associates, Inc., Bethesda, MD	Same as 14-day studies	Same as 14-day studies
Strain and Species F344/N rats	F344/N rats	F344/N rats
Animal Source Harlan Industries, Indianapolis, IN	Frederick Cancer Research Center, Frederick, MD	Charles River Breeding Laboratories, Kingston, NY
Date of Birth 29 December 1980	13 May 1981	13-20 April 1982
Time Held Before Study 19 days	18 days	19 days
Age When Placed on Study 49 days	54 days	48-55 days
Date of First Dose 16 February 1981	6 July 1981	7 June 1982
Duration of Dosing 2 weeks (5 days/week plus 2 days)	13 weeks (5 days/week)	103 weeks (5 days/week)
Date of Last Dose 3 March 1981	6-7 October 1981	25 May 1984
Necropsy Dates 4-5 March 1981	7-8 October 1981	Controls: 11-12 June 1984 Low and high dose groups: 4-5 June 1984
Age at Necropsy 9 weeks (65 days)	21 weeks	111-112 weeks
Size of Study Groups 5 males and 5 females	10 males and 10 females	60 males and 60 females
Method of Animal Distribution Animals were assigned to weight groups and then assigned to cages according to a random number table. Group numbers were then assigned according to a random number table.	Same as 14-day studies	Same as 14-day studies
Animals per Cage 5	5	5
Method of Animal Identification Ear punch	Ear punch and clip	Ear tag

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Sodium Azide (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Feed NIH-07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA), available *ad libitum*	Same as 14-day studies	Same as 14-day studies
Maximum Storage Time for Feed 120 days after milling	Same as 14-day studies	Same as 14-day studies
Feeders Stainless steel (Lab Products, Inc., Rochelle Park, NJ), changed weekly	Same as 14-day studies	Same as 14-day studies
Water Tap water, available *ad libitum*, by automatic watering system (Lab Products, Rochelle Park, NJ)	Same as 14-day studies	Same as 14-day studies
Cages Polycarbonate (Lab Products, Inc., Rochelle Park, NJ, or Hazelton Systems, Aberdeen, MD), changed twice a week	Same as 14-day studies	Same as 14-day studies
Bedding Hardwood chips (P.J. Murphy Forest Products, Warrensburg, NJ), changed twice a week	Same as 14-day studies	Same as 14-day studies
Cage Filters Spun-bonded polyester filter sheets (Snow Filtration, Co., Cincinnati, OH), changed once every two weeks	Same as 14-day studies	Same as 14-day studies
Racks Stainless steel (Lab Products, Inc., Rochelle Park, NJ, or Hazelton Systems, Aberdeen, MD), changed once every two weeks	Same as 14-day studies	Same as 14-day studies
Animal Room Environment Temperature: 67°-78° F Humidity: 26%-72% Light: fluorescent, 12 hours/day Room air changes: 12-15/hour	Temperature: 71°-84° F Humidity: 41%-82% Light: fluorescent, 12 hours/day Room air changes: 12-15/hour	Temperature: 68°-79° F Humidity: 10%-84% Light: fluorescent, 12 hours/day Room air changes: 12-15/hour

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Sodium Azide (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Doses		
0, 5, 10, 20, 40, and 80 mg/kg body weight in deionized water by gavage, given in single dose. Dose volume was 5 mL/kg.	0, 1.25, 2.5, 5, 10, and 20 mg/kg body weight in distilled water by gavage, given in single dose. Dose volume was 5 mL/kg.	0, 5, and 10 mg/kg body weight in distilled water by gavage, given in single dose. Dose volume was 5 mL/kg.
Storage Conditions for Dosing Solutions		
Refrigeration at 4°-8° C	Refrigeration at 4°-8° C	Refrigeration at 5° C
Maximum Storage Time for Dosing Solutions		
3 weeks	2 weeks	3 weeks
Type and Frequency of Observation		
Observed daily	Observed twice daily. Physical examination was conducted weekly, or as necessary.	Observed twice daily. Physical examination was conducted monthly.
Necropsy and Histopathologic Examinations		
Necropsy	**Necropsy**	**Necropsy**
Necropsy performed on all animals. Brain, heart, liver, lungs, right kidney, and thymus were weighed for all surviving animals.	Necropsy performed on all animals. Brain, heart, liver, lungs, right kidney, and thymus were weighed for all surviving animals.	Necropsy performed on all animals.
Histopathology	***Histopathology***	**Histopathology**
Histopathology performed on 40 mg/kg males, 20 mg/kg females, and all controls. Tissues examined included heart, kidney, liver, lung, pituitary gland, salivary gland, thyroid gland, trachea, and urinary bladder.	Histopathology performed on all animals in the control, 10 mg/kg, and 20 mg/kg dose groups. Tissues examined microscopically included gross lesions, adrenal gland, brain, esophagus, heart, kidney, liver, lung, lymph node (mesenteric), pancreas, prostate gland, rectum, salivary gland, skin and subcutis, spleen, thymus, trachea, urinary bladder, and vagina.	Histopathology performed on all animals. Tissues examined microscopically included adrenal gland, bone, brain (forebrain, midbrain, cerebellum), clitoral gland, esophagus, heart, intestine (duodenum, jejunum, ileum, colon, cecum, rectum), kidney, liver, lung and mainstem bronchi, lymph node (mandibular, mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spinal cord, sciatic nerve, spleen, stomach (forestomach, glandular), testis, epididymis, seminal vesicle, thymus, thyroid gland, tissue masses and gross lesions, trachea, urinary bladder, and uterus.

RESULTS

14-DAY STUDIES

All male and female rats in the 40 and 80 mg/kg dose groups died by the fourth day of dosing. In addition, two of the five female rats receiving 20 mg/kg sodium azide died by day 5. There were no other deaths due to toxicity. The survival and body weights of rats in these studies are shown in Table 2.

The mean body weights of dosed and control animals were generally similar throughout the studies, with body weights of dosed animals remaining within 5% of control values.

Weight gains in the groups of male rats were all within 5% of the weight gained by control males. The three surviving female rats that received 20 mg/kg sodium azide gained an average of 18% less weight than did the female controls. Weight gains of female rats receiving 5 mg and 10 mg/kg sodium azide were within 8% of the control group weight gain.

Clinical findings included lethargy and inactivity, and were observed prior to death in all 80 mg/kg group rats. These findings were also observed in three female rats receiving 20 mg/kg sodium azide.

TABLE 2
Survival and Mean Body Weights of Rats in the 14-Day Gavage Studies of Sodium Azide

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	131 ± 3	224 ± 3	93 ± 5	
5	5/5	129 ± 3	223 ± 2	93 ± 4	99
10	5/5	131 ± 5	219 ± 6	88 ± 9	98
20	5/5	131 ± 3	225 ± 5	94 ± 4	100
40	0/5[c]	131 ± 3	–[d]	–	–
80	0/5[e]	132 ± 4	–	–	–
Female					
0	5/5	109 ± 3	148 ± 4	39 ± 3	
5	5/5	109 ± 3	150 ± 5	42 ± 3	101
10	5/5	108 ± 2	150 ± 2	42 ± 4	101
20	3/5[f]	109 ± 3	141 ± 13	31 ± 16	95
40	0/5[g]	111 ± 3	–	–	–
80	0/5[h]	110 ± 3	–	–	–

[a] Number of animals surviving at 14 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the control group are not significant by Dunn's test. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Day of death: 2,3,3,3,4
[d] No data reported due to 100% mortality in this group.
[e] Day of death: all 2
[f] Day of death: 4,5
[g] Day of death: all 2
[h] Day of death: 1,2,2,2,3

Mean absolute and relative liver weights of the highest surviving dose group of male rats (20 mg/kg) were 11% and 10% greater than those of control males (Table D1). The relative liver-weight-to-body-weight ratio for this dose group was significantly increased ($P \leq 0.05$). With one exception, the mean weights of the other organs for both male and female groups differed from the control group by less than 10%. The mean thymus weight of the females receiving 5 mg/kg was 13% above that of control females (Table D2). These increases in absolute organ weight were not significant, with the exception of the increase in mean heart weight of males receiving 20 mg/kg sodium azide ($P \leq 0.05$).

No gross lesions attributable to sodium azide were observed in any dose group.

13-WEEK STUDIES

Mortality occurred only in the highest dose groups (20 mg/kg). Eighteen of 20 rats receiving 20 mg/kg died as a result of chemical toxicity (Table 3). The weight gain at the end of the studies for all groups of male and female rats was within 10% of the controls, although a trend toward reduced weight gain was noted in male rats receiving 10 or 20 mg/kg sodium azide (Table 3).

Clinical findings of toxicity in all high-dose male and female rats included hunched posture after dosing, ruffled fur, lethargy, decreased appetite, and impaired breathing. Males receiving 10 mg/kg exhibited hunched posture after dosing from week 8 until the end of the study. There were no clinical findings of toxicity in the lower dose groups.

TABLE 3
Survival and Mean Body Weights of Rats in the 13-Week Gavage Studies of Sodium Azide

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	163 ± 4	377 ± 5	214 ± 3	
1.25	10/10	163 ± 4	380 ± 6	217 ± 4	101
2.5	10/10	158 ± 5	380 ± 7	223 ± 6	101
5	10/10	165 ± 3	378 ± 10	213 ± 9	100
10	10/10	158 ± 6	354 ± 8*	196 ± 6*	94
20	2/9[c]	159 ± 7	357 ± 12	189 ± 4	95
Female					
0	10/10	122 ± 2	207 ± 3	85 ± 2	
1.25	10/10	123 ± 3	215 ± 3	92 ± 3	104
2.5	10/10	123 ± 2	213 ± 4	90 ± 4	103
5	10/10	122 ± 3	210 ± 3	88 ± 3	101
10	10/10	124 ± 2	203 ± 5	80 ± 4	98
20	0/10[d]	123 ± 2	–[e]	–	–

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Week of death: 7,8,10,10,11,11,13. A tenth animal, which died during week 1, was found to be missexed at necropsy.
[d] Week of death: 2,2,6,6,7,7,7,7,7,7
[e] No data reported due to 100% mortality in this group.

The absolute liver weights of male rats in all dose groups were within 6% of the control values (Table D3). The relative liver weights for dosed males were within 10% of control values. In female rats receiving 1.25, 2.5, and 5 mg/kg sodium azide, absolute liver weights were significantly ($P \leq 0.01$) higher than controls (Table D4). Females in all dose groups had significantly ($P \leq 0.01$) elevated (8%-15%) relative liver weights.

Compound-related histopathologic lesions were limited to the brain in male and female rats receiving 20 mg/kg sodium azide. These lesions were observed in five males and eight females. All females exhibiting the brain lesions died within 7 weeks, and all affected males died within 11 weeks; the brain lesions were considered to be the cause of death. The lesions were characterized by cerebral necrosis, particularly prominent in the area of the caudate nucleus and putamen. In some instances, the necrosis involved the thalamus and, rarely, the corpus callosum. No brain lesions were observed in rats receiving 10 mg/kg sodium azide.

Pulmonary congestion and hemorrhage, with or without edema, were observed in seven male and seven female rats receiving 20 mg/kg sodium azide. All rats exhibiting these pulmonary lesions died during the studies, and the lesions were attributed to cardiovascular collapse secondary to brain necrosis. The two high-dose males killed at the end of the study did not exhibit lesions of this nature, nor were similar lesions observed in rats receiving 10 mg/kg sodium azide.

Dose Selection Rationale

The doses selected for the 2-year studies were 5 mg/kg and 10 mg/kg. This selection was based on the mortality, body weight depressions, and brain lesions observed in the 13-week studies.

2-YEAR STUDIES

Body Weights and Feed Consumption

Mean body weights of male and female rats receiving sodium azide were consistently lower than those of controls throughout the studies (Tables 4 and 5 and Figure 1). After week 24, the mean body weights of high-dose male and female rats were notably lower than those of the control animals.

High-dose males consistently consumed less feed than control males. High-dose females consumed considerably less feed than control females between week 16, when feed consumption measurements were initiated, and week 56. After week 56, feed consumption by high-dose females was still below that of controls, but by a smaller margin than seen previously. Mean feed consumption values for low- and high-dose rats were lower than control values.

Clinical Findings

Of rats receiving 10 mg/kg, 49/60 males and 53/60 females became very lethargic after dosing at some time during the studies. In comparison, lethargy was observed in eight control males, eight low-dose males, four control females, and six low-dose females. Four male and four female rats receiving 10 mg/kg and one male receiving 5 mg/kg sodium azide convulsed at the time of dosing, and five high-dose males, eight high-dose females, and two low-dose females became comatose for 1 to 2 hours. Many of these animals died within 3 to 5 days following the appearance of these clinical findings. These early deaths were attributed to the brain necrosis found upon microscopic examination of brain tissue sections from these animals.

Additional clinical findings in high-dose rats included recumbency (males, 22/60; females, 5/60), rough hair (males, 60/60; females, 53/60), emaciation (females, 29/60), and toe-walking (males, 11/60; females, 51/60).

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

Weeks on Study	Vehicle Control		5 mg/kg			10 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
1	156	60	154	99	60	153	98	60
2	198	60	196	99	60	194	98	60
3	228	60	224	98	60	221	97	60
4	251	60	247	98	60	244	97	60
5	266	60	262	99	60	264	99	60
6	286	60	278	97	60	277	97	60
8	319	60	309	96	60	304	95	60
9	326	60	318	97	60	318	98	60
10	334	60	327	98	60	327	98	60
11	347	60	333	96	60	333	96	60
12	350	60	341	97	60	343	98	60
13	361	60	342	95	60	343	95	60
17	388	60	366	94	60	360	93	60
19	404	60	380	94	60	365	91	60
21	412	60	386	94	60	374	91	60
22	414	60	390	94	60	376	91	60
23	419	59	393	94	60	378	90	60
24	424	59	398	94	60	382	90	60
25	429	59	399	93	60	380	89	60
26	435	59	406	93	60	388	89	60
27	440	59	411	93	60	390	89	60
28	445	59	417	94	60	397	89	60
29	447	59	419	94	60	398	89	60
30	450	59	420	93	60	398	88	60
31	453	59	422	93	60	399	88	60
34	454	59	430	95	58	405	89	58
38	455	59	441	97	58	418	92	57
42	477	59	450	94	58	426	89	57
46	484	58	454	94	58	429	89	57
51	487	58	460	95	58	443	91	51
54	489	58	460	94	58	445	91	51
58	495	58	466	94	58	449	91	51
62	496	58	468	94	57	444	89	48
66	494	58	463	94	56	442	89	46
70	497	58	466	94	56	441	89	44
74	495	57	465	94	55	433	87	43
78	483	55	465	96	53	432	90	42
82	491	51	461	94	52	433	88	36
86	485	48	462	95	48	432	89	33
90	473	45	453	96	48	421	89	31
94	486	40	446	92	43	409	84	23
98	465	35	444	95	39	393	85	11
100	457	30	445	97	35	388	85	11
102	465	27	440	95	31	394	85	10
104	457	25	437	96	27	394	86	9
Terminal sacrifice		24			27			9
Mean for weeks								
1-13	285		278	98		277	97	
17-51	440		413	94		395	90	
54-104	482		456	95		423	88	

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

Weeks on Study	Vehicle Control		5 mg/kg			10 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
1	121	60	117	97	60	116	96	60
2	139	60	136	98	60	135	97	60
3	151	60	148	98	60	146	97	60
4	161	60	159	99	60	157	97	60
5	170	60	168	99	60	168	99	60
6	176	60	174	98	60	170	96	60
8	190	60	187	98	60	183	96	60
9	192	60	189	98	60	191	99	60
10	193	60	193	100	60	191	99	59
11	200	60	196	98	60	193	97	59
12	198	60	196	99	60	195	99	59
13	203	60	200	98	60	192	95	59
17	212	60	205	97	60	193	91	53
19	219	60	210	96	60	193	88	53
21	224	60	215	96	60	195	87	52
22	222	60	215	97	60	195	88	52
23	223	60	215	97	60	194	87	51
24	225	60	215	96	60	196	87	51
25	226	60	217	96	60	192	85	51
26	229	60	220	96	60	196	86	51
27	231	60	223	96	60	198	86	51
28	232	60	224	97	60	199	86	51
29	235	60	226	96	60	198	85	51
30	236	60	226	96	60	196	83	50
31	237	60	228	96	60	199	84	49
34	245	60	235	96	60	205	84	49
38	247	60	239	97	60	209	85	49
42	260	60	246	95	60	218	84	49
46	267	58	254	95	60	224	84	49
51	275	58	263	96	60	227	83	49
54	280	57	265	94	60	231	83	49
58	290	57	272	94	60	238	82	48
62	300	56	282	94	60	243	81	48
66	309	55	287	93	59	246	79	47
70	316	55	297	94	59	248	79	46
74	320	53	299	94	58	246	77	42
78	320	53	306	95	57	259	81	41
82	326	52	310	95	56	255	78	39
86	334	48	310	93	56	255	77	39
90	335	47	312	93	54	257	77	37
94	338	45	311	92	52	245	72	28
98	337	43	309	92	51	247	73	24
100	334	41	308	92	49	254	76	22
102	338	39	305	90	48	259	77	21
104	337	37	304	90	45	256	76	21
Terminal sacrifice		37			43			21
Mean for weeks								
1-13	175		172	98		169	97	
16-52	236		226	96		202	86	
56-104	321		298	93		249	78	

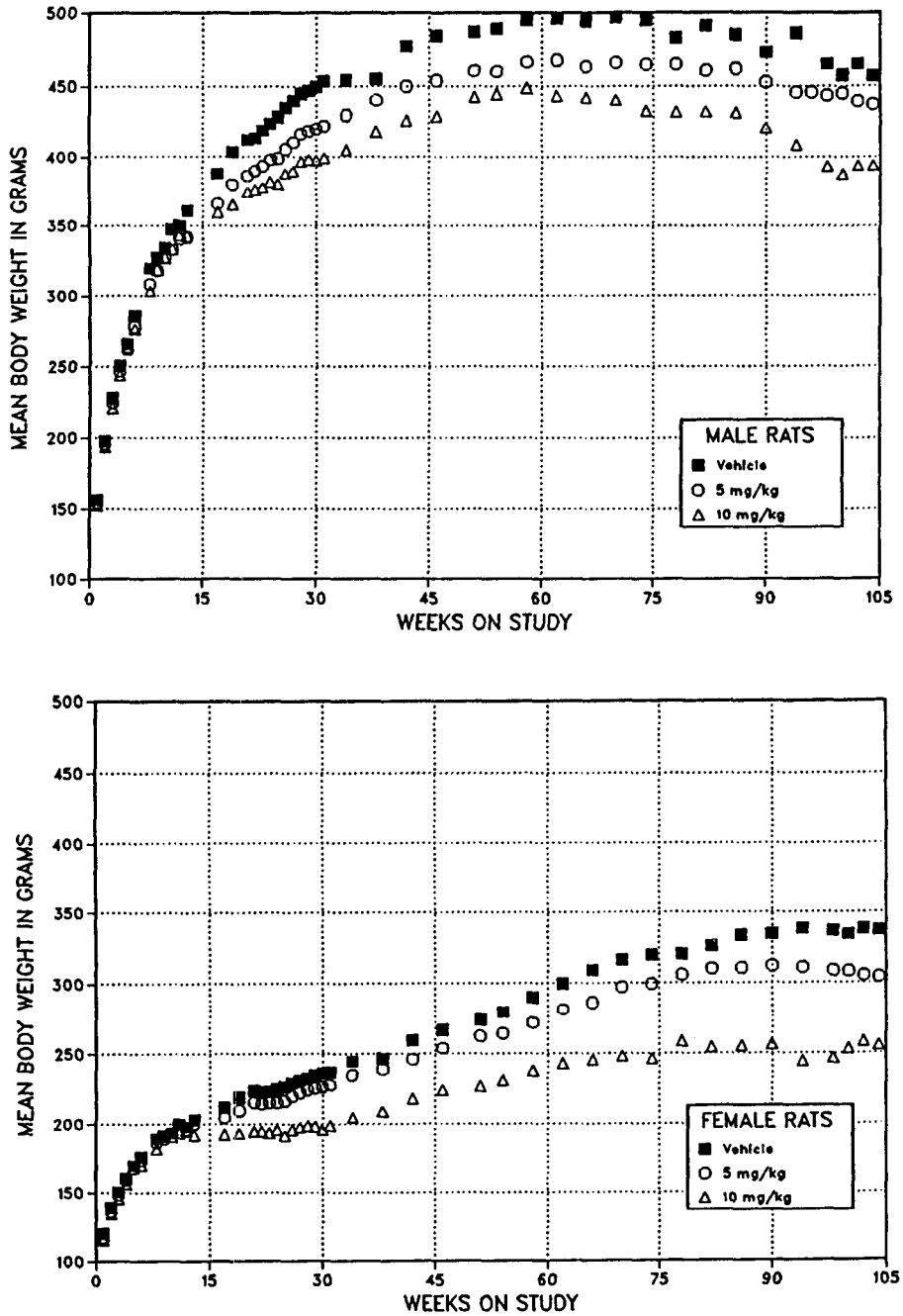


FIGURE 1
Growth Curves for Male and Female Rats Administered Sodium Azide by Gavage for 2 Years

Survival

Estimates of the probabilities of survival for male and female rats are shown in Table 6 and in the Kaplan-Meier curves in Figure 2a; the overall survival profile (with no deaths censored) is shown in Figure 2b. Survival was substantially reduced in high-dose males and females. Brain necrosis, most notably in the cerebrum and thalamus, was a major cause of mortality in high-dose male and female rats and was attributed to the toxicity of sodium azide. The lower than usual survival rate (less than 50%) of the control and low-dose male rats was probably due to the high incidence of mononuclear cell leukemia in these groups.

TABLE 6
Survival of Rats in the 2-Year Gavage Studies of Sodium Azide

	Vehicle Control	5 mg/kg	10 mg/kg
Male			
Animals initially in study	60	60	60
Natural deaths	16	14	27
Moribund kills	19	18	15
Accidental deaths[a]	1	1	9[b]
Animals surviving to study termination	24	27	9
Percent survival at end of study[c]	41	47	19
Mean survival (days)[d]	660	662	572
Survival P values[e]	0.003	0.555N	0.002
Female			
Animals initially in study	60	60	60
Natural deaths	11	5	22
Moribund kills	10	12	11
Accidental deaths[a]	2	0	5[b]
Missexed	0	0	1
Animals surviving to study termination	37[f]	43	21
Percent survival at end of study[c]	62	72	39
Mean survival (days)[d]	670	704	565
Survival P values[e]	0.010	0.223N	0.015

[a] Censored from survival analyses.
[b] The increased number of accidental deaths in this group appeared to be secondary to brain necrosis induced by the chemical.
[c] Kaplan-Meier determinations. Survival rates adjusted for accidental deaths.
[d] Mean of all deaths (uncensored, censored, terminal sacrifice).
[e] The entry under the "control" column is the trend test (Tarone, 1975) result. Subsequent entries are the results of pairwise tests (Cox, 1972). Negative trends are indicated by "N".
[f] One of these animals was found dead on the last day of the study.

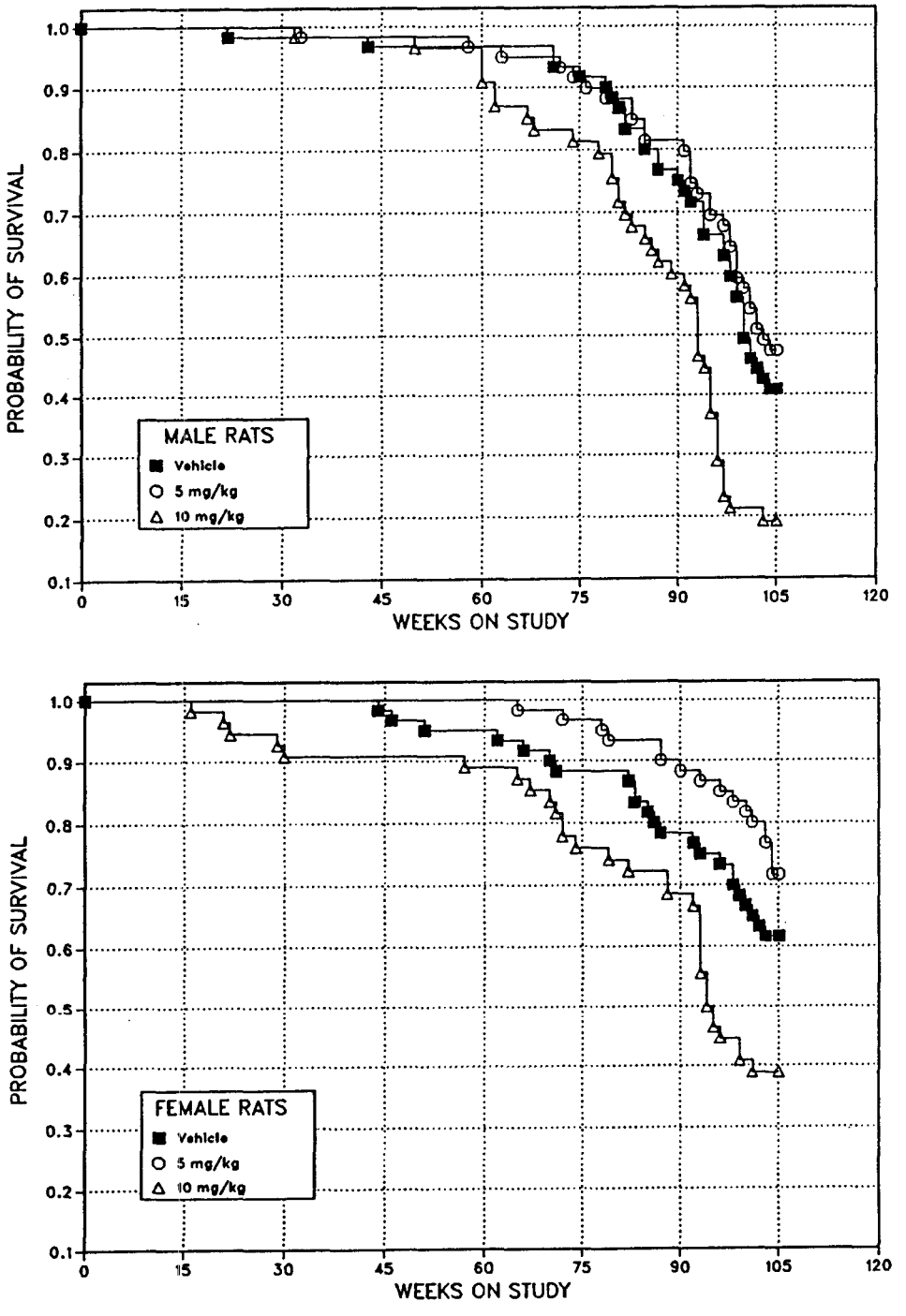


FIGURE 2a
Kaplan-Meier Survival Curves for Male and Female Rats Administered Sodium Azide by Gavage for 2 Years

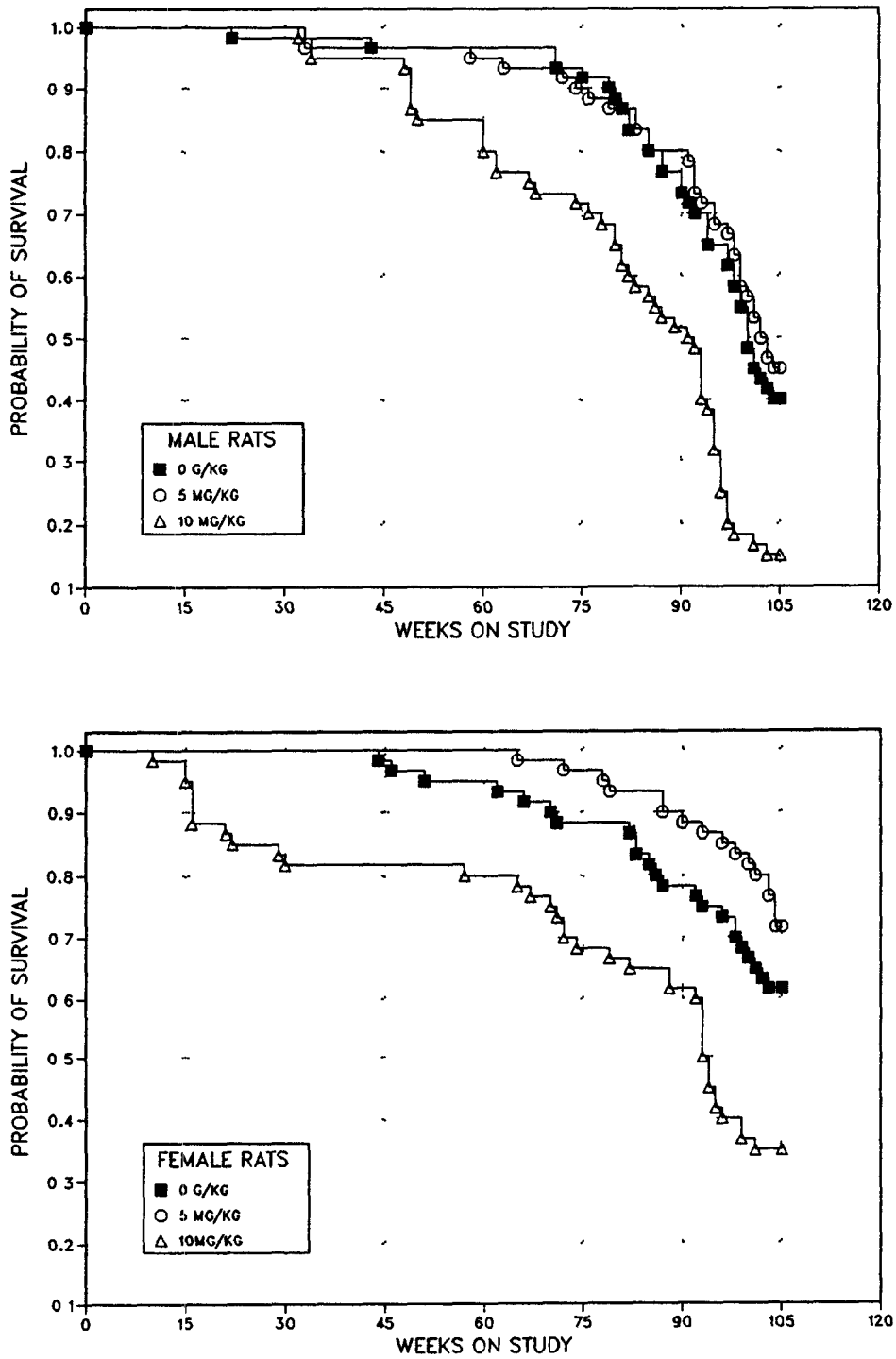


FIGURE 2b
Kaplan-Meier Survival Curves (unadjusted) for Male and Female Rats Administered Sodium Azide by Gavage for 2 Years

Pathology and Statistical Analyses of Results

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented for male and female rats in Appendixes A and B.

Neoplastic Lesions

A variety of neoplasms occurred randomly throughout the groups with no apparent compound-related increase in incidence. Significantly decreased incidences were observed for certain neoplasms (Tables A3 and B3), including mononuclear cell leukemia in male rats (control, 33/60; low-dose, 28/60; high-dose, 14/60), adrenal gland pheochromocytoma in male rats (26/55; 16/56; 6/54), mammary gland fibroadenoma in female rats (20/60; 11/60; 8/59), and pituitary gland neoplasms in female rats (37/60; 28/60; 17/59). These decreases were attributed to the reduced survival of the high-dose groups and possibly were also associated with reduced body weights (Rao *et al.*, 1987).

Nonneoplastic Lesions

A high incidence of brain necrosis was observed in the high-dose males and females. The brain lesions were often of sufficient severity to result in the death of the affected animals. The high-dose animals also had an increased incidence of pulmonary congestion, sometimes with hemorrhage, which was considered to be a secondary effect of brain necrosis.

Brain: The significant treatment-related finding in the brain was necrosis of the cerebrum, thalamus, or both. This lesion was observed in a large percentage of the high-dose males and females (Table 7). There was a single occurrence of cerebral necrosis in a low-dose male and a low-dose female and a single occurrence of thalamic necrosis in a low-dose male. These lesions were not observed in control animals. The brain lesions were usually bilaterally symmetrical. Cerebral necrosis occurred at a specific subcortical site, apparently in the region of the caudate-putamen basal ganglia. Three high-dose females with cerebral necrosis also had necrosis of the hippocampus, a deep portion of the cerebral cortex. Thalamic necrosis was usually localized either in the dorsal region of the thalamus, just ventral to the hippocampus, or in the center of the thalamus. One high-dose male had necrosis in the pons, a portion of the brainstem caudal to the thalamus. The areas of necrosis varied in size, and the severity of necrosis ranged from acute to chronic. Acute lesions consisted of necrosis of neurons that was often accompanied by necrosis of elements of the neuropil (Figure 3). Necrotic cells had deeply eosinophilic cytoplasm with pyknotic or karyorrhectic nuclei (Figure 4). Inflammatory cell infiltrate was minimal or absent from acute lesions. Chronic lesions were characterized by the loss of neurons and neuropil, infiltration of macrophages, and proliferation of glial cells and blood vessels (Figure 5). Acute and chronic lesions were often seen in the same animal. Only a few neoplasms of the brain were found in these studies. A single glioma occurred in a high-dose male, an oligodendroglioma in one low-dose female, and a single astrocytoma in a high-dose

TABLE 7
Numbers of Rats with Nonneoplastic Lesions of the Brain in the 2-Year Gavage Studies of Sodium Azide

	Vehicle Control	5 mg/kg	10 mg/kg
Males (number examined)	60	60	60
Cerebrum, necrosis	0	1 (2%)	24 (40%)*
Thalamus, necrosis	0	1 (2%)	25 (42%)*
Females (number examined)	60	60	58
Cerebrum, necrosis	0	1 (2%)	33 (57%)*
Thalamus, necrosis	0	0	21 (36%)*

* $P<0.001$ vs. controls by both logistic regression analysis and life table tests

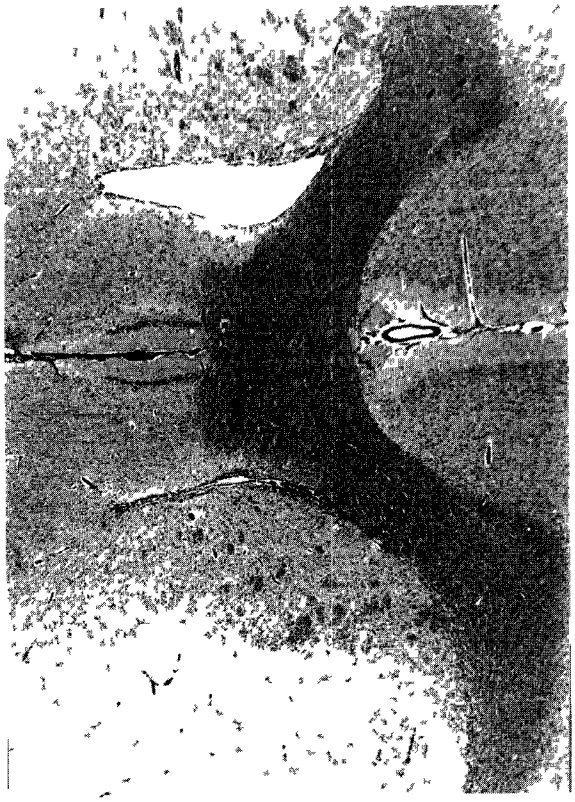


FIGURE 3. Necrosis of the caudate/putamen region of the cerebrum (elongated pale area at bottom edge of field) in a female F344/N rat from the 2-year study treated with 10 mg/kg sodium azide (× 28)

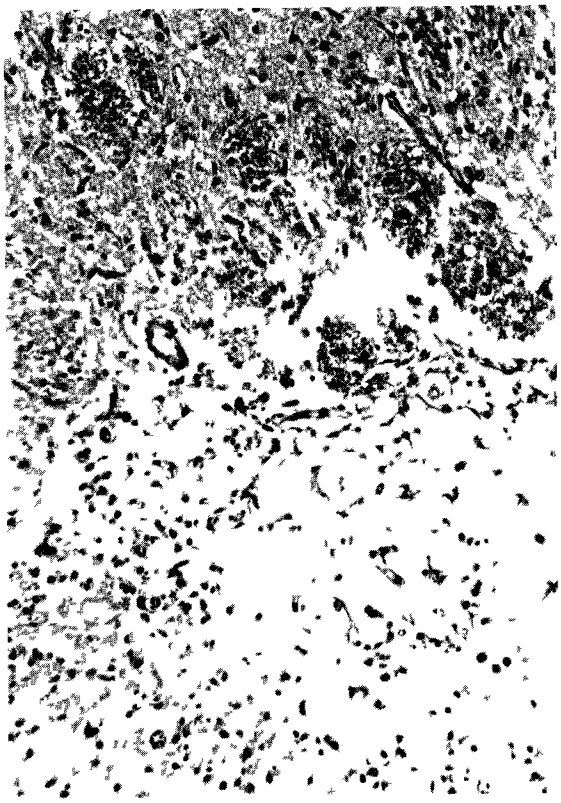


FIGURE 4. Higher magnification of FIGURE 3 showing necrosis of the caudate/putamen. In the center of the lesion (pale area in lower right corner) there is a complete loss of neurons and neuropil leaving only a scattering of blood vessels and glial cells. There is also diffuse necrosis of cells in the brain substance surrounding the necrotic center as indicated by the dark shrunken (pyknotic) nuclei. (× 160)

FIGURE 5. Necrosis of the caudate/putamen region of the cerebrum in a female F344/N rat treated with 10 mg/kg sodium azide during the 2-year study This chronic lesion is being filled with proliferating blood vessels and glial cells. (× 140)

female. A granular cell tumor, presumably of meningeal cell origin, occurred in one high-dose male. None of these neoplasms was considered to be treatment related.

Lung: The incidence of congestion in high-dose male and female rats and of hemorrhage in high-dose male rats was higher than that in low-dose and control animals (congestion-males: control, 6/60; low-dose, 4/60; high-dose, 30/60; females: 6/60; 3/60; 21/59; hemorrhage-males: 4/60; 5/60; 17/60; females: 5/60; 5/60; 5/59). These pulmonary lesions were seen primarily in animals dying during the studies and were consistent with cardiovascular collapse and brain necrosis.

Liver: The incidence of hepatodiaphragmatic nodules in the livers of low- and high-dose female rats was higher than that in controls (controls, 1/60; low-dose, 8/60; high-dose, 11/59). Common in aging F344/N rats, these lesions consist of nodular masses of hepatic parenchyma that project from the capsular surface of the liver and protrude into the thorax at points of weakness in the skeletal muscle of the diaphragm. There was no increase in the incidence of this lesion in male rats. No other effects on skeletal muscle attributable to sodium azide administration were found in these studies, and the results of previous studies do not indicate that sodium azide has an effect on skeletal muscle. Therefore, the increased incidence of hepatodiaphragmatic nodules in the female rats was not considered to be treatment related.

GENETIC TOXICOLOGY

Sodium azide (dose range of 0.03 to 33.3 μg/plate) produced a strong, dose-related increase in mutant colonies in *Salmonella typhimurium* strains TA100 and TA1535 when tested in a preincubation protocol with or without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9; no mutagenic activity was observed in strains TA1537 or TA98 with or without S9 (Zeiger *et al.*, 1987; Appendix C, Table C1). In cytogenetic tests with Chinese hamster ovary cells, sodium azide produced a significant increase in sister chromatid exchanges in both the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9; higher doses tested in the absence of S9 required delayed harvest to offset chemical-induced cell-cycle delay and allow recovery of sufficient metaphase cells for analysis (Appendix C, Tables C2 and C3). No induction of chromosomal aberrations occurred in Chinese hamster ovary cells after exposure to sodium azide with or without S9; delayed harvest was used in the trial without S9 to ensure adequate cells for analysis (Appendix C, Table C4).

DISCUSSION AND CONCLUSIONS

Sodium azide was nominated by the National Cancer Institute for evaluation of its carcinogenic activity because of the high potential for human exposure and the lack of adequate carcinogenicity testing. Sodium azide (>99% pure) was administered orally since the oral route is the common route of human exposure. Because sodium azide is unstable in feed formulations, the compound was administered by gavage.

In the 14-day studies all male and female rats receiving 40 and 80 mg/kg sodium azide and two females receiving 20 mg/kg died during the first week of the studies. No deaths occurred in the lower dose groups. Similarly, in the 13-week studies 7 of the 9 males and all 10 females receiving 20 mg/kg died, and no deaths occurred in the lower dose groups. There were no significant differences in mean body weight among the various dose groups. Clinical findings (labored breathing and hunched posture) and histopathologic lesions (brain necrosis and pulmonary congestion and hemorrhage) were seen in the rats administered 20 mg/kg sodium azide. Deaths in 20 mg/kg dose groups were attributed to brain necrosis. No treatment-related histopathologic lesions were observed in the lower dose groups. The results of these studies demonstrate a steep dose response for compound-related toxic effects of sodium azide in F344/N rats. The highest dose chosen was 10 mg/kg for the 2-year studies because of the lack of compound-related effects at this dose level in the 14-day and 13-week studies.

In the 2-year studies survival of the males and females receiving 10 mg/kg was significantly ($P<0.05$) lower than that of controls. The greatest decrease in survival occurred after week 90 of the studies; at week 90 approximately 52% of the high-dose males and 62% of the high-dose females were still alive. In contrast, the survival of low-dose animals was similar to that of controls; 47% of the low-dose males and 72% of the low-dose females survived until the end of the studies. Survival of control males and females was 41% and 62%. Most of the animals in the high-dose groups that died early had brain necrosis and pulmonary congestion, which were also noted in the early deaths in the 13-week studies. Brain necrosis was also seen in two low-dose males and one low-dose female that died early.

The 2-year studies demonstrate a cumulative toxicity from the long-term administration of sodium azide at doses that were not toxic in the short-term studies. Consequently, the maximum dose selected for the 2-year studies exceeded the maximum tolerated dose (MTD) and caused decreased survival. However, because the survival in the high-dose group of each sex was greater than 50% at week 90 of the studies, the majority of the animals were at risk for developing neoplasms. Moreover, survival was not reduced at 5 mg/kg, a dose very close to the MTD. Therefore, these studies are considered adequate for carcinogenicity assessment.

There was no increase in the incidence of neoplasms associated with the administration of sodium azide in the 2-year studies. The lack of carcinogenic activity may be partly explained by the fact that sodium azide, while acting as a potent mutagen in plant and bacterial species, is a weak mutagen in mammalian cells (Arenaz *et al.*, 1989). The mutagenic activity of sodium azide is thought to be mediated through its metabolite, azidoalanine. Arenaz *et al.* (1989) reported that both bacterial and mammalian systems possess the enzyme necessary to convert sodium azide, but mammalian cells do not appear to be able to produce significant quantities of the mutagenic metabolite. The authors offered two explanations for this difference in metabolite quantity. First, it is possible that further metabolic conversion is required to produce the compound ultimately responsible for mutagenicity and mammalian cells are unable to carry out this conversion. Alternatively, mammalian cells may contain enzyme systems that are capable of rapidly converting sodium azide to a nonmutagenic metabolite.

The most notable effect of long-term administration of sodium azide was necrosis of the brain in dosed rats. Many of the animals with brain necrosis also

had congestion and hemorrhage of the lung, lesions considered to be nonspecific and due to cardiovascular collapse. The lesions observed in the 2-year studies were similar to those seen in the 13-week studies. Administration of 20 mg/kg sodium azide in 13-week studies or 10 mg/kg in 2-year studies resulted in focal, bilaterally symmetrical necrosis of the caudate nucleus, putamen, or thalamus, or a combination, in most animals. Other areas of the brain (corpus callosum, hippocampus, or pons) were affected in a few animals. Similar findings have been reported previously in rats (Hicks, 1950) and in monkeys (Hurst, 1942) treated with sodium azide. Hurst (1942) found that brain necrosis occurred in monkeys after the administration of a single large dose or multiple large doses that caused unconsciousness, or after the administration of multiple small doses that caused no clinical signs. These results are similar to the results of the 2-year rodent studies, which demonstrate a cumulative toxicity in rats associated with repeated administration of small doses.

Brain necrosis was associated with substantial early mortality in the 13-week and 2-year studies. Brains of animals that died during the 2-year studies generally contained foci of acute brain necrosis as well as chronic lesions containing proliferating glial cells and blood vessels, indicative of a healing response secondary to necrosis. The presence of these chronic lesions demonstrates that animals could develop foci of brain necrosis and not necessarily die immediately. This agrees with the findings of the study conducted by Hicks (1950) in which rats were administered sodium azide at doses large enough to cause unconsciousness. Some of the rats died, but many regained consciousness, although there were no clinical findings of neurologic damage resulting from the treatment. It appears that whether an animal died from sodium azide-induced brain necrosis depended upon the extent and location of the lesions. Thus, it is possible that repeated administration of small doses produced foci of brain necrosis that in themselves were not lethal; however, when enough foci of necrosis occurred to produce extensive brain damage, or when necrosis occurred in a vital area, death resulted. This may explain the apparent cumulative toxicity seen in these 2-year studies.

The toxicity of sodium azide has been studied extensively and has been reviewed in detail (Kleinhofs *et al.*, 1978a; Frederick and Babish, 1982). Sodium azide produces toxicity by inhibiting cellular metabolism. It is known to inhibit cytochrome oxidase and may interfere with other enzymes as well. The consequence of this metabolic inhibition is cytotoxic anoxia, in which cellular damage occurs despite the presence of adequate oxygen. In this respect the mechanism of toxicity of sodium azide is similar to that of cyanide. Thus, toxic effects would not be expected to occur until intracellular levels of sodium azide were high enough to cause sufficient enzyme inhibition, which could explain the steep dose response to sodium azide. In addition, since enzyme levels vary from one individual to another, some animals may experience toxicity at a given dose, while other animals remain unaffected. Likewise, because enzyme levels can vary among cell types, some cells may be more susceptible to toxicity than others.

An interesting effect of sodium azide in these studies was its selective toxicity for the caudate nucleus, putamen, and thalamus. The selective toxicity of various compounds for specific areas of the brain is a well-known but incompletely understood phenomenon (Norton, 1986). Factors that have been implicated in the pathogenesis of this selective toxicity include: (1) selective exposure of specific areas of the brain due to the ability of the compound to reach those areas, (2) selective compound-induced anoxia due to differences in the blood flow or metabolic requirements of cells in different areas of the brain, and (3) selective susceptibility of specific cells to the compound due to biochemical differences among cells. The exact pathogenesis of the sodium azide-induced brain necrosis is unknown. However, it is possible that both factors (2) and (3) are involved, i.e., that the metabolic requirements of cells in the affected areas may be higher and the enzyme levels may be lower so that the cells are more susceptible to enzyme inhibition and subsequent cytotoxic anoxia.

The possibility that sodium azide may have had an effect on blood flow cannot be completely ruled out. Sodium azide is a potent hypotensive agent in humans and animals, acting directly on vascular smooth muscle to produce dilation of peripheral vessels (Kleinhofs *et al.*, 1978a; Frederick and Babish, 1982). Therapeutic doses (0.6 to 3.9 mg/day) in humans have been shown to lower blood pressure in hypertensive individuals, but have little or no effect in individuals with normal blood

pressure. A dose of 5 mg/kg sodium azide has been reported to decrease blood pressure in hypertensive rats. The effect on the blood pressure of normotensive rats has not been investigated. However, if sodium azide is capable of producing hypotension in normal rats the possibility exists for decreased perfusion of some areas of the brain, which could potentiate the cellular metabolic effects of the chemical.

Conclusions

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of sodium azide for male or female F344/N rats administered 5 or 10 mg/kg.

Sodium azide induced necrosis in the cerebrum and the thalamus of the brain in both male and female rats.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7. A summary of peer review comments and public discussion on this Technical Report appears on page 9.

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

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

	Vehicle Control	5 mg/kg	10 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Early deaths			
Dead	16	14	27
Moribund	19	18	15
Gavage death	1	1	9
Survivors			
Terminal sacrifice	24	27	9
Animals examined microscopically	60	60	60
Alimentary System			
Intestine large, colon	(50)	(54)	(55)
Intestine small, duodenum	(46)	(54)	(46)
Adenocarcinoma		1 (2%)	
Leiomyoma	1 (2%)		
Intestine small, ileum	(43)	(52)	(48)
Intestine small, jejunum	(42)	(51)	(44)
Liver	(60)	(60)	(60)
Hepatocellular adenoma		2 (3%)	
Neoplastic nodule	3 (5%)	1 (2%)	
Mesentery	(9)	(13)	(8)
Pancreas	(57)	(60)	(60)
Hemangiosarcoma, metastatic, spleen	1 (2%)		
Acinus, adenoma			1 (2%)
Salivary glands	(59)	(60)	(60)
Stomach, forestomach	(58)	(59)	(60)
Stomach, glandular	(58)	(60)	(59)
Leiomyosarcoma		1 (2%)	
Cardiovascular System			
Heart	(60)	(60)	(60)
Pericardium, carcinoma, metastatic, lung	1 (2%)		
Endocrine System			
Adrenal gland, cortex	(60)	(60)	(60)
Adrenal gland, medulla	(55)	(56)	(53)
Pheochromocytoma malignant	1 (2%)	1 (2%)	2 (4%)
Pheochromocytoma benign	17 (31%)	13 (23%)	3 (6%)
Bilateral, pheochromocytoma benign	8 (15%)	2 (4%)	1 (2%)
Islets, pancreatic	(59)	(60)	(60)
Adenoma	3 (5%)	2 (3%)	1 (2%)
Carcinoma	2 (3%)	2 (3%)	
Pituitary gland	(59)	(60)	(60)
Pars distalis, adenoma	23 (39%)	23 (38%)	15 (25%)
Thyroid gland	(57)	(58)	(59)
C-cell, adenoma	3 (5%)	7 (12%)	3 (5%)
C-cell, carcinoma		1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Sodium Azide
(continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Genital System			
Epididymis	(60)	(60)	(60)
Preputial gland	(59)	(59)	(55)
Adenoma	7 (12%)	9 (15%)	3 (5%)
Carcinoma		1 (2%)	
Prostate	(60)	(60)	(60)
Seminal vesicle	(59)	(60)	(60)
Testes	(60)	(60)	(60)
Bilateral, interstitial cell, adenoma	43 (72%)	35 (58%)	35 (58%)
Interstitial cell, adenoma	9 (15%)	16 (27%)	9 (15%)
Hematopoietic System			
Bone marrow	(59)	(60)	(60)
Lymph node	(58)	(56)	(58)
Mediastinal, carcinoma, metastatic, lung	1 (2%)		
Lymph node, mandibular	(55)	(55)	(55)
Spleen	(60)	(60)	(60)
Fibrosarcoma		1 (2%)	
Hemangiosarcoma	1 (2%)		1 (2%)
Thymus	(49)	(45)	(49)
Carcinoma, metastatic, lung	1 (2%)		
Integumentary System			
Mammary gland	(47)	(52)	(50)
Adenoma	1 (2%)		
Fibroadenoma	2 (4%)		
Skin	(58)	(59)	(60)
Keratoacanthoma	1 (2%)	1 (2%)	1 (2%)
Papilloma squamous	1 (2%)		2 (3%)
Squamous cell carcinoma	2 (3%)		
Trichoepithelioma	2 (3%)	1 (2%)	
Subcutaneous tissue, fibroma	2 (3%)	4 (7%)	2 (3%)
Subcutaneous tissue, fibroma, multiple		1 (2%)	
Subcutaneous tissue, fibrosarcoma			1 (2%)
Subcutaneous tissue, schwannoma malignant			2 (3%)
Musculoskeletal System			
Bone	(1)		(2)
Femur, osteosarcoma			1 (50%)
Sternum, carcinoma, metastatic, lung	1 (100%)		
Nervous System			
Brain	(60)	(60)	(60)
Cerebrum, glioma benign			1 (2%)
Cerebrum, granular cell tumor benign			1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Sodium Azide
(continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Respiratory System			
Lung	(60)	(60)	(60)
Alveolar/bronchiolar adenoma	1 (2%)		
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	
Carcinoma, metastatic, Zymbal's gland	1 (2%)		
Fibrosarcoma, metastatic, spleen		1 (2%)	
Osteosarcoma, metastatic, nose			1 (2%)
Nose	(59)	(60)	(60)
Osteosarcoma			1 (2%)
Squamous cell carcinoma		1 (2%)	
Trachea	(58)	(60)	(60)
Special Senses System			
Eye	(10)	(4)	(4)
Zymbal's gland	(3)	(1)	
Adenoma		1 (100%)	
Carcinoma	3 (100%)		
Urinary System			
Kidney	(60)	(60)	(60)
Renal tubule, adenoma	2 (3%)	1 (2%)	1 (2%)
Urinary bladder	(60)	(60)	(59)
Systemic Lesions			
Multiple organs[a]	(60)	(60)	(60)
Leukemia mononuclear	33 (55%)	28 (47%)	14 (23%)
Mesothelioma malignant	1 (2%)	2 (3%)	2 (3%)
Tumor Summary			
Total animals with primary neoplasms[b]	59	58	50
Total primary neoplasms	173	159	103
Total animals with benign neoplasms	58	57	49
Total benign neoplasms	129	119	79
Total animals with malignant neoplasms	40	33	23
Total malignant neoplasms	44	40	24
Total animals with secondary neoplasms[c]	4	2	3
Total secondary neoplasms	10	4	4

[a] The number in parentheses is the number of animals with any tissue examined microscopically.
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

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

Number of Days on Study	1 5 1	3 0 0	4 9 5	4 9 5	5 2 0	5 4 9	5 5 5	5 6 1	5 6 8	5 7 2	5 8 9	5 9 0	6 0 3	6 0 4	6 2 6	6 2 7	6 3 3	6 4 0	6 5 2	6 5 4	6 5 8	6 7 4	6 7 8	6 8 1	6 8 1
Carcass ID Number	0 4 5	1 1 5	0 1 5	0 4 4	0 6 5	0 8 5	1 2 5	0 7 5	1 1 4	1 0 5	0 8 4	0 5 5	1 1 3	2 7 4	0 7 4	0 7 3	0 2 4	1 1 2	0 3 5	1 2 3	0 8 3	0 2 3	1 2 2	0 5 4	0 7 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	A	+	+	+	A	+	+	A	+	A	+	A	+	+	+	+	+	+	A	+	A	A	+	+
Intestine large, cecum	+	A	A	+	+	A	+	+	A	A	A	+	A	+	+	+	+	+	+	A	+	A	A	+	+
Intestine large, colon	+	A	+	+	+	A	+	+	A	+	A	+	A	+	+	+	+	+	+	A	+	A	A	+	+
Intestine large, rectum	+	A	+	+	+	A	+	+	A	+	A	+	A	+	+	+	+	+	+	A	+	A	A	+	+
Intestine small	+	A	A	+	+	A	+	+	A	A	A	+	A	+	A	+	+	+	+	A	A	A	A	+	+
Intestine small, duodenum	+	A	A	+	+	A	+	+	A	A	A	+	A	+	A	+	+	+	+	A	A	A	A	+	+
Leiomyoma																									
Jejunum, mesothelioma malignant, metastatic, testes												X													
Intestine small, ileum	+	A	A	A	+	A	+	+	A	A	A	A	A	+	A	+	+	+	+	A	A	A	A	+	+
Intestine small, jejunum	+	A	A	A	M	A	+	+	A	A	A		A	+	A	+	+	+	A	A	A	A	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Mesentery						+						+													
Mesothelioma malignant, metastatic, testes												X													
Pancreas	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+
Hemangiosarcoma, metastatic, spleen																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pericardium, carcinoma, metastatic, lung							X																		
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign							X												X				X	X	
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Carcinoma																									

+: Tissue examined
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 Sodium Azide: Vehicle Control (continued)

Number of Days on Study	6 9 0	6 9 3	6 9 4	6 9 4	6 9 5	6 9 7	7 0 3	7 0 3	7 1 1	7 1 9	7 2 7	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	1 2 1	0 9 5	0 3 4	0 5 3	1 0 4	0 9 4	1 0 2	0 0 3	1 1 1	0 8 2	0 3 1	0 1 1	0 1 2	0 1 3	0 1 4	0 2 1	0 2 2	0 2 5	0 3 2	0 3 3	0 4 1	0 4 2	0 4 3	0 5 1	0 5 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Intestine large	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Jejunum, mesothelioma malignant, metastatic, testes																									
Intestine small, ileum	+	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule							X																X		
Mesentery											+							+							
Mesothelioma malignant, metastatic testes																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																					X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Stomach	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	A	+	+		+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pericardium, carcinoma, metastatic, lung																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																X									
Pheochromocytoma benign			X		X							X	X							X		X	X		
Bilateral, pheochromocytoma benign						X	X	X	X		X						X	X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X	X		
Carcinoma							X		X																

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: Vehicle Control (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 6 1	0 6 2	0 6 3	0 6 4	0 7 2	0 8 1	0 9 1	0 9 2	0 9 3	1 0 1	**Total Tissues/ Tumors**
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	59
Intestine large	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	46
Leiomyoma	X										1
Jejunum, mesothelioma malignant, metastatic, testes											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	60
Neoplastic nodule				X							3
Mesentery				+		+	+	+		+	9
Mesothelioma malignant, metastatic, testes											1
Pancreas	+	+	+	+	+	+	+	+	+	+	57
Hemangiosarcoma, metastatic, spleen											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	59
Stomach	+	+	+	+	+	+	+	+	+	+	59
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	58
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	58
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	60
Pericardium, carcinoma, metastatic, lung											1
Endocrine System											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	55
Pheochromocytoma malignant											1
Pheochromocytoma benign	X	X		X		X	X	X			17
Bilateral, pheochromocytoma benign										X	8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Adenoma											3
Carcinoma											2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: Vehicle Control (continued)

Number of Days on Study	1 5 1	3 0 0	4 9 5	4 9 5	5 2 0	5 4 9	5 5 5	5 6 1	5 6 8	5 7 2	5 8 9	5 9 0	6 0 3	6 0 4	6 2 6	6 2 7	6 3 3	6 4 0	6 5 2	6 5 4	6 5 8	6 7 4	6 7 8	6 8 1	6 8 1
Carcass ID Number	0 4 5	1 1 5	0 1 5	0 4 4	0 6 5	0 8 5	1 2 5	0 7 5	1 1 4	1 0 5	0 8 4	0 5 5	1 1 3	1 2 4	0 7 4	0 7 3	0 2 4	1 1 2	0 3 5	1 2 3	0 8 3	0 2 3	1 2 2	0 5 4	0 7 1
Endocrine System (continued)																									
Parathyroid gland	+	+	M	+	M	+	+	+	M	+	+	+	+	+	M	+	+	M	+	M	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X		X														X			X		X	X
Thyroid gland	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
General Body System																									
Tissue NOS							+																		
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes												X													
Preputial gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X								X													
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X	X			X	X	X	X		X	X	X			X	X	X	X	X	
Interstitial cell, adenoma				X	X			X	X					X					X						X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Mediastinal, carcinoma, metastatic, lung							X																		
Lymph node, mandibular	+	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	M
Carcinoma, metastatic, lung							X																		
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	M	A	M	M	+	M	+
Adenoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Keratoacanthoma		X																							
Papilloma squamous																	X								
Squamous cell carcinoma																						X			
Trichoepithelioma																									
Subcutaneous tissue, fibroma																					X				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: Vehicle Control (continued)

Number of Days on Study	6 9 0	6 9 3	6 9 4	6 9 4	6 9 5	6 9 7	7 0 3	7 0 3	7 1 1	7 1 9	7 2 7	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	1 2 1	0 9 5	0 3 4	0 5 3	1 0 4	0 9 4	1 0 2	1 0 3	1 1 1	0 8 2	0 3 1	0 1 1	0 1 2	0 1 3	0 2 4	0 2 1	0 2 2	0 2 5	0 3 2	0 3 3	0 4 1	0 4 2	0 4 3	0 5 1	0 5 2
Endocrine System (continued)																									
Parathyroid gland	+	M	+	M	+	+	+	M	+	M	M	+	+	M	+	M	+	+	M	+	+	M	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X			X					X		X	X		X		X		X			X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
C-cell, adenoma				X																					
General Body System																									
Tissue NOS																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X						X					X											
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, carcinoma, metastatic, lung																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X					
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+
Carcinoma, metastatic, lung																									
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+	M	+
Adenoma													X									X			
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Papilloma squamous																									
Squamous cell carcinoma																									
Trichoepithelioma														X											
Subcutaneous tissue, fibroma																								X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: Vehicle Control (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 6 1	0 6 2	0 6 3	0 6 4	0 7 2	0 8 1	0 9 1	0 9 2	0 9 3	1 0 1	Total Tissues/ Tumors
Endocrine System (continued)											
Parathyroid gland	+	+	+	+	+	+	M	+	+	M	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	59
Pars distalis, adenoma	X	X		X		X		X			23
Thyroid gland	+	+	+	+	+	+	+	+	+	+	57
C-cell, adenoma			X				X				3
General Body System											
Tissue NOS											1
Genital System											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Mesothelioma malignant, metastatic, testes											1
Preputial gland	+	+	+	+	+	+	+	+	+	+	59
Adenoma				X						X	7
Prostate	+	+	+	+	+	+	+	+	+		60
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	59
Testes	+	+	+	+	+	+	+	+	+	+	60
Bilateral, interstitial cell, adenoma	X		X	X	X	X	X	X	X	X	43
Interstitial cell, adenoma		X									9
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	59
Lymph node	+	+	+	+	+	+	+	+	+	+	58
Mediastinal, carcinoma, metastatic, lung											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	55
Spleen	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma											1
Thymus	+	M	M	+	+	+	+	M	M	+	49
Carcinoma, metastatic, lung											1
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	47
Adenoma											1
Fibroadenoma		X									2
Skin	+	+	+	+	+	+	+	+	+	+	58
Keratoacanthoma											1
Papilloma squamous											1
Squamous cell carcinoma				X							2
Trichoepithelioma		X									2
Subcutaneous tissue, fibroma											2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: Vehicle Control (continued)

Number of Days on Study	1 5 1	3 0 0	4 9 5	4 9 5	5 2 0	5 4 9	5 5 5	5 6 1	5 6 8	5 7 2	5 8 9	5 9 0	6 0 3	6 0 4	6 2 6	6 2 7	6 3 3	6 4 0	6 5 2	6 5 4	6 5 8	6 7 4	6 7 8	6 8 1	6 8 1
Carcass ID Number	0 4 5	1 1 5	0 1 5	0 4 4	0 6 5	0 8 5	1 2 5	0 7 5	1 1 4	1 0 5	0 8 4	0 5 5	1 1 3	1 2 4	0 7 4	0 7 3	0 2 4	1 1 2	0 3 5	1 2 3	0 8 3	0 2 3	0 2 2	1 5 4	0 7 1
Musculoskeletal System																									
Bone							+																		
Sternum, carcinoma, metastatic, lung							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma							X																		
Carcinoma, metastatic, Zymbal's gland																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																+		+							
Eye	+				+		+	+						+			+	+							
Zymbal's gland																+		+							
Carcinoma																X		X							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes												X													
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X		X	X		X		X	X			X		X	X		X	X	X	
Mesothelioma malignant												X													

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: Vehicle Control (continued)

Number of Days on Study	6 9 0	6 9 3	6 9 4	6 9 4	6 9 5	6 9 7	7 0 3	7 0 3	7 1 1	7 1 9	7 2 7	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	1 2 1	0 9 5	0 3 4	0 5 3	1 0 4	0 9 4	1 0 2	1 0 3	1 1 1	1 8 2	0 3 1	0 1 1	0 1 2	0 1 3	0 1 4	0 2 1	0 2 2	0 2 5	0 3 2	0 3 3	0 4 1	0 4 2	0 4 3	0 5 1	0 5 2
Musculoskeletal System																									
Bone																									
Sternum, carcinoma, metastatic, lung																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X										
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, Zymbal's gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Special Senses System																									
Ear																									
Eye											A								+						
Zymbal's gland					+																				
Carcinoma					X																				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																	X	X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X	X	X		X	X	X	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 Sodium Azide: Vehicle Control (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 6 1	0 6 2	0 6 3	0 6 4	0 7 2	0 8 1	0 9 1	0 9 2	0 9 3	1 0 1	Total Tissues/ Tumors
Musculoskeletal System											
Bone											1
Sternum, carcinoma, metastatic, lung											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	58
Spinal cord	+	+	+	+	+	+	+	+	+	+	58
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma											1
Alveolar/bronchiolar carcinoma											1
Carcinoma, metastatic, Zymbal's gland											1
Nose	+	+	+	+	+	+	+	+	+	+	59
Trachea	+	+	+	+	+	+	+	+	+	+	58
Special Senses System											
Ear		+	+								4
Eye		+	+								10
Zymbal's gland											3
Carcinoma											3
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Renal tubule, adenoma											2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Mesothelioma malignant, metastatic, testes											1
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear	X	X			X				X	X	33
Mesothelioma malignant											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg

Number of Days on Study	2 2 4 4 5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 2 2 0 3 0 1 2 4 7 7 8 9 3 3 4 4 4 5 6 7 8 8 9 9 9 6 7 3 7 2 6 9 7 6 9 9 1 2 9 0 1 8 9 0 3 1 3 0 0 3
Carcass ID Number	4 4 4 4 4 4 5 4 4 4 4 4 4 4 4 4 4 5 5 4 5 4 4 5 4 7 5 1 3 8 4 1 1 6 5 3 7 2 6 7 8 5 1 0 6 0 0 4 1 0 5 5 5 5 5 5 5 4 5 4 4 4 5 4 3 4 3 4 5 3 4 5 4 3 4
Alimentary System	
Esophagus	+ +
Intestine large	+ A + + + A + + + + A + + + + + + + + + + + + +
Intestine large, cecum	+ A + + + A + + A + A + + A + + + + + A + + + + A
Intestine large, colon	+ A + + + A + + + + A + + A + + + + + A + + + + A
Intestine large, rectum	+ A + + + A + + + + A + + + + + + + + + + + + A
Intestine small	+ A + + + + A + + + A + + + + + + + + + + + + A
Intestine small, duodenum	+ A + + + + A + + + A + + + + + + A + A + + + + A
Adenocarcinoma	X
Intestine small, ileum	+ A + + + A A + A + A + + A + + + + + A + + + + A
Intestine small, jejunum	A A + + + A A + A + A + + A + + + A + + + + + + A
Liver	+ +
Hepatocellular adenoma	X
Neoplastic nodule	
Mesentery	+ + +
Pancreas	+ +
Salivary glands	+ +
Stomach	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ +
Leiomyosarcoma	X
Tooth	
Cardiovascular System	
Heart	+ +
Endocrine System	
Adrenal gland	+ +
Adrenal gland, cortex	+ +
Adrenal gland, medulla	M + + + + + + + + + + + + + + + + + + M + + + + +
Pheochromocytoma malignant	
Pheochromocytoma benign	X X
Bilateral, pheochromocytoma benign	
Islets, pancreatic	+ +
Adenoma	X
Carcinoma	X
Parathyroid gland	+ M M + + M + + + M + M + + + + + + + M M + + M + +
Pituitary gland	+ +
Pars distalis, adenoma	X X X X X X X X
Thyroid gland	+ A +
C-cell, adenoma	X
C-cell, carcinoma	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

Number of Days on Study	6 9 8	7 0 2	7 0 4	7 0 8	7 1 2	7 1 6	7 1 7	7 2 3	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 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	4 8 3	5 0 1	4 0 3	5 0 3	4 6 2	4 1 3	4 0 2	4 5 2	4 0 1	4 1 1	4 1 2	4 2 1	4 2 2	4 2 3	4 2 4	4 3 1	4 3 2	4 3 3	4 4 1	4 4 2	4 4 3	4 5 1	4 6 1	4 7 1	4 7 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Neoplastic nodule					X																				
Mesentery					+		+				+			+	+								+		+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Tooth	+																								
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																		X							
Pheochromocytoma benign							X	X						X					X	X	X		X	X	X
Bilateral, pheochromocytoma benign									X																
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma										X															
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X		X					X		X	X	X	X	X								X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma								X	X	X					X							X			
C-cell, carcinoma											X														

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	4811	4882	4891	4992	4993	4994	4995	5052	5111	5112	**Total Tissues/ Tumors**
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Intestine	+	+	+	+	+	+	+	+	+	+	57
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	54
Intestine large, rectum	+	+	+	+	+	+	+	+	+	M	55
Intestine small	+	+	+	+	+	+	+	+	+	+	56
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	54
Adenocarcinoma											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	52
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular adenoma										X	2
Neoplastic nodule											1
Mesentery					+	+					13
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	M	+	59
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Leiomyosarcoma											1
Tooth											1
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, medulla	+	+	+	M	+	+	+	M	+	+	56
Pheochromocytoma malignant											1
Pheochromocytoma benign		X				X					13
Bilateral, pheochromocytoma benign					X						2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Adenoma			X								2
Carcinoma											2
Parathyroid gland	+	M	M	+	M	+	M	+	M	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma				X	X			X	X	X	23
Thyroid gland	+	+	+	+	M	+	+	+	+	+	58
C-cell, adenoma		X									7
C-cell, carcinoma											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

Number of Days on Study	226	227	403	437	502	516	529	547	576	579	589	591	632	639	640	641	648	659	660	673	681	683	690	690	693
Carcass ID Number	475	455	415	435	485	445	515	414	465	454	434	474	425	464	473	484	453	514	505	463	504	405	444	513	404
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																							X		
Preputial gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X		X										X								
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																							X		
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																							X		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma												X	X	X	X	X	X	X		X	X		X	X	X
Interstitial cell, adenoma				X		X			X	X	X											X			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Thymus	+	+	+	+	+	+	M	M	+	+	M	M	+	M	+	+	M	M	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+	+	+	+
Skin	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Trichoepithelioma																									
Subcutaneous tissue, fibroma															X										X
Subcutaneous tissue, fibroma multiple																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

Number of Days on Study	6 9 8	7 0 2	7 0 4	7 0 8	7 1 2	7 1 6	7 1 7	7 2 3	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 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	4 8 3	5 0 1	4 0 3	5 0 3	4 6 2	4 1 3	4 0 2	4 5 2	4 0 1	4 1 1	4 1 2	4 2 1	4 2 2	4 2 3	4 2 4	4 3 1	4 3 2	4 3 3	4 4 1	4 4 2	4 4 3	4 5 1	4 6 1	4 7 1	4 7 2
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X					X	X				X					
Carcinoma								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									
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	X					X									X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																					X				
Thymus	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	M	+	M	M	+	+	M	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Trichoepithelioma																					X				
Subcutaneous tissue, fibroma			X																				X		
Subcutaneous tissue, fibroma, multiple																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

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	
Carcass ID Number	4 8 1	4 8 2	4 9 1	4 9 2	4 9 3	4 9 4	4 9 5	5 0 2	5 1 1	5 1 2	**Total Tissues/ Tumors**
General Body System											
None											
Genital System											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Mesothelioma malignant, metastatic, testes											1
Preputial gland	+	+	+	+	+	+	+	+	+	+	59
Adenoma			X				X				9
Carcinoma											1
Prostate	+	+	+	+	+	+	+	+	+	+	60
Mesothelioma malignant, metastatic, testes											1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	60
Mesothelioma malignant, metastatic, testes											1
Testes	+	+	+	+	+	+	+	+	+	+	60
Bilateral, interstitial cell, adenoma	X	X	X			X				X	35
Interstitial cell, adenoma				X			X		X		16
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+	+	M	+	+	+	+	+	+	56
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	55
Spleen	+	+	+	+	+	+	+	+	+	+	60
Fibrosarcoma											1
Thymus	+	+	+	+	+	+	+	+	+	+	45
Integumentary System											
Mammary gland	+	+	+	M	+	+	+	+	+	+	52
Skin	+	+	+	+	+	+	+	+	+	+	59
Keratoacanthoma	X										1
Trichoepithelioma											1
Subcutaneous tissue, fibroma											4
Subcutaneous tissue, fibroma, multiple		X									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

Number of Days on Study	2 2 4 4 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 2 2 0 3 0 1 2 4 7 7 8 9 3 3 4 4 4 5 6 7 8 8 9 9 9 6 7 3 7 2 6 9 7 6 9 9 1 2 9 0 1 8 9 0 3 1 3 0 0 3
Carcass ID Number	4 4 4 4 4 4 5 4 4 4 4 4 4 4 4 4 4 4 5 5 4 5 4 4 5 4 7 5 1 3 8 4 1 1 6 5 3 7 2 6 7 8 5 1 0 6 0 0 4 1 0 5 5 5 5 5 5 5 4 5 4 4 4 5 4 3 4 3 4 5 3 4 5 4 3 4
Musculoskeletal System	
None	
Nervous System	
Brain	+ +
Peripheral nerve	+ +
Spinal cord	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar carcinoma	
Fibrosarcoma, metastatic, spleen	
Nose	+ +
Squamous cell carcinoma	X
Trachea	+ +
Special Senses System	
Ear	+
Eye	A + +
Harderian gland	+
Zymbal's gland	
Adenoma	
Urinary System	
Kidney	+ +
Renal tubule, adenoma	
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X X X X X X X X X X X
Mesothelioma malignant	X X X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg *(continued)*

Number of Days on Study	6 9 8	7 0 2	7 0 4	7 0 8	7 1 2	7 1 6	7 1 7	7 2 3	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 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	4 8 3	5 0 1	4 0 3	5 0 3	4 6 2	4 1 3	4 0 2	4 5 2	4 0 1	4 1 1	4 1 2	4 2 1	4 2 2	4 2 3	4 2 4	4 3 1	4 3 2	4 3 3	4 4 1	4 4 2	4 4 3	4 5 1	4 6 1	4 7 1	4 7 2
Musculoskeletal System																									
None																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																X									
Fibrosarcoma, metastatic, spleen																					X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																		+							
Harderian gland																									
Zymbal's gland																					+				
Adenoma																					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	X		X		X			
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

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	
Carcass ID Number	4 8 1	4 8 2	4 9 1	4 9 2	4 9 3	4 9 4	4 9 5	5 0 2	5 1 1	5 1 2	**Total Tissues/ Tumors**
Musculoskeletal System											
None											
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	58
Spinal cord	+	+	+	+	+	+	+	+	+	+	59
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar carcinoma											1
Fibrosarcoma, metastatic, spleen											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Squamous cell carcinoma											1
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Ear									+		2
Eye									+		4
Harderian gland											1
Zymbal's gland											1
Adenoma											1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Renal tubule, adenoma											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear	X		X							X	28
Mesothelioma malignant											2

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

Number of Days on Study	2 2 0	2 3 3	2 3 5	3 3 2	3 3 9	3 4 1	3 4 1	3 4 1	3 4 8	4 1 4	4 1 5	4 1 5	4 1 3	4 4 2	4 4 2	4 6 6	4 7 4	5 1 2	5 2 6	5 4 3	5 5 7	5 5 7	5 6 3	5 6 3	5 6 9	5 7 9
Carcass ID Number	3 3 1	3 6 5	2 7 5	2 8 5	2 9 4	2 9 2	2 9 3	2 9 5	2 6 5	3 1 5	3 1 3	3 1 4	3 4 4	3 4 5	3 8 4	3 3 5	3 6 4	3 5 5	3 2 5	2 5 4	2 5 5	2 6 4	2 6 3	2 7 4	2 8 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine large, cecum	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A
Intestine large, colon	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A
Intestine large, rectum	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A
Intestine small, duodenum	A	+	+	+	A	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	A	A	A
Intestine small, ileum	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A
Intestine small, jejunum	A	+	+	A	A	+	+	+	A	+	A	A	+	+	+	+	+	+	A	+	+	+	A	A	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery										+							+		+						
Mesothelioma malignant, metastatic																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	M	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Bilateral, pheochromocytom benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Parathyroid gland	+	+	+	+	M	+	+	+	M	M	+	M	+	+	+	+	+	M	+	M	+	+	+	M	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma													X		X		X								
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X																			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	5 9 1	5 9 6	6 0 7	6 1 7	6 3 7	6 4 0	6 4 5	6 4 5	6 4 8	6 4 9	6 5 0	6 5 4	6 5 9	6 6 2	6 6 2	6 6 2	6 6 7	6 6 7	6 6 9	6 7 0	6 7 7	6 7 7	6 7 7	6 8 1	7 0 1
Carcass ID Number	3 0 5	3 1 2	2 5 3	3 2 4	3 4 3	3 4 2	2 7 3	3 0 4	2 7 2	3 2 3	2 8 2	3 5 4	3 3 4	3 2 2	3 5 3	3 6 2	3 0 2	3 0 3	2 6 3	3 1 1	2 5 2	2 8 1	3 2 1	3 6 1	2 6 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	A	+	+	A	+	+	+	+	+	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	+	+	A	+	+	+	A	+	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	A	+	+	+	A	A	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	A	+	+	+	A	+	+	A	+	+	A	+	A	A	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	A	+	+	+	A	+	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+										+												+
Mesothelioma malignant, metastatic																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																			+						
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pheochromocytoma malignant																								X	
Pheochromocytoma benign															X										
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	M	+	M	M	+	+	+	+	M	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X					X	X	X	X						X	X				X	X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	7 1 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	2 7 1	2 5 1	2 6 1	2 9 1	3 0 1	3 3 2	3 3 3	3 4 1	3 5 1	3 5 2	**Total Tissues/ Tumor**
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Intestine large	+	+	+	+	+	+	+	+	+	+	56
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	55
Intestine large, rectum	+	+	M	+	+	+	+	+	+	+	55
Intestine small	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	60
Mesentery							+	+			8
Mesothelioma malignant, metastatic							X				1
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Acinus, adenoma			X								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	59
Tongue											1
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, medulla	+	+	+	+	M	+	+	+	+	+	53
Pheochromocytoma malignant									X		2
Pheochromocytoma benign	X									X	3
Bilateral, pheochromocytoma benign								X			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Adenoma											1
Parathyroid gland	+	M	+	M	+	+	+	M	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma						X	X				15
Thyroid gland	+	+	+	+	+	+	+	+	+	+	59
C-cell, adenoma					X					X	3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	2 2 2 3 3 3 3 3 3 4 4 4 4 4 4 4 5 5 5 5 5 5 5 5 5 2 3 3 3 3 4 4 4 4 1 1 1 3 3 6 7 1 2 4 5 5 6 6 6 7 0 3 5 2 9 1 1 1 8 4 5 5 2 2 6 4 2 6 3 7 7 3 3 9 9
Carcass ID Number	3 3 2 2 2 2 2 2 2 3 3 3 3 3 2 3 3 3 3 2 2 2 3 2 2 3 6 7 8 9 9 9 9 6 1 1 1 4 4 8 3 6 5 2 5 5 6 6 7 8 1 5 5 5 4 2 3 5 5 5 3 4 4 5 4 5 4 5 5 4 5 4 3 4 3
General Body System	
Tissue NOS	
Genital System	
Epididymis	+ +
Mesothelioma malignant, metastatic, testes	X
Preputial gland	+ + + M + M M M + + + + + + + + + + + + + + + + +
Adenoma	
Prostate	+ +
Seminal vesicle	+ +
Testes	+ +
Bilateral, interstitial cell, adenoma	X X X X X X X X
Interstitial cell, adenoma	X X X X X
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ + + + + + M + + + + + + + + + + + + + + + + + +
Lymph node, mandibular	+ + + + + + M + + + + + + M M + + + + + + + + + +
Spleen	+ +
Hemangiosarcoma	X
Thymus	+ + + + + + + + + M + + + + + + + + M + + + + + +
Integumentary System	
Mammary gland	M + + M + + + M + + + + M + + + + + M + M + + + +
Skin	+ +
Keratoacanthoma	
Papilloma squamous	X
Subcutaneous tissue, fibroma	
Subcutaneous tissue, fibrosarcoma	
Subcutaneous tissue, schwannoma malignant	X
Musculoskeletal System	
Bone	
Femur, osteosarcoma	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	5 9 1	5 9 6	6 0 7	6 1 7	6 3 7	6 4 0	6 4 5	6 4 5	6 4 8	6 4 9	6 5 0	6 5 4	6 5 9	6 6 2	6 6 2	6 6 2	6 6 7	6 6 7	6 6 9	6 7 0	6 7 7	6 7 7	6 7 7	6 8 1	7 0 1
Carcass ID Number	3 0 5	3 1 2	2 5 3	3 2 4	3 4 3	3 4 2	2 7 3	3 0 4	2 7 2	3 2 3	2 8 2	3 5 4	3 3 4	3 2 2	3 5 3	3 6 2	3 0 2	3 0 3	2 6 3	3 1 1	2 5 2	2 8 1	3 2 1	3 6 1	2 6 2
General Body System																									
Tissue NOS																				+					
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										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
Interstitial cell, adenoma	X						X										X					X			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	M	+	+	+	M	M	+	M	M	+	+	M	+	+	M	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma							X																		
Papilloma squamous																	X								
Subcutaneous tissue, fibroma				X																				X	
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, schwannoma malignant								X																	
Musculoskeletal System																									
Bone																					+				
Femur, osteosarcoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	7 1 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	2 7 1	2 5 1	2 6 1	2 9 1	3 0 1	3 3 2	3 3 3	3 4 1	3 5 1	3 5 2	**Total Tissues/ Tumors**
General Body System											
Tissue NOS											1
Genital System											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Mesothelioma malignant, metastatic, testes							X				2
Preputial gland	+	+	+	+	+	+	+	+	+	+	55
Adenoma								X			3
Prostate	+	+	+	+	+	+	+	+	+	+	60
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	60
Testes	+	+	+	+	+	+	+	+	+	+	60
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	35
Interstitial cell, adenoma											9
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+	+	+	+	+	+	+	+	+	58
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	55
Spleen	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma											1
Thymus	+	+	+	+	+	+	+	+	M	+	49
Integumentary System											
Mammary gland	M	+	+	+	+	+	+	+	+	M	50
Skin	+	+	+	+	+	+	+	+	+	+	60
Keratoacanthoma											1
Papilloma squamous											2
Subcutaneous tissue, fibroma											2
Subcutaneous tissue, fibrosarcoma											1
Subcutaneous tissue, schwannoma malignant											2
Musculoskeletal System											
Bone							+				2
Femur, osteosarcoma							X				1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	220	233	235	233	233	234	241	241	241	241	241	241	241	241	241	246	247	251	252	254	255	255	256	263	263	267	279
Carcass ID Number	331	366	375	385	394	402	409	423	435	465	511	513	514	544	545	548	553	564	525	545	555	564	543	633	644	653	683
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebrum, glioma benign																											
Cerebrum, granular cell tumor benign																											
Peripheral nerve	+	+	M	M	M	M	M	M	M	M	+	+	+	+	M	+	+	+	+	+	+	M	+	M	M		
Spinal cord	+	+	M	M	M	M	M	M	M	M	+	+	+	+	M	+	+	+	+	+	+	M	+	M	M		
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Osteosarcoma, metastatic, nose																									X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Osteosarcoma																									X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Special Senses System																											
Eye																+								+			
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Renal tubule, adenoma																											
Urinary bladder	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Leukemia mononuclear																X							X				
Mesothelioma malignant															X												

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	591	596	607	617	637	640	645	645	648	649	650	654	659	662	662	662	667	667	669	670	677	677	677	681	701
Carcass ID Number	305	312	253	324	343	342	273	304	272	323	282	354	334	322	353	362	302	303	263	311	252	281	321	361	262
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebrum, glioma benign								X																	
Cerebrum, granular cell tumor benign								X																	
Peripheral nerve	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, nose																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye			+													+									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma								X																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X							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 Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	7 1 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	2 7 1	2 5 1	2 6 1	2 9 1	3 0 1	3 3 2	3 3 3	3 4 1	3 5 1	3 5 2	Total Tissues/ Tumors
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Cerebrum, glioma benign											1
Cerebrum, granular cell tumor benign											1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	47
Spinal cord	+	+	+	+	+	+	+	+	+	+	47
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Osteosarcoma, metastatic, nose											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Osteosarcoma											1
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Eye											4
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Renal tubule, adenoma											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	59
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear	X				X	X					14
Mesothelioma malignant							X				2

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

	Vehicle Control	5 mg/kg	10 mg/kg
Adrenal Gland (Medulla): Pheochromocytoma Benign			
Overall rates[a]	25/55 (45%)	15/56 (27%)	4/54 (7%)
Adjusted rates[b]	70.5%	50.0%	35.6%
Terminal rates[c]	14/24 (58%)	11/25 (44%)	2/8 (25%)
First incidence (days)	555	579	662
Life table tests[d]	P=0.011N	P=0.027N	P=0.056N
Logistic regression tests[d]	P<0.001N	P=0.015N	P=0.002N
Cochran-Armitage test[d]	P<0.001N		
Fisher exact test[d]		P=0.032N	P<0.001N
Adrenal Gland (Medulla): Pheochromocytoma (Benign or Malignant)			
Overall rates	26/55 (47%)	16/56 (29%)	6/54 (11%)
Adjusted rates	73.4%	53.6%	50.8%
Terminal rates	15/24 (63%)	12/25 (48%)	3/8 (38%)
First incidence (days)	555	579	662
Life table tests	P=0.041N	P=0.026N	P=0.169N
Logistic regression tests	P=0.003N	P=0.014N	P=0.010N
Cochran-Armitage test	P<0.001N		
Fisher exact test		P=0.033N	P<0.001N
Islets, Pancreatic: Adenoma			
Overall rates	3/59 (5%)	2/60 (3%)	1/60 (2%)
Adjusted rates	10.6%	5.8%	2.2%
Terminal rates	2/24 (8%)	1/27 (4%)	0/9 (0%)
First incidence (days)	658	641	466
Life table tests	P=0.411N	P=0.455N	P=0.563N
Logistic regression tests	P=0.256N	P=0.484N	P=0.349N
Cochran-Armitage test	P=0.217N		
Fisher exact test		P=0.492N	P=0.303N
Islets, Pancreatic: Adenoma or Carcinoma			
Overall rates	5/59 (8%)	4/60 (7%)	1/60 (2%)
Adjusted rates	16.9%	12.0%	2.2%
Terminal rates	2/24 (8%)	2/27 (7%)	0/9 (0%)
First incidence (days)	658	641	466
Life table tests	P=0.274N	P=0.437N	P=0.367N
Logistic regression tests	P=0.134N	P=0.473N	P=0.164N
Cochran-Armitage test	P=0.078N		
Fisher exact test		P=0.489N	P=0.100N
Liver: Hepatocellular Adenoma or Neoplastic Nodule			
Overall rates	3/60 (5%)	3/60 (5%)	0/60 (0%)
Adjusted rates	11.5%	8.8%	0.0%
Terminal rates	2/24 (8%)	1/27 (4%)	0/9 (0%)
First incidence (days)	703	632	–[e]
Life table tests	P=0.254N	P=0.602N	P=0.345N
Logistic regression tests	P=0.201N	P=0.644N	P=0.309N
Cochran-Armitage test	P=0.102N		
Fisher exact test		P=0.660N	P=0.122N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Mammary Gland: Adenoma or Fibroadenoma			
Overall rates	3/60 (5%)	0/60 (0%)	0/60 (0%)
Adjusted rates	12.5%	0.0%	0.0%
Terminal rates	3/24 (13%)	0/27 (0%)	0/9 (0%)
First incidence (days)	729 (T)	–	–
Life table tests	P=0.070N	P=0.099N	P=0.335N
Logistic regression tests	P=0.070N	P=0.099N	P=0.335N
Cochran-Armitage test	P=0.037N		
Fisher exact test		P=0.122N	P=0.122N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	23/59 (39%)	23/60 (38%)	15/60 (25%)
Adjusted rates	65.2%	58.7%	56.9%
Terminal rates	13/24 (54%)	13/27 (48%)	2/9 (22%)
First incidence (days)	495	502	432
Life table tests	P=0.206	P=0.428N	P=0.156
Logistic regression tests	P=0.270N	P=0.536N	P=0.359N
Cochran-Armitage test	P=0.065N		
Fisher exact test		P=0.546N	P=0.075N
Preputial Gland: Adenoma			
Overall rates	7/59 (12%)	9/59 (15%)	3/55 (5%)
Adjusted rates	21.3%	26.7%	18.4%
Terminal rates	3/24 (13%)	6/27 (22%)	1/9 (11%)
First incidence (days)	495	502	649
Life table tests	P=0.543N	P=0.461	P=0.582N
Logistic regression tests	P=0.276N	P=0.394	P=0.321N
Cochran-Armitage test	P=0.180N		
Fisher exact test		P=0.394	P=0.191N
Preputial Gland: Adenoma or Carcinoma			
Overall rates	7/59 (12%)	10/59 (17%)	3/55 (5%)
Adjusted rates	21.3%	29.3%	18.4%
Terminal rates	3/24 (13%)	6/27 (22%)	1/9 (11%)
First incidence (days)	495	502	649
Life table tests	P=0.552	P=0.369	P=0.582N
Logistic regression tests	P=0.301N	P=0.301	P=0.321N
Cochran-Armitage test	P=0.187N		
Fisher exact test		P=0.301	P=0.191N
Skin: Squamous Cell Papilloma or Carcinoma			
Overall rates	3/60 (5%)	0/60 (0%)	2/60 (3%)
Adjusted rates	8.7%	0.0%	7.7%
Terminal rates	1/24 (4%)	0/27 (0%)	0/9 (0%)
First incidence (days)	633	–	563
Life table tests	P=0.596N	P=0.112N	P=0.583
Logistic regression tests	P=0.432N	P=0.120N	P=0.597N
Cochran-Armitage test	P=0.391N		
Fisher exact test		P=0.122N	P=0.500N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Skin (Subcutaneous Tissue): Fibroma			
Overall rates	2/60 (3%)	5/60 (8%)	2/60 (3%)
Adjusted rates	6.6%	14.6%	11.2%
Terminal rates	1/24 (4%)	2/27 (7%)	0/9 (0%)
First incidence (days)	658	640	617
Life table tests	P=0.251	P=0.267	P=0.412
Logistic regression tests	P=0.405	P=0.227	P=0.577
Cochran-Armitage test	P=0.583		
Fisher exact test		P=0.219	P=0.691N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma			
Overall rates	2/60 (3%)	5/60 (8%)	3/60 (5%)
Adjusted rates	6.6%	14.6%	21.1%
Terminal rates	1/24 (4%)	2/27 (7%)	1/9 (11%)
First incidence (days)	658	640	617
Life table tests	P=0.116	P=0.267	P=0.180
Logistic regression tests	P=0.224	P=0.227	P=0.310
Cochran-Armitage test	P=0.421		
Fisher exact test		P=0.219	P=0.500
Testes: Adenoma			
Overall rates	52/60 (87%)	51/60 (85%)	44/60 (73%)
Adjusted rates	100.0%	96.2%	100.0%
Terminal rates	24/24 (100%)	25/27 (93%)	9/9 (100%)
First incidence (days)	495	437	341
Life table tests	P=0.002	P=0.271N	P=0.001
Logistic regression tests	P=0.425	P=0.532N	P=0.530
Cochran-Armitage test	P=0.038N		
Fisher exact test		P=0.500N	P=0.054N
Thyroid Gland (C-Cell): Adenoma			
Overall rates	3/57 (5%)	7/58 (12%)	3/59 (5%)
Adjusted rates	11.5%	23.9%	23.6%
Terminal rates	2/23 (9%)	5/26 (19%)	2/9 (22%)
First incidence (days)	694	648	341
Life table tests	P=0.168	P=0.207	P=0.277
Logistic regression tests	P=0.361	P=0.191	P=0.578
Cochran-Armitage test	P=0.549N		
Fisher exact test		P=0.168	P=0.644N
Thyroid Gland (C-Cell): Adenoma or Carcinoma			
Overall rates	3/57 (5%)	8/58 (14%)	3/59 (5%)
Adjusted rates	11.5%	27.5%	23.6%
Terminal rates	2/23 (9%)	6/26 (23%)	2/9 (22%)
First incidence (days)	694	648	341
Life table tests	P=0.151	P=0.139	P=0.277
Logistic regression tests	P=0.334	P=0.126	P=0.578
Cochran-Armitage test	P=0.546N		
Fisher exact test		P=0.107	P=0.644N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Zymbal's Gland: Carcinoma			
Overall rates	3/60 (5%)	0/60 (0%)	0/60 (0%)
Adjusted rates	7.6%	0.0%	0.0%
Terminal rates	0/24 (0%)	0/27 (0%)	0/9 (0%)
First incidence (days)	627	–	–
Life table tests	P=0.060N	P=0.110N	P=0.240N
Logistic regression tests	P=0.038N	P=0.121N	P=0.148N
Cochran-Armitage test	P=0.037N		
Fisher exact test		P=0.122N	P=0.122N
Zymbal's Gland: Adenoma or Carcinoma			
Overall rates	3/60 (5%)	1/60 (2%)	0/60 (0%)
Adjusted rates	7.6%	3.7%	0.0%
Terminal rates	0/24 (0%)	1/27 (4%)	0/9 (0%)
First incidence (days)	627	729 (T)	–
Life table tests	P=0.115N	P=0.276N	P=0.240N
Logistic regression tests	P=0.077N	P=0.304N	P=0.148N
Cochran-Armitage test	P=0.061N		
Fisher exact test		P=0.309N	P=0.122N
All Organs: Mononuclear Leukemia			
Overall rates	33/60 (55%)	28/60 (47%)	14/60 (23%)
Adjusted rates	69.0%	60.3%	57.7%
Terminal rates	10/24 (42%)	10/27 (37%)	2/9 (22%)
First incidence (days)	520	226	474
Life table tests	P=0.306N	P=0.188N	P=0.433N
Logistic regression tests	P=0.003N	P=0.229N	P=0.009N
Cochran-Armitage test	P<0.001N		
Fisher exact test		P=0.233N	P<0.001N
All Organs: Benign Tumors			
Overall rates	58/60 (97%)	57/60 (95%)	49/60 (82%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	24/24 (100%)	27/27 (100%)	9/9 (100%)
First incidence (days)	300	437	341
Life table tests	P=0.002	P=0.272N	P=0.001
Logistic regression tests	P=0.237N	P=0.614N	P=0.304N
Cochran-Armitage test	P=0.003N		
Fisher exact test		P=0.500N	P=0.008N
All Organs: Malignant Tumors			
Overall rates	40/60 (67%)	33/60 (55%)	23/60 (38%)
Adjusted rates	77.6%	68.7%	80.7%
Terminal rates	13/24 (54%)	13/27 (48%)	5/9 (56%)
First incidence (days)	520	226	466
Life table tests	P=0.403	P=0.125N	P=0.297
Logistic regression tests	P=0.014N	P=0.128N	P=0.038N
Cochran-Armitage test	P=0.001N		
Fisher exact test		P=0.131N	P=0.002N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Sodium Azide
(continued)

	Vehicle Control	5 mg/kg	10 mg/kg
All Organs: Benign and Malignant Tumors			
Overall rates	59/60 (98%)	58/60 (97%)	50/60 (83%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	24/24 (100%)	27/27 (100%)	9/9 (100%)
First incidence (days)	300	226	341
Life table tests	P=0.002	P=0.274N	P=0.001
Logistic regression tests	P=0.040N	P=0.570N	P=0.116N
Cochran-Armitage test	P=0.001N		
Fisher exact test		P=0.500N	P=0.004N

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly to the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no tumors in animals group.

TABLE A4a
Historical Incidence of Tumors of the Adrenal Gland in Male F344/N Rats Receiving Vehicle by Gavage[a]

Study	Incidence in Controls	
	Pheochromocytoma, Benign	Pheochromocytoma, Malignant
Historical Incidence at Microbiological Associates		
Methyl carbamate	23/50	4/50
Overall Historical Incidence		
Total	126/349 (36.1%)	11/349 (3.2%)
Standard deviation	13.4%	4.1%
Range	10%-46%	0%-10%

[a] Data as of 22 November 1989 for studies of at least 104 weeks

TABLE A4b
Historical Incidence of Mononuclear Cell Leukemia in Male F344/N Rats Receiving Vehicle by Gavage[a]

Study	Incidence of Mononuclear Cell Leukemia in Controls
Historical Incidence at Microbiological Associates	
Methyl carbamate	23/50
Overall Historical Incidence	
Total	143/350 (40.9%)
Standard deviation	15.5%
Range	14%-60%

[a] Data as of 22 November 1989 for studies of at least 104 weeks

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

	Vehicle Control	5 mg/kg	10 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Early deaths			
Dead	16	14	27
Moribund	19	18	15
Gavage death	1	1	9
Survivors			
Terminal sacrifice	24	27	9
Animals examined microscopically	60	60	60
Alimentary System			
Intestine large, cecum	(48)	(53)	(49)
Epithelium, hyperplasia, focal		1 (2%)	
Liver	(60)	(60)	(60)
Angiectasis	13 (22%)	7 (12%)	12 (20%)
Basophilic focus	2 (3%)		1 (2%)
Basophilic focus, focal		1 (2%)	4 (7%)
Basophilic focus, multifocal	2 (3%)	3 (5%)	3 (5%)
Congestion	1 (2%)		3 (5%)
Cytoplasmic alteration, focal			1 (2%)
Degeneration, cystic	4 (7%)		
Eosinophilic focus, focal		1 (2%)	
Eosinophilic focus, multifocal		1 (2%)	
Fatty change, diffuse	1 (2%)	1 (2%)	
Fatty change, focal	1 (2%)		1 (2%)
Fatty change, multifocal	1 (2%)		
Fibrosis	1 (2%)		
Hepatodiaphragmatic nodule	3 (5%)	1 (2%)	4 (7%)
Hyperplasia, nodular, multifocal	1 (2%)		
Inflammation, granulomatous, multifocal	4 (7%)		1 (2%)
Leukocytosis	5 (8%)	3 (5%)	2 (3%)
Necrosis, focal	1 (2%)	1 (2%)	
Necrosis, multifocal	2 (3%)		
Pigmentation	1 (2%)		
Thrombus	1 (2%)		
Bile duct, hyperplasia	53 (88%)	56 (93%)	53 (88%)
Centrilobular, hemorrhage	1 (2%)		
Centrilobular, necrosis	2 (3%)	5 (8%)	1 (2%)
Periportal, fatty change	1 (2%)		
Mesentery	(9)	(13)	(8)
Inflammation, granulomatous, focal		1 (8%)	1 (13%)
Necrosis, focal		1 (8%)	
Artery, inflammation, chronic			1 (13%)
Fat, necrosis, focal	6 (67%)	10 (77%)	5 (63%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Alimentary System (continued)			
Pancreas	(57)	(60)	(60)
Cytoplasmic alteration, focal	1 (2%)		
Cytoplasmic alteration, multifocal		1 (2%)	
Acinus, atrophy	18 (32%)	20 (33%)	22 (37%)
Acinus, hyperplasia, focal	5 (9%)		
Artery, inflammation, chronic		1 (2%)	
Artery, inflammation, chronic active			1 (2%)
Duct, ectasia		1 (2%)	
Salivary glands	(59)	(60)	(60)
Acinus, atrophy	1 (2%)		1 (2%)
Stomach, forestomach	(58)	(59)	(60)
Erosion			3 (5%)
Hyperplasia, focal		1 (2%)	1 (2%)
Inflammation, chronic active	2 (3%)	1 (2%)	1 (2%)
Ulcer	5 (9%)	2 (3%)	5 (8%)
Stomach, glandular	(58)	(60)	(59)
Degeneration		1 (2%)	
Degeneration, cystic	37 (64%)	48 (80%)	35 (59%)
Erosion	1 (2%)		
Infiltration cellular, lymphocytic, focal		1 (2%)	1 (2%)
Infiltration cellular, lymphocytic, multifocal		1 (2%)	
Inflammation, chronic active	1 (2%)		1 (2%)
Mineralization			1 (2%)
Ulcer	1 (2%)	1 (2%)	
Tooth		(1)	
Dysplasia		1 (100%)	
Peridontal tissue, inflammation, suppurative		1 (100%)	
Cardiovascular System			
Heart	(60)	(60)	(60)
Cardiomyopathy	40 (67%)	26 (43%)	36 (60%)
Mineralization			1 (2%)
Thrombus		1 (2%)	
Artery, myocardium, degeneration			1 (2%)
Atrium, dilatation	1 (2%)		1 (2%)
Atrium, thrombus	10 (17%)	4 (7%)	
Epicardium, inflammation, chronic active, focal			1 (2%)
Myocardium, degeneration, hyaline	1 (2%)		
Myocardium, inflammation, chronic, focal			1 (2%)
Myocardium, atrium, inflammation, chronic		1 (2%)	
Valve, inflammation, suppurative	1 (2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Endocrine System			
Adrenal gland, cortex	(60)	(60)	(60)
Accessory adrenal cortical nodule			1 (2%)
Angiectasis		2 (3%)	
Congestion	1 (2%)		
Hemorrhage	1 (2%)		
Hyperplasia, focal	7 (12%)	6 (10%)	5 (8%)
Hypertrophy			1 (2%)
Hypertrophy, focal		1 (2%)	
Necrosis	1 (2%)		
Necrosis, multifocal		1 (2%)	
Vacuolization cytoplasmic, focal	15 (25%)	15 (25%)	8 (13%)
Adrenal gland, medulla	(55)	(56)	(53)
Hyperplasia, focal	15 (27%)	11 (20%)	11 (21%)
Parathyroid gland	(41)	(43)	(43)
Hyperplasia			1 (2%)
Pituitary gland	(59)	(60)	(60)
Angiectasis	3 (5%)	1 (2%)	1 (2%)
Cyst		3 (5%)	2 (3%)
Hemorrhage	1 (2%)	1 (2%)	
Pigmentation, hemosiderin	4 (7%)	1 (2%)	
Pigmentation, hemoglobin		1 (2%)	
Pars distalis, hyperplasia	1 (2%)		1 (2%)
Pars distalis, hyperplasia, focal	4 (7%)	7 (12%)	12 (20%)
Pars distalis, hyperplasia, multifocal	1 (2%)		
Pars nervosa, hyperplasia		1 (2%)	
Thyroid gland	(57)	(58)	(59)
Ultimobranchial cyst	1 (2%)		4 (7%)
C-cell, hyperplasia	5 (9%)	5 (9%)	1 (2%)
Follicle, cyst	1 (2%)	1 (2%)	
General Body System			
Tissue, NOS	(1)		(1)
Mineralization			1 (100%)
Thrombus	1 (100%)		
Genital System			
Epididymis	(60)	(60)	(60)
Spermatocele			1 (2%)
Preputial gland	(59)	(59)	(55)
Cyst			1 (2%)
Hyperplasia, glandular, focal	1 (2%)	1 (2%)	
Inflammation, chronic active	20 (34%)	10 (17%)	11 (20%)
Inflammation, suppurative			2 (4%)
Duct, ectasia		1 (2%)	1 (2%)
Prostate	(60)	(60)	(60)
Inflammation, chronic active	13 (22%)	4 (7%)	1 (2%)
Inflammation, suppurative		1 (2%)	1 (2%)
Epithelium, hyperplasia, focal	8 (13%)	9 (15%)	3 (5%)
Serosa, inflammation, suppurative		1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Genital System (continued)			
Seminal vesicle	(59)	(60)	(60)
Atrophy	1 (2%)	2 (3%)	
Inflammation, chronic active		1 (2%)	
Serosa, inflammation, suppurative		1 (2%)	
Testes	(60)	(60)	(60)
Hypospermia	5 (8%)	7 (12%)	1 (2%)
Arteriole, inflammation, necrotizing	1 (2%)		
Interstitial cell, hyperplasia	10 (17%)	11 (18%)	17 (28%)
Hematopoietic System			
Bone marrow	(59)	(60)	(60)
Atrophy	1 (2%)	1 (2%)	3 (5%)
Lymph node	(58)	(56)	(58)
Pigmentation, hemosiderin	1 (2%)	1 (2%)	
Lumbar, hemorrhage			2 (3%)
Lumbar, hyperplasia, plasma cell			1 (2%)
Lumbar, pigmentation, hemosiderin			1 (2%)
Mediastinal, hematopoietic cell proliferation		1 (2%)	
Mediastinal, hemorrhage	5 (9%)	9 (16%)	13 (22%)
Mediastinal, hyperplasia, re cell			1 (2%)
Mediastinal, infiltration cellular, mast cell	1 (2%)		
Mediastinal, infiltration cellular, histiocytic	2 (3%)		
Mediastinal, pigmentation, hemosiderin	1 (2%)	2 (4%)	
Mediastinal, sinus, ectasia	2 (3%)	2 (4%)	1 (2%)
Mesenteric, congestion		1 (2%)	
Mesenteric, degeneration, cystic			1 (2%)
Mesenteric, hemorrhage	3 (5%)	6 (11%)	3 (5%)
Mesenteric, inflammation, granulomatous			1 (2%)
Mesenteric, sinus, ectasia	6 (10%)	4 (7%)	5 (9%)
Pancreatic, hemorrhage	1 (2%)		1 (2%)
Pancreatic, sinus, ectasia	1 (2%)		
Lymph node, mandibular	(55)	(55)	(55)
Congestion			1 (2%)
Degeneration, cystic	1 (2%)		
Hemorrhage	3 (5%)		1 (2%)
Hyperplasia, lymphoid			1 (2%)
Hyperplasia, plasma cell		7 (13%)	1 (2%)
Sinus, ectasia	7 (13%)	9 (16%)	4 (7%)
Spleen	(60)	(60)	(60)
Ectopic tissue	4 (7%)	2 (3%)	
Fibrosis, diffuse	3 (5%)	2 (3%)	
Fibrosis, focal	7 (12%)	5 (8%)	4 (7%)
Fibrosis, multifocal	1 (2%)	1 (2%)	
Hematopoietic cell proliferation	1 (2%)	1 (2%)	
Hemorrhage		1 (2%)	
Hyperplasia, re cell		1 (2%)	
Necrosis, focal		1 (2%)	1 (2%)
Necrosis, multifocal		1 (2%)	
Red pulp, atrophy	1 (2%)	1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Hematopoietic System (continued)			
Thymus	(49)	(45)	(49)
Congestion			1 (2%)
Cyst		1 (2%)	
Ectopic tissue	1 (2%)		
Hemorrhage	2 (4%)	1 (2%)	5 (10%)
Epithelial cell, hyperplasia	29 (59%)	36 (80%)	40 (82%)
Integumentary System			
Mammary gland	(47)	(52)	(50)
Galactocele	1 (2%)		
Hyperplasia, nodular		1 (2%)	
Inflammation, granulomatous	1 (2%)	1 (2%)	
Duct, ectasia	3 (6%)	4 (8%)	2 (4%)
Fat, necrosis			1 (2%)
Skin	(58)	(59)	(60)
Abscess			1 (2%)
Ulcer		1 (2%)	
Musculoskeletal System			
Bone	(1)		(2)
Cranium, fibrous osteodystrophy			1 (50%)
Femur, fibrous osteodystrophy			1 (50%)
Nervous System			
Brain	(60)	(60)	(60)
Congestion			2 (3%)
Hemorrhage	7 (12%)	2 (3%)	6 (10%)
Hydrocephalus	1 (2%)		
Inflammation, chronic	1 (2%)		
Mineralization	1 (2%)		
Brain stem, compression		1 (2%)	
Cerebrum, inflammation, suppurative, focal	1 (2%)		
Cerebrum, necrosis		1 (2%)	24 (40%)
Medulla, gliosis		1 (2%)	
Meninges, hyperplasia			1 (2%)
Pons, necrosis			1 (2%)
Thalamus, gliosis			1 (2%)
Thalamus, necrosis		1 (2%)	25 (42%)
Spinal cord	(58)	(59)	(47)
Hemorrhage	2 (3%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Respiratory System			
Lung	(60)	(60)	(60)
Congestion	6 (10%)	4 (7%)	30 (50%)
Hemorrhage	4 (7%)	5 (8%)	17 (28%)
Infiltration cellular, histiocytic	11 (18%)	15 (25%)	21 (35%)
Inflammation, granulomatous, focal	1 (2%)		
Inflammation, suppurative, multifocal	1 (2%)		
Leukocytosis	2 (3%)		
Necrosis, focal	1 (2%)		1 (2%)
Pigmentation	8 (13%)	15 (25%)	19 (32%)
Pigmentation, hemoglobin	1 (2%)		1 (2%)
Thrombus	1 (2%)		
Alveolar epithelium, hyperplasia			1 (2%)
Alveolar epithelium, hyperplasia, focal	8 (13%)	7 (12%)	4 (7%)
Bronchiole, inflammation, suppurative	2 (3%)		
Bronchus, inflammation, suppurative	1 (2%)		
Interstitium, inflammation	3 (5%)	1 (2%)	
Interstitium, inflammation, focal		1 (2%)	
Peribronchiolar, foreign body		1 (2%)	
Peribronchiolar, alveolus, inflammation, suppurative	2 (3%)		
Pleura, fibrosis, focal			1 (2%)
Nose	(59)	(60)	(60)
Congestion	1 (2%)		3 (5%)
Fungus	3 (5%)	1 (2%)	
Hemorrhage	4 (7%)	2 (3%)	4 (7%)
Hyperkeratosis, focal	1 (2%)		
Inflammation, chronic active	1 (2%)		
Inflammation, suppurative	6 (10%)	3 (5%)	3 (5%)
Sinus, inflammation, chronic		1 (2%)	
Sinus, inflammation, chronic active		1 (2%)	
Sinus, inflammation, suppurative	1 (2%)		
Trachea	(58)	(60)	(60)
Infiltration cellular, lymphocytic, focal		1 (2%)	
Special Senses System			
Eye	(10)	(4)	(4)
Cataract	4 (40%)	3 (75%)	2 (50%)
Necrosis	1 (10%)		
Conjunctiva, inflammation, chronic active	2 (20%)		
Retina, degeneration	4 (40%)	4 (100%)	1 (25%)
Sclera, metaplasia, osseous	5 (50%)	2 (50%)	1 (25%)
Harderian gland		(1)	
Pigmentation, porphyrin		1 (100%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Urinary System			
Kidney	(60)	(60)	(60)
Congestion			1 (2%)
Cyst	4 (7%)	1 (2%)	1 (2%)
Inflammation, suppurative, multifocal	1 (2%)		
Necrosis, focal	1 (2%)		
Nephropathy	57 (95%)	57 (95%)	53 (88%)
Pigmentation	3 (5%)	4 (7%)	
Pelvis, epithelium, hyperplasia, focal		1 (2%)	
Renal tubule, necrosis		1 (2%)	
Urinary bladder	(60)	(60)	(59)
Infiltration cellular, lymphocytic	3 (5%)	3 (5%)	
Inflammation, suppurative	1 (2%)		
Ulcer	1 (2%)		
Transitional epithelium, hyperplasia, focal			1 (2%)

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

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

	Vehicle Control	5 mg/kg	10 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Early deaths			
Dead	11	5	22
Moribund	10	12	11
Gavage death	2	0	5
Survivors			
Terminal sacrifice	37[a]	43	21
Missexed	0	0	1
Animals examined microscopically	60	60	59
Alimentary System			
Intestine large, cecum	(54)	(58)	(55)
Hemangioma	1 (2%)		
Intestine large, colon	(56)	(59)	(57)
Polyp adenomatous			1 (2%)
Intestine small, duodenum	(55)	(58)	(52)
Intestine small, ileum	(53)	(58)	(51)
Intestine small, jejunum	(50)	(57)	(49)
Carcinoma		1 (2%)	
Liver	(60)	(60)	(59)
Neoplastic nodule	1 (2%)		
Sarcoma, metastatic, spleen		1 (2%)	
Mesentery	(16)	(10)	(7)
Sarcoma, metastatic, kidney	1 (6%)		
Sarcoma, metastatic, spleen		1 (10%)	
Pancreas	(60)	(60)	(58)
Sarcoma, metastatic, spleen		1 (2%)	
Stomach	(60)	(60)	(58)
Carcinoma, metastatic, intestine small		1 (2%)	
Stomach, forestomach	(60)	(57)	(57)
Papilloma squamous			1 (2%)
Stomach, glandular	(60)	(60)	(57)
Tongue	(1)	(1)	
Papilloma squamous	1 (100%)		
Squamous cell carcinoma		1 (100%)	
Cardiovascular System			
Heart	(60)	(60)	(58)
Endocrine System			
Adrenal gland	(60)	(60)	(59)
Extra adrenal tissue, sarcoma, metastatic, spleen		1 (2%)	
Adrenal gland, cortex	(60)	(60)	(58)
Adenoma	1 (2%)	2 (3%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Sodium Azide
(continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Endocrine System (continued)			
Adrenal gland, medulla	(58)	(54)	(56)
Ganglioneuroma		1 (2%)	
Pheochromocytoma malignant		1 (2%)	
Pheochromocytoma benign	1 (2%)	3 (6%)	1 (2%)
Bilateral, pheochromocytoma benign		1 (2%)	
Islets, pancreatic	(60)	(60)	(58)
Adenoma	1 (2%)	1 (2%)	
Parathyroid gland	(48)	(49)	(48)
Pituitary gland	(60)	(60)	(59)
Pars distalis, adenoma	35 (58%)	27 (45%)	17 (29%)
Pars distalis, carcinoma	2 (3%)	1 (2%)	
Pars intermedia, carcinoma		1 (2%)	
Thyroid gland	(60)	(60)	(56)
Bilateral, c-cell, adenoma		1 (2%)	
C-cell, adenoma	3 (5%)	2 (3%)	3 (5%)
C-cell, carcinoma	3 (5%)	1 (2%)	
Follicular cell, adenoma	1 (2%)	1 (2%)	
Genital System			
Clitoral gland	(55)	(57)	(49)
Adenoma	4 (7%)	2 (4%)	5 (10%)
Carcinoma	1 (2%)	2 (4%)	
Ovary	(60)	(60)	(59)
Carcinoma, metastatic, intestine small		1 (2%)	
Uterus	(60)	(60)	(59)
Adenocarcinoma			1 (2%)
Carcinoma, metastatic, intestine small		1 (2%)	
Polyp stromal	9 (15%)	18 (30%)	8 (14%)
Polyp stromal, multiple	3 (5%)	2 (3%)	3 (5%)
Sarcoma, metastatic, spleen		1 (2%)	
Sarcoma stromal			1 (2%)
Hematopoietic System			
Bone marrow	(60)	(60)	(59)
Histiocytic sarcoma	1 (2%)		
Lymph node	(59)	(59)	(59)
Deep cervical, carcinoma, metastatic	1 (2%)		
Mediastinal, sarcoma, metastatic, spleen		1 (2%)	
Mesenteric, carcinoma, metastatic, intestine small		1 (2%)	
Lymph node, mandibular	(51)	(52)	(50)
Spleen	(60)	(60)	(59)
Sarcoma, metastatic		1 (2%)	
Thymus	(42)	(51)	(49)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Sodium Azide
(continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Integumentary System			
Mammary gland	(58)	(55)	(56)
Adenocarcinoma	1 (2%)	1 (2%)	2 (4%)
Adenoma	2 (3%)		
Carcinoma	1 (2%)		1 (2%)
Fibroadenoma	15 (26%)	9 (16%)	8 (14%)
Fibroadenoma, multiple	5 (9%)	2 (4%)	
Skin	(59)	(60)	(59)
Subcutaneous tissue, fibroma	4 (7%)	1 (2%)	1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)		
Musculoskeletal System			
Bone		(2)	
Vertebra, chondroma		1 (50%)	
Nervous System			
Brain	(60)	(60)	(58)
Astrocytoma benign			1 (2%)
Carcinoma, metastatic, pituitary gland	2 (3%)	1 (2%)	
Oligodendroglioma benign		1 (2%)	
Respiratory System			
Lung	(60)	(60)	(59)
Alveolar/bronchiolar carcinoma		1 (2%)	
Carcinoma, metastatic, mammary gland	1 (2%)		
Carcinoma, metastatic, intestine small		1 (2%)	
Sarcoma, metastatic, spleen		1 (2%)	
Nose	(60)	(60)	(59)
Squamous cell carcinoma	1 (2%)		
Special Senses System			
Eye	(4)	(7)	(3)
Urinary System			
Kidney	(60)	(60)	(59)
Sarcoma	1 (2%)		
Sarcoma, metastatic, spleen		1 (2%)	
Renal tubule, carcinoma			1 (2%)
Urinary bladder	(60)	(58)	(58)
Systemic Lesions			
Multiple organs[b]	(60)	(60)	(59)
Histiocytic sarcoma	1 (2%)		
Leukemia mononuclear	16 (27%)	18 (30%)	11 (19%)
Lymphoma malignant lymphocytic		1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Sodium Azide
(continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Tumor Summary			
Total animals with primary neoplasms[c]	53	54	39
Total primary neoplasms	115	104	66
Total animals with benign neoplasms	47	44	34
Total benign neoplasms	87	75	49
Total animals with malignant neoplasms	25	26	16
Total malignant neoplasms	28	29	17
Total animals with secondary neoplasms[d]	5	3	
Total secondary neoplasms	5	15	

[a] Died last day of study
[b] The number in parentheses is the number of animals with any tissue examined microscopically.
[c] Primary tumors: all tumors except metastatic tumors
[d] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

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

Number of Days on Study	3 0 6	3 1 6	3 5 2	4 2 9	4 5 7	4 8 8	4 9 6	5 6 9	5 7 5	5 7 8	5 9 4	5 9 6	6 0 3	6 4 3	6 4 9	6 7 1	6 8 0	6 8 4	6 9 3	6 9 9	7 0 5	7 1 4	7 1 9	7 3 3	7 3 7
Carcass ID Number	1 8 5	1 8 4	2 2 5	1 5 5	2 2 4	2 1 5	1 3 1	1 6 5	2 1 4	1 8 3	1 7 5	1 3 5	1 7 4	1 9 5	1 5 4	2 0 3	1 5 3	2 4 5	1 5 2	2 4 4	2 0 5	2 3 5	1 9 4	1 8 1	1 3 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	M	+	+	A	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+
Hemangioma																									
Intestine large, colon	+	M	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	M	+	+	+	A	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small, duodenum	M	+	+	+	A	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small, ileum	M	M	+	+	A	+	A	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	A	+
Intestine small, jejunum	M	M	+	+	A	+	A	+	+	M	+	A	+	+	+	+	+	+	A	A	+	A	+	A	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Mesentery								+	+					+		+							+		
Sarcoma, metastatic, kidney																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Papilloma squamous																									
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																		X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	M	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X			X	X					X	X	X			X	X	X		X		
Pars distalis, carcinoma																			X				X		

+: Tissue examined
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 Sodium Azide: Vehicle Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	1 3 3	1 3 4	1 4 1	1 4 2	1 4 3	1 4 4	1 4 5	1 5 1	1 6 1	1 6 2	1 6 3	1 6 4	1 7 1	1 7 2	1 7 3	1 8 2	1 9 1	1 9 2	1 9 3	2 0 1	2 0 2	2 0 4	2 1 1	2 1 2	2 1 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma														X											
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule								X																	
Mesentery					+			+			+				+	+	+			+		+		+	+
Sarcoma, metastatic, kidney																								X	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue	+																								
Papilloma squamous	X																								
Tooth				+																					
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Parathyroid gland	M	+	M	+	+	+	+	+	+	M	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X	X	X	X		X		X	X		X				X			X	X	X	X	X	X	X
Pars distalis, carcinoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: Vehicle Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 2 1	2 2 2	2 2 3	2 3 1	2 3 2	2 3 3	2 3 4	2 4 1	2 4 2	2 4 3	**Total Tissues/ Tumors**
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Intestine large	+	+	+	+	+	+	+	+	+	+	59
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	54
Hemangioma											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	56
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	59
Intestine small	+	+	+	+	+	+	+	+	+	+	55
Intestine small, duodenum											55
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	60
Neoplastic nodule											1
Mesentery		+									16
Sarcoma, metastatic, kidney											1
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Salivary glands	+	+	+	+	+	+	+	+	+	+	59
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Tongue											1
Papilloma squamous											1
Tooth											1
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Adenoma											1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	58
Pheochromocytoma benign											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Adenoma											1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma	X	X	X	X	X		X			X	35
Pars distalis, carcinoma											2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: Vehicle Control (continued)

Number of Days on Study	3 0 6	3 1 6	3 5 2	4 2 9	4 5 7	4 8 8	4 9 6	5 6 9	5 7 5	5 7 8	5 9 4	5 9 6	6 0 3	6 4 3	6 4 9	6 7 1	6 8 0	6 9 4	6 9 3	6 9 9	7 0 5	7 1 4	7 1 9	7 3 3	7 3 7
Carcass ID Number	1 8 5	1 8 4	2 2 5	1 5 5	2 2 4	2 1 5	1 3 1	1 6 5	2 1 4	1 8 3	1 7 5	1 3 5	1 7 4	1 9 5	1 5 4	1 0 3	2 5 3	1 4 5	2 5 2	2 4 4	2 0 5	2 3 5	1 9 4	1 8 1	1 3 2
Endocrine System (continued)																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma										X															
Follicular cell, adenoma																							X		
General Body System																									
Tissue NOS																						+			
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+
Adenoma																		X				X			X
Carcinoma											X														
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal										X															X
Polyp stromal, multiple												X													
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, carcinoma, metastatic																									
Lymph node, mandibular	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma															X										
Carcinoma						X																			
Fibroadenoma									X								X			X					
Fibroadenoma, multiple													X										X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma												X													X
Subcutaneous tissue, sarcoma			X																						
Musculoskeletal System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: Vehicle Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	1 3 3	1 3 4	1 4 1	1 4 2	1 4 3	1 4 4	1 4 5	1 5 1	1 6 1	1 6 2	1 6 3	1 6 4	1 7 1	1 7 2	1 7 3	1 8 2	1 9 1	1 9 2	1 9 3	2 0 1	2 0 2	2 0 4	2 1 1	2 1 2	2 1 3
Endocrine System (continued)																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X																		X
C-cell, carcinoma																									
Follicular cell, adenoma																									
General Body System																									
Tissue NOS																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+
Adenoma															X										
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal	X				X									X		X		X		X					
Polyp stromal, multiple										X													X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, carcinoma, metastatic																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	I	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	M	+	M	+	M	M	+	+	M	+	+	M	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma	X																								
Carcinoma																									
Fibroadenoma	X			X											X							X		X	X
Fibroadenoma, multiple		X			X																				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																X				X					
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: Vehicle Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 2 1	2 2 2	2 2 3	2 3 1	2 3 2	2 3 3	2 3 4	2 4 1	2 4 2	2 4 3	**Total Tissues/ Tumors**
Endocrine System (continued)											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
C-cell, adenoma									X		3
C-cell, carcinoma				X		X					3
Follicular cell, adenoma											1
General Body System											
Tissue NOS											1
Genital System											
Clitoral gland	+	+	+	+	+	+	M	+	+	+	55
Adenoma											4
Carcinoma											1
Ovary	+	+	+	+	+	+	+	+	+	+	60
Uterus	+	+	+	+	+	+	+	+	+	+	60
Polyp stromal						X					9
Polyp stromal, multiple											3
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma							X				1
Lymph node	+	+	+	+	+	+	+	+	+	+	59
Deep cervical, carcinoma, metastatic				X							1
Lymph node, mandibular	+	M	+	+	+	M	M	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	60
Thymus	+	M	+	M	M	M	+	+	+	M	42
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	58
Adenocarcinoma							X				1
Adenoma											2
Carcinoma											1
Fibroadenoma		X	X	X	X	X				X	15
Fibroadenoma, multiple							X				5
Skin	+	+	+	+	+	+	+	+	+	+	59
Subcutaneous tissue, fibroma											4
Subcutaneous tissue, sarcoma											1
Musculoskeletal System											
None											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: Vehicle Control (continued)

Number of Days on Study	3 3 3 4 4 4 4 5 5 5 5 5 6 6 6 6 6 6 6 7 7 7 7 7 0 1 5 2 5 8 9 6 7 7 9 9 0 4 4 7 8 8 9 9 0 1 1 3 3 6 6 2 9 7 8 6 9 5 8 4 6 3 3 9 1 0 4 3 9 5 4 9 3 7
Carcass ID Number	1 1 2 1 2 2 1 1 2 1 1 1 1 1 1 2 1 2 1 2 2 2 1 1 1 8 8 2 5 2 1 3 6 1 8 7 3 7 9 5 0 5 4 5 4 0 3 9 8 3 5 4 5 5 4 5 1 5 4 3 5 5 4 5 4 3 3 5 2 4 5 5 4 1 2
Nervous System	
Brain	+ +
Carcinoma, metastatic, pituitary gland	X X
Peripheral nerve	+ + M + + + + + + + + + + + + + M + + + + + + + +
Spinal cord	+ + M +
Respiratory System	
Lung	+ +
Carcinoma, metastatic, mammary gland	X
Nose	+ +
Squamous cell carcinoma	X
Trachea	+ +
Special Senses System	
Eye	+ A + +
Harderian gland	+
Zymbal's gland	+
Urinary System	
Kidney	+ +
Sarcoma	
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Histiocytic sarcoma	
Leukemia mononuclear	X X X X X X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: Vehicle Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	1 3 3	1 3 4	1 4 1	1 4 2	1 4 3	1 4 4	1 4 5	1 5 1	1 6 1	1 6 2	1 6 3	1 6 4	1 7 1	1 7 2	1 7 3	1 8 2	1 9 1	1 9 2	1 9 3	2 0 1	2 0 2	2 0 4	2 1 1	2 1 2	2 1 3
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																						+			
Harderian gland																						+			
Zymbal's gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																							X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear		X							X	X											X		X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: Vehicle Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 2 1	2 2 2	2 2 3	2 3 1	2 3 2	2 3 3	2 3 4	2 4 1	2 4 2	2 4 3	**Total Tissues/ Tumors**
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, pituitary gland											2
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	58
Spinal cord	+	+	+	+	+	+	+	+	+	+	58
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, mammary gland											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Squamous cell carcinoma											1
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Eye											4
Harderian gland											2
Zymbal's gland											1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Sarcoma											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma							X				1
Leukemia mononuclear	X		X				X	X		X	16

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg

Number of Days on Study	4 5 3	5 0 2	5 4 0	5 4 9	6 0 3	6 0 4	6 2 8	6 4 8	6 7 0	6 8 4	6 9 5	7 0 5	7 1 9	7 2 1	7 2 2	7 2 8	7 2 8	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	6 8 5	7 8 5	7 4 5	7 7 5	6 7 5	6 9 5	7 5 5	6 8 4	7 5 4	7 6 5	7 6 4	7 0 5	7 4 4	7 0 3	6 7 4	6 7 1	6 8 3	6 7 2	6 7 3	6 8 1	6 8 2	6 9 1	6 9 2	6 9 3	6 9 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+
Carcinoma													X												
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, spleen																X									
Mesentery	+											+				+			+						
Sarcoma, metastatic, spleen																X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, spleen																X									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small													X												
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell carcinoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Extra adrenal tissue, sarcoma, metastatic, spleen																X									
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	M	M	+	M	M	+	+	M	+	+	+	+	+	+	M	+	
Ganglioneuroma																									
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	701	700	704	711	711	711	711	711	712	712	712	712	712	713	713	713	713	713	714	714	714	715	715	715	716
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, spleen																									
Mesentery			+											+										+	
Sarcoma, metastatic, spleen																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, spleen																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small																									
Stomach, forestomach	M	+	+	+	+	+	+	+	+	+		+	+	+	+	M	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue															+										
Squamous cell carcinoma															X										
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Extra adrenal tissue, sarcoma, metastatic, spleen																									
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X									X						
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ganglioneuroma							X																		
Pheochromocytoma malignant																									
Pheochromocytoma benign					X															X					
Bilateral, pheochromocytoma benign																								X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	762	763	771	772	773	774	781	782	783	784	**Total Tissues/ Tumors**
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Intestine large	+	+	+	+	+	+	+	+	+	+	60
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	58
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	59
Intestine large, rectum	+	+	M	+	+	+	+	+	+	+	59
Intestine small	+	+	+	+	+	+	+	+	+	+	59
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	58
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	58
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	57
Carcinoma											1
Liver	+	+	+	+	+	+	+	+	+	+	60
Sarcoma, metastatic, spleen											1
Mesentery	+						+		+		10
Sarcoma, metastatic, spleen											1
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Sarcoma, metastatic, spleen											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, intestine small											1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	57
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Tongue											1
Squamous cell carcinoma											1
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Extra adrenal tissue, sarcoma, metastatic, spleen											1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Adenoma											2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	54
Ganglioneuroma											1
Pheochromocytoma malignant					X						1
Pheochromocytoma benign		X									3
Bilateral, pheochromocytoma benign											1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

Number of Days on Study	4 5 3	5 0 2	5 4 0	5 4 9	6 0 3	6 0 4	6 2 8	6 4 8	6 7 0	6 8 4	6 9 5	7 0 5	7 1 9	7 2 1	7 2 2	7 2 8	7 2 8	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	6 8 5	7 8 5	7 4 5	7 7 5	6 7 5	6 9 5	7 5 5	6 8 4	7 5 4	7 6 5	7 6 4	6 0 5	7 4 4	6 0 3	6 7 4	6 7 1	6 8 3	7 7 2	6 8 3	6 8 1	6 8 2	6 9 1	6 9 2	6 9 3	6 9 4
Endocrine System (continued)																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X			X		X	X		X				X	X			X				X		X	X	X
Pars distalis, carcinoma										X															
Pars intermedia, carcinoma															X										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma																X									
C-cell, carcinoma																									
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma		X																							
Carcinoma	X																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small													X												
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small													X												
Polyp stromal			X	X							X										X	X	X		
Polyp stromal, multiple																				X					
Sarcoma, metastatic, spleen																X									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, sarcoma, metastatic, spleen																X									
Mesenteric, carcinoma, metastatic, intestine small													X												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	M	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic																X									
Thymus	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	701	702	704	711	712	713	714	715	721	722	723	724	725	731	732	733	734	735	741	742	743	751	752	753	761
Endocrine System (continued)																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X																							
Parathyroid gland	+	+	+	+	+	M	+	M	+	M	+	+	+	+	M	+	M	+	M	+	M	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X			X				X	X	X		X	X				X			X				X	
Pars distalis, carcinoma																									
Pars intermedia, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma		X																							
C-cell, carcinoma					X																				
Follicular cell, adenoma					X																				
General Body System																									
None																									
Genital System																									
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																						
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small																									
Polyp stromal	X		X				X	X	X	X								X				X		X	
Polyp stromal, multiple																									
Sarcoma, metastatic, spleen																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, sarcoma, metastatic, spleen																									
Mesenteric, carcinoma, metastatic, intestine small																									
Lymph node, mandibular	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

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	
Carcass ID Number	7 6 2	7 6 3	7 7 1	7 7 2	7 7 3	7 7 4	7 8 1	7 8 2	7 8 3	7 8 4	**Total Tissues/ Tumors**
Endocrine System (continued)											
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Adenoma											1
Parathyroid gland	+	+	M	+	+	M	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma	X	X	X					X	X		27
Pars distalis, carcinoma											1
Pars intermedia, carcinoma											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
Bilateral, C-cell, adenoma								X			1
C-cell, adenoma											2
C-cell, carcinoma											1
Follicular cell, adenoma											1
General Body System											
None											
Genital System											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	57
Adenoma											2
Carcinoma										X	2
Ovary	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, intestine small											1
Uterus	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, intestine small											1
Polyp stromal					X	X			X		18
Polyp stromal, multiple							X				2
Sarcoma, metastatic, spleen											1
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+	+	+	+	+	+	+	+	+	59
Mediastinal, sarcoma, metastatic, intestine small											1
Mesenteric, carcinoma, metastatic, intestine small											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	52
Spleen	+	+	+	+	+	+	+	+	+	+	60
Sarcoma, metastatic											1
Thymus	+	+	+	+	+	+	M	+	+	+	51

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

Number of Days on Study	4 5 3	5 0 2	5 4 0	5 4 9	6 0 3	6 0 4	6 2 8	6 4 8	6 7 0	6 8 4	6 9 5	7 0 5	7 1 9	7 2 1	7 2 2	7 2 8	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	6 8 5	7 8 5	7 4 5	7 7 5	6 7 5	6 9 5	7 5 5	6 8 4	7 5 4	7 6 5	7 6 4	7 6 5	7 4 4	7 0 3	6 7 4	6 7 1	6 8 3	6 7 2	6 7 3	6 8 1	6 8 2	6 9 1	6 9 2	6 9 3	6 9 4
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	M	+	+
Adenocarcinoma																									
Fibroadenoma													X							X					
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone									+																
Vertebra, chondroma									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland										X															
Oligodendroglioma benign																							X		
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, intestine small													X												
Sarcoma, metastatic, spleen																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear				+																					
Eye	+		+	+	+																				
Harderian gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, spleen																X									
Urinary bladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X		X	X			X	X	X										X		
Lymphoma malignant lymphocytic																			X						

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

Number of Days on Study	730	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700
Carcass ID Number	701	702	704	711	712	713	714	715	721	722	723	724	725	731	732	733	734	735	741	742	743	751	752	753	761
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma													X												
Fibroadenoma			X	X							X											X		X	
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma													X												
Musculoskeletal System																									
Bone		+																							
Vertebra, chondroma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Oligodendroglioma benign																									
Peripheral nerve	+	+	M	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma	X																								
Carcinoma, metastatic, intestine small																									
Sarcoma, metastatic, spleen																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear											+														
Eye											+	+													
Harderian gland											+														
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, spleen																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X											X		X		X			X	X		X
Lymphoma malignant lymphocytic																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 5 mg/kg (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	762	763	771	772	773	774	781	782	783	784	**Total Tissues/ Tumors**
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	55
Adenocarcinoma											1
Fibroadenoma	X	X									9
Fibroadenoma, multiple					X			X			2
Skin	+	+	+	+	+	+	+	+	+	+	60
Subcutaneous tissue, fibroma											1
Musculoskeletal System											
Bone											2
Vertebra, chondroma											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, pituitary gland											1
Oligodendroglioma benign											1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	58
Spinal cord	+	+	+	+	+	+	+	+	+	+	60
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar carcinoma											1
Carcinoma, metastatic, intestine small											1
Sarcoma, metastatic, spleen											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Ear					+						3
Eye					+						7
Harderian gland											1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Sarcoma, metastatic, spleen											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	58
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear							X			X	18
Lymphoma malignant lymphocytic											1

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

Number of Days on Study	0 6 5	1 0 3	1 0 4	1 0 6	1 0 8	1 0 8	1 0 9	1 4 1	1 5 2	2 0 1	2 0 6	3 9 5	4 4 9	4 6 8	4 8 8	4 9 5	5 0 2	5 0 2	5 1 6	5 4 9	5 6 9	6 1 0	6 1 2	6 4 2	6 4 6
Carcass ID Number	5 7 1	5 5 5	5 6 5	5 7 5	5 6 4	5 7 4	6 0 5	6 6 3	5 5 4	5 8 5	6 2 5	6 1 5	6 3 5	6 3 4	5 7 3	5 4 5	5 8 4	6 3 3	5 4 4	5 2 5	6 0 4	5 9 5	6 2 4	5 3 5	5 3 2
Alimentary System																									
Esophagus		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large		+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum		+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine large, colon		+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous														X											
Intestine large, rectum		+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small		+	A	+	+	+	A	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+
Intestine small, duodenum		+	A	+	+	+	A	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+
Intestine small, ileum		+	A	+	+	+	A	A	+	+	+	A	+	+	A	+	A	+	+	+	+	+	A	+	+
Intestine small, jejunum		+	A	+	+	+	A	A	+	+	+	A	+	+	A	+	A	+	+	+	+	+	A	+	+
Liver		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery						+										+						+			
Pancreas		+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach		+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach		+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									X
Stomach, glandular		+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+
Tooth																									
Cardiovascular System																									
Heart		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla		+	+	+	+	I	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic		+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Parathyroid gland		+	+	+	M	M	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	M	+
Pituitary gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																	X	X							
Thyroid gland		+	+	+	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	6 4 6	6 4 6	6 4 7	6 4 9	6 5 0	6 5 3	6 5 4	6 5 4	6 5 9	6 6 0	6 6 7	6 8 8	6 9 1	7 0 5	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	5 3 3	5 3 4	5 3 1	5 5 3	6 1 2	6 1 4	5 8 3	6 1 3	5 2 4	5 5 2	5 9 4	5 8 2	5 4 3	5 9 3	5 2 1	5 2 2	5 2 3	5 4 1	5 4 2	5 5 1	5 6 1	5 6 2	5 7 2	5 8 1	5 9 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery									+																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X		X	X							X					X	X	X	X					X	X
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																			X						

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	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	5 9 2	6 0 1	6 0 2	6 0 3	6 1 1	6 2 1	6 2 2	6 2 3	6 3 1	6 3 2	**Total Tissues/ Tumors**
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	59
Intestine large	+	+	+	+	+	+	+	+	+	+	58
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	55
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	57
Polyp adenomatous											1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	58
Intestine small	+	+	+	+	+	+	+	+	+	+	52
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	52
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	59
Mesentery				+			+	+			7
Pancreas	+	+	+	+	+	+	+	+	+	+	58
Salivary glands	+	+	+	+	+	+	+	+	+	+	59
Stomach	+	+	+	+	+	+	+	+	+	+	58
Stomach, forestomach	+	+	+	+	+	+	+	+	+		57
papilloma squamous											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	57
Tooth										+	1
Cardiovascular System											
Heart	+	+	+	+	+	+	+	+	+	+	58
Endocrine System											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	59
Adrenal gland, cortex	+	+	+	+	+	+		+	+	+	58
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	56
Pheochromocytoma benign						X					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	58
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	59
Pars distalis, adenoma	X				X			X	X	X	17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	56
C-cell, adenoma						X		X			3

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	0 6 5	1 0 3	1 0 4	1 0 6	1 0 8	1 0 8	1 0 9	1 4 1	1 5 2	2 0 1	2 0 6	3 9 5	4 4 9	4 6 8	4 8 8	4 9 5	5 0 2	5 0 2	5 1 6	5 4 9	5 6 9	6 1 0	6 1 2	6 4 2	6 4 6
Carcass ID Number	5 7 1	5 5 5	5 6 5	5 7 5	5 6 4	5 7 4	6 0 5	5 6 3	5 5 4	5 8 5	6 2 5	6 1 5	6 3 5	6 3 4	5 7 3	5 4 5	5 8 4	5 3 3	5 4 4	5 2 5	6 0 4	5 9 5	6 2 4	5 3 5	5 3 2
General Body System																									
None																									
Genital System																									
Clitoral gland	M	M	+	M	M	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Polyp stromal															X				X						
Polyp stromal, multiple																									
Sarcoma stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	I	+	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																X									
Carcinoma																									
Fibroadenoma																		X					X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	6 4 6	6 4 6	6 4 7	6 4 9	6 5 0	6 5 3	6 5 4	6 5 4	6 5 9	6 6 0	6 6 7	6 8 8	6 9 1	7 0 5	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	5 3 3	5 3 4	5 3 1	5 5 3	6 1 2	6 1 4	5 8 3	6 1 3	5 2 4	5 5 2	5 9 4	5 8 2	5 4 3	5 9 3	5 2 1	5 2 2	5 2 3	5 4 1	5 4 2	5 5 1	5 6 1	5 6 2	5 7 2	5 8 1	5 9 1
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X		X	X	X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma													X											
Polyp stromal				X					X	X								X						
Polyp stromal, multiple						X														X				
Sarcoma stromal																								X
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	M	+	+
Integumentary System																								
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma														X										
Carcinoma																		X						
Fibroadenoma	X	X															X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma								X																
Musculoskeletal System																								
None																								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	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	5 9 2	6 0 1	6 0 2	6 0 3	6 1 1	6 1 1	6 2 2	6 2 3	6 3 1	6 3 2	**Total Tissues/ Tumors**
General Body System											
None											
Genital System											
Clitoral gland	+	+	+	+	+	+	M	+	+	+	49
Adenoma											5
Ovary	+	+	+	+	+	+	+	+	+	+	59
Uterus	+	+	+	+	+	+	+	+	+	+	59
Adenocarcinoma											1
Polyp stromal		X							X		8
Polyp stromal, multiple							X				3
Sarcoma stromal											1
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	59
Lymph node	+	+	+	+	+	+	+	+	+	+	59
Lymph node, mandibular	+		+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	59
Thymus	+	+	M	+	+	+	+	+	+	+	49
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	56
Adenocarcinoma											2
Carcinoma											1
Fibroadenoma							X	X		X	8
Skin	+	+	+	+	+	+	+	+	+	+	59
Subcutaneous tissue, fibroma											1
Musculoskeletal System											
None											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	0 6 5	1 0 3	1 0 4	1 0 6	1 0 8	1 0 8	1 0 9	1 4 1	1 5 2	2 0 1	2 0 6	3 9 5	4 4 9	4 6 8	4 8 8	4 9 5	5 0 2	5 0 2	5 1 6	5 4 9	5 6 9	6 1 0	6 1 2	6 4 2	6 4 6
Carcass ID Number	5 7 1	5 5 5	5 6 5	5 7 5	5 6 4	5 7 4	6 0 5	5 6 3	5 5 4	5 8 5	6 2 5	6 1 5	6 3 5	6 3 4	5 7 3	5 4 5	5 8 4	5 3 3	5 4 4	5 2 5	6 0 4	5 9 5	6 2 4	5 3 5	5 3 2
Nervous System																									
Brain		+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma benign													X												
Peripheral nerve		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																+			+						
Eye													+						+						
Harderian gland		+																							
Urinary System																									
Kidney		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																								X	
Urinary bladder		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X	X					X		X		X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	6 4 6	6 4 6	6 4 7	6 4 9	6 5 0	6 5 3	6 5 4	6 5 4	6 5 9	6 6 0	6 6 7	6 8 8	6 9 1	7 0 5	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	5 3 3	5 3 4	5 3 1	5 5 3	6 1 2	6 1 4	5 8 3	6 1 3	5 2 4	5 5 2	5 9 4	5 8 2	5 4 3	5 9 3	5 2 1	5 2 2	5 2 3	5 4 1	5 4 2	5 5 1	5 6 1	5 6 2	5 7 2	5 8 1	5 9 1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma benign																									
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																									
Harderian gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X						X						X	X							

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Sodium Azide: 10 mg/kg (continued)

Number of Days on Study	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	5 9 2	6 0 1	6 0 2	6 0 3	6 1 1	6 2 1	6 2 2	6 2 3	6 3 1	6 3 2	**Total Tissues/ Tumors**
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	58
Astrocytoma benign											1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	59
Spinal cord	+	+	+	+	+	M	+	+	+	+	58
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	59
Nose	+	+	+	+	+	+	+	+	+	+	59
Trachea	+	+	+	+	+	+	+	+	+	+	59
Special Senses System											
Ear					+						3
Eye					+						3
Harderian gland											1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	59
Renal tubule, carcinoma											1
Urinary bladder	+	+	+	+	+	+	+	M	+	+	58
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear						X					11

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

	Vehicle Control	5 mg/kg	10 mg/kg
Adrenal Gland (Medulla): Pheochromocytoma Benign			
Overall rates[a]	1/58 (2%)	4/54 (7%)	1/56 (2%)
Adjusted rates[b]	2.3%	9.5%	4.8%
Terminal rates[c]	0/36 (0%)	4/42 (10%)	1/21 (5%)
First incidence (days)	684	729 (T)	729 (T)
Life table tests[d]	P=0.407	P=0.231	P=0.631
Logistic regression tests[d]	P=0.441	P=0.199	P=0.690
Cochran-Armitage test[d]	P=0.586		
Fisher exact test[d]		P=0.160	P=0.743
Adrenal Gland (Medulla): Pheochromocytoma (Benign or Malignant)			
Overall rates	1/58 (2%)	5/54 (9%)	1/56 (2%)
Adjusted rates	2.3%	11.9%	4.8%
Terminal rates	0/36 (0%)	5/42 (12%)	1/21 (5%)
First incidence (days)	684	729 (T)	729 (T)
Life table tests	P=0.383	P=0.144	P=0.631
Logistic regression tests	P=0.413	P=0.120	P=0.690
Cochran-Armitage test	P=0.577		
Fisher exact test		P=0.087	P=0.743
Clitoral Gland: Adenoma			
Overall rates	4/55 (7%)	2/57 (4%)	5/49 (10%)
Adjusted rates	10.4%	4.0%	21.7%
Terminal rates	2/34 (6%)	1/42 (2%)	4/20 (20%)
First incidence (days)	684	502	449
Life table tests	P=0.210	P=0.260N	P=0.215
Logistic regression tests	P=0.353	P=0.325N	P=0.366
Cochran-Armitage test	P=0.362		
Fisher exact test		P=0.323N	P=0.426
Clitoral Gland: Adenoma or Carcinoma			
Overall rates	5/55 (9%)	4/57 (7%)	5/49 (10%)
Adjusted rates	12.2%	7.9%	21.7%
Terminal rates	2/34 (6%)	2/42 (5%)	4/20 (20%)
First incidence (days)	594	453	449
Life table tests	P=0.327	P=0.399N	P=0.326
Logistic regression tests	P=0.513	P=0.575N	P=0.514
Cochran-Armitage test	P=0.497		
Fisher exact test		P=0.477N	P=0.554
Mammary Gland: Fibroadenoma			
Overall rates	20/60 (33%)	11/60 (18%)	8/59 (14%)
Adjusted rates	47.0%	24.9%	27.3%
Terminal rates	15/37 (41%)	10/43 (23%)	4/21 (19%)
First incidence (days)	575	719	502
Life table tests	P=0.080N	P=0.016N	P=0.179N
Logistic regression tests	P=0.030N	P=0.017N	P=0.060N
Cochran-Armitage test	P=0.006N		
Fisher exact test		P=0.047N	P=0.009N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Mammary Gland: Adenocarcinoma or Carcinoma			
Overall rates	2/60 (3%)	1/60 (2%)	3/59 (5%)
Adjusted rates	4.5%	2.3%	11.2%
Terminal rates	1/37 (3%)	1/43 (2%)	1/21 (5%)
First incidence (days)	488	729 (T)	502
Life table tests	P=0.248	P=0.457N	P=0.319
Logistic regression tests	P=0.389	P=0.562N	P=0.472
Cochran-Armitage test	P=0.393		
Fisher exact test		P=0.500N	P=0.492
Mammary Gland: Adenoma, Fibroadenoma, Adenocarcinoma, or Carcinoma			
Overall rates	22/60 (37%)	12/60 (20%)	11/59 (19%)
Adjusted rates	49.1%	27.1%	36.2%
Terminal rates	15/37 (41%)	11/43 (26%)	5/21 (24%)
First incidence (days)	488	719	502
Life table tests	P=0.179N	P=0.011N	P=0.326N
Logistic regression tests	P=0.058N	P=0.015N	P=0.101N
Cochran-Armitage test	P=0.015N		
Fisher exact test		P=0.034N	P=0.023N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	35/60 (58%)	27/60 (45%)	17/59 (29%)
Adjusted rates	73.9%	52.2%	60.1%
Terminal rates	25/37 (68%)	19/43 (44%)	11/21 (52%)
First incidence (days)	429	453	502
Life table tests	P=0.124N	P=0.030N	P=0.225N
Logistic regression tests	P=0.010N	P=0.056N	P=0.020N
Cochran-Armitage test	P<0.001N		
Fisher exact test		P=0.100N	P=0.001N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rates	37/60 (62%)	28/60 (47%)	17/59 (29%)
Adjusted rates	75.2%	53.2%	60.1%
Terminal rates	25/37 (68%)	19/43 (44%)	11/21 (52%)
First incidence (days)	429	453	502
Life table tests	P=0.081N	P=0.022N	P=0.161N
Logistic regression tests	P=0.004N	P=0.036N	P=0.008N
Cochran-Armitage test	P<0.001N		
Fisher exact test		P=0.071N	P<0.001N
Skin (Subcutaneous Tissue): Fibroma			
Overall rates	4/60 (7%)	1/60 (2%)	1/59 (2%)
Adjusted rates	10.0%	2.3%	3.4%
Terminal rates	3/37 (8%)	1/43 (2%)	0/21 (0%)
First incidence (days)	596	729 (T)	654
Life table tests	P=0.179N	P=0.141N	P=0.347N
Logistic regression tests	P=0.136N	P=0.159N	P=0.263N
Cochran-Armitage test	P=0.105N		
Fisher exact test		P=0.182N	P=0.187N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Skin (Subcutaneous Tissue): Fibroma or Sarcoma			
Overall rates	5/60 (8%)	1/60 (2%)	1/59 (2%)
Adjusted rates	11.5%	2.3%	3.4%
Terminal rates	3/37 (8%)	1/43 (2%)	0/21 (0%)
First incidence (days)	352	729 (T)	654
Life table tests	P=0.094N	P=0.080N	P=0.229N
Logistic regression tests	P=0.044N	P=0.142N	P=0.110N
Cochran-Armitage test	P=0.051N		
Fisher exact test		P=0.103N	P=0.107N
Thyroid Gland (C-Cell): Adenoma			
Overall rates	3/60 (5%)	3/60 (5%)	3/56 (5%)
Adjusted rates	8.1%	6.8%	14.3%
Terminal rates	3/37 (8%)	2/43 (5%)	3/21 (14%)
First incidence (days)	729 (T)	728	729 (T)
Life table tests	P=0.334	P=0.587N	P=0.385
Logistic regression tests	P=0.389	P=0.568N	P=0.385
Cochran-Armitage test	P=0.550		
Fisher exact test		P=0.660N	P=0.627
Thyroid Gland (C-Cell): Carcinoma			
Overall rates	3/60 (5%)	1/60 (2%)	0/56 (0%)
Adjusted rates	7.3%	2.3%	0.0%
Terminal rates	2/37 (5%)	1/43 (2%)	0/21 (0%)
First incidence (days)	578	729 (T)	–[e]
Life table tests	P=0.096N	P=0.260N	P=0.216N
Logistic regression tests	P=0.077N	P=0.296N	P=0.165N
Cochran-Armitage test	P=0.067N		
Fisher exact test		P=0.309N	P=0.135N
Thyroid Gland (C-Cell): Adenoma or Carcinoma			
Overall rates	6/60 (10%)	4/60 (7%)	3/56 (5%)
Adjusted rates	15.2%	9.0%	14.3%
Terminal rates	5/37 (14%)	3/43 (7%)	3/21 (14%)
First incidence (days)	578	728	729 (T)
Life table tests	P=0.420N	P=0.283N	P=0.550N
Logistic regression tests	P=0.362N	P=0.300N	P=0.474N
Cochran-Armitage test	P=0.217N		
Fisher exact test		P=0.372N	P=0.281N
Uterus: Polyp Stromal			
Overall rates	12/60 (20%)	20/60 (33%)	11/59 (19%)
Adjusted rates	29.9%	42.8%	36.9%
Terminal rates	10/37 (27%)	17/43 (40%)	5/21 (24%)
First incidence (days)	578	540	488
Life table tests	P=0.138	P=0.164	P=0.207
Logistic regression tests	P=0.343	P=0.119	P=0.423
Cochran-Armitage test	P=0.478N		
Fisher exact test		P=0.074	P=0.518N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
All Organs: Mononuclear Leukemia			
Overall rates	16/60 (27%)	18/60 (30%)	11/59 (19%)
Adjusted rates	36.1%	35.0%	31.5%
Terminal rates	10/37 (27%)	11/43 (26%)	3/21 (14%)
First incidence (days)	457	540	449
Life table tests	P=0.454	P=0.531N	P=0.498
Logistic regression tests	P=0.300N	P=0.466	P=0.339N
Cochran-Armitage test	P=0.185N		
Fisher exact test		P=0.420	P=0.205N
All Organs: Benign Tumors			
Overall rates	47/60 (78%)	44/60 (73%)	34/59 (58%)
Adjusted rates	90.3%	79.7%	88.4%
Terminal rates	32/37 (86%)	32/43 (74%)	17/21 (81%)
First incidence (days)	429	453	449
Life table tests	P=0.247	P=0.083N	P=0.201
Logistic regression tests	P=0.154N	P=0.175N	P=0.220N
Cochran-Armitage test	P=0.009N		
Fisher exact test		P=0.335N	P=0.013N
All Organs: Malignant Tumors			
Overall rates	25/60 (42%)	27/60 (45%)	16/59 (27%)
Adjusted rates	49.9%	49.4%	43.8%
Terminal rates	13/37 (35%)	16/43 (37%)	4/21 (19%)
First incidence (days)	352	453	449
Life table tests	P=0.532N	P=0.448N	P=0.552N
Logistic regression tests	P=0.119N	P=0.379	P=0.137N
Cochran-Armitage test	P=0.063N		
Fisher exact test		P=0.427	P=0.070N
All Organs: Benign and Malignant			
Overall rates	53/60 (88%)	54/60 (90%)	39/59 (66%)
Adjusted rates	93.0%	90.0%	90.3%
Terminal rates	33/37 (89%)	37/43 (86%)	17/21 (81%)
First incidence (days)	352	453	449
Life table tests	P=0.189	P=0.192N	P=0.183
Logistic regression tests	P=0.079N	P=0.604N	P=0.118N
Cochran-Armitage test	P=0.001N		
Fisher exact test		P=0.500	P=0.003N

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no tumors in animal group.

TABLE B4a
Historical Incidence of Tumors of the Mammary Gland in Female F344/N Rats Receiving Vehicle by Gavage[a]

Study	Incidence of Fibroadenoma in Controls
Historical Incidence at Microbiological Associates	
Methyl carbamate	15/50
Overall Historical Incidence	
Total	94/349 (26.9%)
Standard deviation	9.2%
Range	12%-42%

[a] Data as of 22 November 1989 for studies of at least 104 weeks

TABLE B4b
Historical Incidence of Tumors of the Pituitary/Anterior Pituitary in Female F344/N Rats Receiving Vehicle by Gavage[a]

Study	Incidence in Controls	
	Adenoma	Carcinoma
Historical Incidence at Microbiological Associates		
Methyl carbamate	21/50	3/50
Overall Historical Incidence		
Total	152/340 (44.7%)	6/340 (1.8%)
Standard deviation	8.0%	2.4%
Range	32%-54%	0%-6%

[a] Data as of 22 November 1989 for studies of at least 104 weeks

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Sodium Azide

	Vehicle Control	5 mg/kg	10 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Early deaths			
Dead	11	5	22
Moribund	10	12	11
Gavage death	2	0	5
Survivors			
Dead	1	0	0
Terminal sacrifice	36	43	21
Animals examined microscopically	60	60	59
Alimentary System			
Esophagus	(60)	(60)	(59)
Inflammation, subacute	1 (2%)		
Ulcer			1 (2%)
Intestine large, rectum	(59)	(59)	(58)
Ulcer		1 (2%)	
Liver	(60)	(60)	(59)
Angiectasis	3 (5%)	1 (2%)	4 (7%)
Basophilic focus	4 (7%)		5 (8%)
Basophilic focus, focal			1 (2%)
Basophilic focus, multifocal	19 (32%)	26 (43%)	18 (31%)
Congestion	1 (2%)		1 (2%)
Eosinophilic focus		1 (2%)	
Fatty change, diffuse	2 (3%)	2 (3%)	1 (2%)
Fatty change, focal	3 (5%)		
Fatty change, multifocal	4 (7%)	1 (2%)	2 (3%)
Hematopoietic cell proliferation	1 (2%)		
Hepatodiaphragmatic nodule	1 (2%)	8 (13%)	11 (19%)
Hyperplasia, nodular, multifocal	1 (2%)		
Infiltration cellular, lymphocytic, multifocal	1 (2%)		
Inflammation, acute, multifocal		1 (2%)	
Inflammation, chronic active, focal		1 (2%)	
Inflammation, chronic active, multifocal	1 (2%)		
Inflammation, granulomatous	2 (3%)		
Inflammation, granulomatous, multifocal	24 (40%)	16 (27%)	28 (47%)
Leukocytosis	4 (7%)	1 (2%)	
Mixed cell focus		1 (2%)	
Necrosis, focal	1 (2%)		
Necrosis, multifocal	4 (7%)		
Bile duct, hyperplasia	34 (57%)	37 (62%)	27 (46%)
Centrilobular, fatty change	1 (2%)	2 (3%)	
Centrilobular, necrosis	2 (3%)	1 (2%)	1 (2%)
Centrilobular, necrosis, coagulative		2 (3%)	
Hepatocyte, periportal, necrosis	1 (2%)		
Periportal, fatty change	1 (2%)	3 (5%)	
Mesentery	(16)	(10)	(7)
Fat, necrosis, focal	15 (94%)	7 (70%)	7 (100%)
Fat, necrosis, multifocal	1 (6%)	1 (10%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Alimentary System (continued)			
Pancreas	(60)	(60)	(58)
Ectopic tissue	1 (2%)		
Acinus, atrophy	16 (27%)	13 (22%)	11 (19%)
Acinus, cytoplasmic alteration, focal			2 (3%)
Acinus, cytoplasmic alteration, multifocal	1 (2%)		
Acinus, hyperplasia, focal		1 (2%)	
Salivary glands	(59)	(60)	(59)
Inflammation, necrotizing	1 (2%)		
Stomach, forestomach	(60)	(57)	(57)
Hyperplasia, focal	1 (2%)		2 (4%)
Inflammation, chronic	2 (3%)		2 (4%)
Ulcer	1 (2%)	2 (4%)	2 (4%)
Epithelium, hyperplasia, focal	1 (2%)		
Stomach, glandular	(60)	(60)	(57)
Degeneration, cystic	39 (65%)	56 (93%)	37 (65%)
Erosion	1 (2%)		
Hyperplasia, focal	1 (2%)		
Infiltration cellular, lymphocytic, focal		1 (2%)	
Inflammation, chronic active, focal	1 (2%)		
Ulcer			1 (2%)
Lamina propria, fibrosis, focal		1 (2%)	
Tooth	(1)		(1)
Peridontal tissue, inflammation, chronic active	1 (100%)		1 (100%)
Cardiovascular System			
Heart	(60)	(60)	(58)
Cardiomyopathy	20 (33%)	21 (35%)	19 (33%)
Aortic valve, inflammation, chronic active		1 (2%)	
Aortic valve, inflammation, subacute	1 (2%)		
Artery, degeneration			1 (2%)
Myocardium, atrium right, necrosis	1 (2%)		
Myocardium, ventricle, necrosis	1 (2%)		
Pericardium, inflammation, necrotizing	1 (2%)		
Endocrine System			
Adrenal gland, cortex	(60)	(60)	(58)
Accessory adrenal cortical nodule	1 (2%)	1 (2%)	
Angiectasis	6 (10%)	2 (3%)	2 (3%)
Degeneration, ballooning, focal	1 (2%)		
Hyperplasia, focal	12 (20%)	3 (5%)	2 (3%)
Hyperplasia, multifocal	1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, lymphocytic	1 (2%)		
Necrosis, focal		1 (2%)	
Necrosis, multifocal	2 (3%)		1 (2%)
Vacuolization cytoplasmic	1 (2%)		
Vacuolization cytoplasmic, diffuse		2 (3%)	
Vacuolization cytoplasmic, focal	6 (10%)	6 (10%)	5 (9%)
Vacuolization cytoplasmic, multifocal	2 (3%)	1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Endocrine System (continued)			
Adrenal gland, medulla	(58)	(54)	(56)
Angiectasis	1 (2%)		
Hyperplasia, focal	3 (5%)	1 (2%)	1 (2%)
Hyperplasia, multifocal	2 (3%)	2 (4%)	
Infiltration cellular, lymphocytic	1 (2%)		
Bilateral, hyperplasia, focal			1 (2%)
Bilateral, hyperplasia, multifocal			1 (2%)
Islets, pancreatic	(60)	(60)	(58)
Hyperplasia, focal		1 (2%)	
Pituitary gland	(60)	(60)	(59)
Angiectasis	10 (17%)	7 (12%)	5 (8%)
Cyst	9 (15%)	15 (25%)	15 (25%)
Hemorrhage			1 (2%)
Pigmentation, hemosiderin	2 (3%)	2 (3%)	
Pars distalis, hyperplasia	3 (5%)	4 (7%)	3 (5%)
Pars distalis, hyperplasia, focal	5 (8%)	3 (5%)	6 (10%)
Pars nervosa, hyperplasia	1 (2%)		
Thyroid gland	(60)	(60)	(56)
Inflammation, subacute		1 (2%)	
Ultimobranchial cyst		2 (3%)	2 (4%)
C-cell, hyperplasia	8 (13%)	10 (17%)	2 (4%)
Follicle, cyst	1 (2%)		
General Body System			
Tissue, NOS	(1)		
Hemorrhage	1 (100%)		
Genital System			
Clitoral gland	(55)	(57)	(49)
Hyperplasia	1 (2%)		
Inflammation, chronic active	2 (4%)	2 (4%)	
Duct, ectasia	5 (9%)	7 (12%)	4 (8%)
Ovary	(60)	(60)	(59)
Congestion			1 (2%)
Cyst	3 (5%)	3 (5%)	4 (7%)
Uterus	(60)	(60)	(59)
Hydrometra		3 (5%)	
Inflammation, chronic active		1 (2%)	
Cervix, cyst	9 (15%)	12 (20%)	5 (8%)
Cervix, hypertrophy		1 (2%)	
Cervix, inflammation, chronic active	2 (3%)		
Cervix, inflammation, suppurative	1 (2%)	2 (3%)	1 (2%)
Endometrium, cyst	2 (3%)	1 (2%)	3 (5%)
Endometrium, cyst, multiple	1 (2%)		
Endometrium, hyperplasia	1 (2%)	1 (2%)	
Endometrium, hyperplasia, cystic		6 (10%)	1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Hematopoietic System			
Bone marrow	(60)	(60)	(59)
Atrophy			3 (5%)
Lymph node	(59)	(59)	(59)
Hemorrhage		1 (2%)	
Pigmentation, hemosiderin			1 (2%)
Mediastinal, congestion	1 (2%)		
Mediastinal, hemorrhage	13 (22%)	7 (12%)	9 (15%)
Mediastinal, hyperplasia, lymphoid	1 (2%)		
Mediastinal, hyperplasia, reticulum cell		1 (2%)	
Mediastinal, inflammation, granulomatous	2 (3%)		
Mediastinal, pigmentation, hemosiderin	9 (15%)	7 (12%)	6 (10%)
Mediastinal, sinus, ectasia	1 (2%)	1 (2%)	
Mesenteric, hemorrhage	3 (5%)	3 (5%)	2 (3%)
Mesenteric, pigmentation, hemosiderin		1 (2%)	
Mesenteric, sinus, ectasia	7 (12%)	14 (24%)	6 (10%)
Pancreatic, hemorrhage	3 (5%)	2 (3%)	
Pancreatic, pigmentation, hemosiderin	3 (5%)	4 (7%)	2 (3%)
Pancreatic, sinus, ectasia	2 (3%)	1 (2%)	
Renal, infiltration cellular, histiocytic		1 (2%)	
Renal, pigmentation, hemosiderin	1 (2%)	1 (2%)	
Lymph node, mandibular	(51)	(52)	(50)
Hemorrhage	1 (2%)		2 (4%)
Hyperplasia, plasma cell	4 (8%)	6 (12%)	6 (12%)
Inflammation, granulomatous	1 (2%)		
Pigmentation, hemosiderin			1 (2%)
Sinus, ectasia	4 (8%)	1 (2%)	1 (2%)
Spleen	(60)	(60)	(59)
Ectopic tissue	2 (3%)	2 (3%)	2 (3%)
Fibrosis, focal	3 (5%)	4 (7%)	1 (2%)
Hematopoietic cell proliferation	3 (5%)	3 (5%)	
Hemorrhage, focal			1 (2%)
Inflammation, granulomatous	2 (3%)		
Inflammation, necrotizing			1 (2%)
Necrosis	2 (3%)		
Red pulp, atrophy		1 (2%)	1 (2%)
Thymus	(42)	(51)	(49)
Congestion	1 (2%)	1 (2%)	1 (2%)
Cyst		1 (2%)	2 (4%)
Depletion lymphoid			1 (2%)
Ectopic tissue	1 (2%)	1 (2%)	
Hemorrhage	4 (10%)	1 (2%)	3 (6%)
Epithelial cell, hyperplasia	38 (90%)	48 (94%)	35 (71%)
Integumentary System			
Mammary gland	(58)	(55)	(56)
Galactocele	2 (3%)		
Hyperplasia, nodular, multifocal	1 (2%)		
Inflammation, chronic active	1 (2%)		
Duct, ectasia	9 (16%)	7 (13%)	2 (4%)
Skin	(59)	(60)	(59)
Cyst epithelial inclusion	1 (2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Musculoskeletal System			
Bone		(2)	
Femur, osteopetrosis		1 (50%)	
Vertebra, osteopetrosis		1 (50%)	
Nervous System			
Brain	(60)	(60)	(58)
Hemorrhage			1 (2%)
Cerebrum, gliosis		1 (2%)	
Cerebrum, necrosis		1 (2%)	33 (57%)
Hippocampus, necrosis			3 (5%)
Thalamus, necrosis			21 (36%)
Spinal cord	(58)	(60)	(58)
Hemorrhage	1 (2%)	1 (2%)	
Necrosis, focal	1 (2%)		
Respiratory System			
Lung	(60)	(60)	(59)
Congestion	6 (10%)	3 (5%)	21 (36%)
Fungus		1 (2%)	
Hemorrhage	5 (8%)	5 (8%)	5 (8%)
Infiltration cellular, histiocytic	49 (82%)	51 (85%)	42 (71%)
Inflammation, granulomatous, focal		1 (2%)	
Inflammation, granulomatous, multifocal	1 (2%)		
Leukocytosis	1 (2%)		
Necrosis, multifocal	1 (2%)		
Pigmentation	49 (82%)	51 (85%)	42 (71%)
Pigmentation, hemosiderin, diffuse		1 (2%)	
Alveolar epithelium, hyperplasia	1 (2%)		1 (2%)
Alveolar epithelium, hyperplasia, focal	3 (5%)	3 (5%)	2 (3%)
Alveolar epithelium, hyperplasia, multifocal		1 (2%)	
Nose	(60)	(60)	(59)
Foreign body	1 (2%)		2 (3%)
Fungus		1 (2%)	2 (3%)
Hemorrhage			1 (2%)
Inflammation	1 (2%)		
Inflammation, suppurative	5 (8%)	4 (7%)	5 (8%)
Trachea	(60)	(60)	(59)
Inflammation, suppurative	1 (2%)		
Artery, inflammation, chronic active	1 (2%)		
Special Senses System			
Ear		(3)	(3)
Middle ear, inflammation, suppurative		1 (33%)	
Eye	(4)	(7)	(3)
Cataract	1 (25%)	3 (43%)	1 (33%)
Necrosis	1 (25%)	2 (29%)	
Anterior chamber, inflammation, suppurative	1 (25%)		
Retina, degeneration	1 (25%)	2 (29%)	1 (33%)
Sclera, metaplasia, osseous	1 (25%)	2 (29%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Sodium Azide (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Special Senses System (continued)			
Harderian gland	(2)	(1)	(1)
Infiltration cellular, lymphocytic	2 (100%)	1 (100%)	1 (100%)
Urinary System			
Kidney	(60)	(60)	(59)
Concretion	1 (2%)		
Cyst	1 (2%)		2 (3%)
Hydronephrosis	1 (2%)		
Nephropathy	54 (90%)	51 (85%)	23 (39%)
Pigmentation	1 (2%)		
Urinary bladder	(60)	(58)	(58)
Infiltration cellular, lymphocytic		4 (7%)	
Serosa, inflammation, chronic		1 (2%)	
Serosa, inflammation, subacute	1 (2%)		
Transitional epithelium, hyperplasia, focal		1 (2%)	

APPENDIX C
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA PROTOCOL

Testing was performed as reported by Ames *et al.* (1975) with modifications as listed below and described in greater detail in Haworth *et al.* (1983) and Zeiger *et al.* (1987). Sodium azide was sent to the laboratories as coded aliquots from Radian Corporation, Austin, TX. The test chemical was incubated with the *Salmonella typhimurium* tester strain (TA98, TA100, TA1535, 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 prior to the addition of soft agar supplemented with *l*-histidine and *d*-biotin, and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

In this assay, each test consisted of triplicate plates of concurrent positive and negative controls and of at least 5 doses of test chemical. High dose was limited by toxicity or solubility, but did not exceed 33.3 μg/plate. Generally, all negative assays were repeated and all positive assays were repeated under the conditions that elicited the positive response.

A positive response was defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response was defined as an increase in revertants that was not dose-related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A negative response was obtained when no increase in revertant colonies was observed following chemical treatment.

CHINESE HAMSTER OVARY CYTOGENETICS ASSAYS

Testing was performed as reported by Galloway *et al.* (1985, 1987) and presented briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation, Austin, TX. Chemicals were tested in cultured Chinese hamster ovary cells for induction of sister chromatid exchanges and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of test chemical; the high dose was limited by toxicity or solubility, but did not exceed 5 mg/mL.

In the sister chromatic exchange (SCE) test without S9, Chinese hamster ovary cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2 mM), and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing the test chemical was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 more hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with the chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no test chemical and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining procedures were the same as for cells treated without S9.

In the chromosome aberration (Abs) test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was

removed and the cells incubated for 10 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

For the SCE test, if significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test: if cell cycle delay was anticipated, the incubation period was extended approximately 6 to 8 hours.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. For the SCE test, usually 50 second-division metaphase cells were scored for frequency of SCE per cell from each dose level; 200 first-division metaphase cells were scored at each dose level for the Abs test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. A sister chromatid exchange frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCE, both the dose-response curve and individual dose points were statistically analyzed. For a single trial, a statistically significant ($P<0.05$) difference for one dose point and a significant trend ($P<0.015$) was considered weak evidence for a positive response (w+); significant differences for two or more doses indicated the trial was positive (+) (Galloway *et al.*, 1987).

RESULTS

Sodium azide (dose range of 0.03 to 33.3 μg/plate) produced a strong, dose-related increase in mutant colonies in *Salmonella typhimurium* strains TA100 and TA1535 when tested in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9; no mutagenic activity was observed in strains TA1537 or TA98 (Zeiger *et al.*, 1987; Table C1). In cytogenetic tests with Chinese hamster ovary (CHO) cells, sodium azide produced a significant increase in sister chromatid exchanges in both the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9; higher doses tested in the absence of S9 required delayed harvest to offset chemical-induced cell-cycle delay and allow recovery of sufficient metaphase cells for analysis (Tables C2, C3). No induction of chromosomal aberrations occurred in CHO cells after exposure to sodium azide with or without S9; delayed harvest was used in the trial without S9 to ensure adequate cells for analysis (Table C4).

TABLE C1
Mutagenicity of Sodium Azide in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0.00	102 ± 5.3		112 ± 1.7	108 ± 9.7	115 ± 8.2	111 ± 8.1
	0.03	167 ± 20.0					
	0.1	255 ± 9.2					
	0.3	446 ± 11.7		137 ± 11.3	88 ± 3.3	114 ± 4.2	122 ± 5.2
	1.0			175 ± 2.1	127 ± 1.5	123 ± 0.3	140 ± 5.8
	3.3	755 ± 10.3		306 ± 14.2	276 ± 17.2	290 ± 10.7	293 ± 11.5
	10.0	1083 ± 19.7		1011 ± 35.6	817 ± 37.0	929 ± 58.8	951 ± 44.7
	33.3			1313 ± 10.7	1124 ± 38.6	1363 ± 8.8	1390 ± 49.1
Trial summary		Positive		Positive	Positive	Positive	Positive
Positive control[c]		526 ± 12.0		1006 ± 58.0	1278 ± 34.7	593 ± 4.4	627 ± 18.2
TA1535	0.00	20 ± 2.6	25 ± 3.1	13 ± 2.0	10 ±0.7	9 ± 2.9	9 ± 0.3
	0.03		119 ± 8.4				
	0.1		247 ± 7.7				
	0.3	296 ± 12.0	474 ± 16.3	33 ± 2.5	16 ± 3.8	24 ± 2.9	28 ± 8.8
	1.0	508 ± 25.5		78 ± 3.7	45 ± 4.4	77 ± 14.1	50 ± 4.5
	3.3	818 ± 40.4	688 ± 28.8	262 ± 5.1	161 ± 13.0	290 ± 34.3	251 ± 5.8
	10.0	1147 ± 53.6	957 ± 62.1	927 ± 21.8	795 ± 3.2	928 ± 8.4	899 ± 29.6
	33.3	1403 ± 34.2		1335 ± 24.1	1317 ± 40.4	1325 ± 36.1	1320 ± 64.1
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control[c]		512 ± 18.9	444 ± 17.0	400 ± 19.3	300 ± 6.3	311 ± 6.4	374 ± 12.8

TABLE C1
Mutagenicity of Sodium Azide in *Salmonella typhimurium*[a] (continued)

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA1537	0.00	8 ± 1.0		15 ± 1.2		13 ± 3.2	
	0.3	11 ± 1.0		24 ± 2.6		15 ± 1.2	
	1.0	8 ± 0.7		22 ± 2.8		8 ± 2.3	
	3.3	8 ± 0.9		17 ± 4.9		9 ± 2.2	
	10.0	9 ± 1.7		13 ± 0.6		9 ± 2.5	
	33.3	10 ± 1.8		16 ± 1.2		10 ± 2.4	
Trial summary		Negative		Negative		Negative	
Positive control[c]		119 ± 22.5		376 ± 12.0		493 ± 132.1	
TA98	0.00	46 ± 2.4		53 ± 3.4		60 ± 5.0	
	0.3	41 ± 6.9		27 ± 1.8		65 ± 8.0	
	1.0	45 ± 7.2		31 ± 5.8		54 ± 3.9	
	3.3	52 ± 6.7		31 ± 3.5		62 ± 6.5	
	10.0	51 ± 6.9		26 ± 2.9		51 ± 7.2	
	33.3	54 ± 2.8		30 ± 0.3		59 ± 4.2	
Trial summary		Negative		Negative		Negative	
Positive control[c]		850 ± 18.0		1,170 ± 9.5		509 ± 20.5	

[a] Study performed at SRI International. The detailed protocol is presented in Zeiger *et al.* (1987). Cells and study compound or solvent (distilled water) were incubated in the absence of exogenous metabolic activation (-S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague-Dawley rat liver. High dose was limited by toxicity or solubility, but did not exceed 33.3 μg/plate; 0 μg/plate dose is the solvent control.

[b] Revertants are presented as mean ± the standard error from three plates.

[c] 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.

TABLE C2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Sodium Azide (−S9)[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCE/ Chromosome	SCE/ Cell	Hrs in BrdU	Rel. SCEs/ Chromosome (%)[b]
Trial 1--Summary: Positive								
Medium		50	1,050	324	0.31	6.5	25.8	
Mitomycin-C	0.001	50	1,050	709	0.68	14.2	25.8	118.83
	0.010	5	105	223	2.12	44.6	25.8	588.27
Sodium azide	1.34	50	1,048	361	0.34	7.2	25.8	11.63
	4.02	50	1,050	441	0.42	8.8	25.8	36.11*
	13.40	50	1,047	436	0.42	8.7	33.5[c]	34.95*
	40.20	(Toxic)						
								P<0.001[d]
Trial 2--Summary: Weak positive								
Medium		50	1,049	329	0.31	6.6	25.7	
Mitomycin-C	0.001	50	1,049	541	0.52	10.8	25.7	64.44
	0.010	5	105	181	1.72	36.2	25.7	449.63
Sodium azide	13.40	50	1,049	320	0.31	6.4	25.7	−2.74
	26.80	50	1,047	366	0.35	7.3	31.7[c]	11.46
	40.20	50	1,041	413	0.40	8.3	31.7[c]	26.50*
								P<0.001

* Positive (≥20% increase over solvent control)
[a] Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1987). Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and Colcemid was added, and incubation was continued for 2 to 3 hours. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
[b] Percentage increase in SCEs/chromosome of culture exposed to study chemical relative to those of culture exposed to solvent.
[c] Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.
[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

TABLE C3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Sodium Azide (+S9)[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromo-somes	No. of SCEs	SCE/ Chromo-some	SCE/ Cell	Hrs in BrdU	Rel. SCEs/ Chromo-some (%)[b]
Trial 1--Summary: Positive								
Medium		50	1,050	371	0.35	7.4	25.8	
Cyclophosphamide	0.4	50	1,050	813	0.77	16.3	25.8	119.14
	2.0	5	105	210	2.00	42.0	25.8	466.04
Sodium azide	402	50	1,050	390	0.37	7.8	25.8	5.12
	1,340	50	1,049	448	0.43	9.0	25.8	20.87*
	4,020	50	1,050	620	0.59	12.4	25.8	67.12*
								P<0.001[c]
Trial 2--Summary: Weak positive								
Medium		50	1,040	318	0.31	6.4	25.7	
Cyclophosphamide	0.4	50	1,045	593	0.57	11.9	25.7	85.59
	2.0	5	102	155	1.52	31.0	25.7	396.99
Sodium azide	1,340	50	1,049	300	0.29	6.0	25.7	-6.47
	2,068	50	1,044	299	0.29	6.0	25.7	-6.34
	4,020	50	1,050	402	0.38	8.0	25.7	25.21*
								P<0.001

* Positive (≥20% increase over solvent control)

[a] Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1987). Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. The cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with Colcemid present for the final 2 to 3 hours. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained. S9 was prepared from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

[b] Percentage increase in SCEs/chromosome of culture exposed to study chemical relative to those of culture exposed to solvent.

[c] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

Table C4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Sodium Azide[a]

-S9[b]					+S9[c]				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs[d] (%)	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs[d] (%)
Trial 1--Harvest time: 20.2 hours[e]					**Trial 1--Harvest time: 12.0 hours**				
Medium					Medium				
	200	4	0.02	2.0		200	0	0.00	0.0
Mitomycin-C					Cyclophosphamide				
0.05	200	30	0.15	13.5	7.5	200	19	0.10	9.5
0.08	25	24	0.96	52.0	37.5	25	11	0.44	40.0
Sodium azide					Sodium azide				
20.0	200	2	0.01	1.0	2020.0	200	0	0.00	0.0
30.0	200	9	0.05	3.5	3015.0	200	0	0.00	0.0
40.0	200	2	0.01	1.0	4020.0	200	0	0.00	0.0
	Summary: Negative					Summary: Negative			
				P=0.495					P=0.500

[a] Study performed at Litton Bionetics, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or medium as indicated in [b] and [c]. Cells were arrested in first metaphase by addition of Colcemid and harvested by mitotic shake off, fixed, and stained in 6% Giemsa.

[b] In the absence of S9, cells were incubated with study compound or medium for 8 to 10 hours at 37° C. Cells were then washed and fresh medium containing Colcemid was added for an additional 2 to 3 hours followed by harvest.

[c] In the presence of S9, cells were incubated with study compound or medium for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8 to 10 hours. Colcemid was added for the last 2 to 3 hours of incubation before harvest. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

[d] Differences in percent cells with abberations between solvent and study compound are not significant by linear regression trend test vs. log of the dose.

[e] Because of significant chemical-induced cell cycle delay, incubation time prior to addition of Colcemid was lengthened to provide sufficient metaphases at harvest.

APPENDIX D
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE D1
Organ Weights[a] for Rats in the 14-Day Gavage Studies of Sodium Azide

Organ	Vehicle Control	5 mg/kg	10 mg/kg	20 mg/kg
Male				
n	5	5	5	5
Brain	1.86 ± 0.03	1.91 ± 0.02	1.74 ± 0.17	1.91 ± 0.03
Heart	0.81 ± 0.01	0.85 ± 0.02	0.82 ± 0.01	0.87 ± 0.02*
R. kidney	1.10 ± 0.04	1.06 ± 0.02	1.04 ± 0.05	1.11 ± 0.02
Liver	10.51 ± 0.07	10.58 ± 0.28	9.82 ± 0.37	11.67 ± 0.28
Lungs	1.54 ± 0.07	1.58 ± 0.04	1.48 ± 0.09	1.56 ± 0.02
Thymus	0.57 ± 0.04	0.59 ± 0.03	0.53 ± 0.04	0.57 ± 0.02
Female				
n	5	5	5	3
Brain	1.77 ± 0.04	1.81 ± 0.02	1.79 ± 0.02	1.77 ± 0.03
Heart	0.61 ± 0.02	0.67 ± 0.02	0.66 ± 0.02	0.62 ± 0.04
R. kidney	0.72 ± 0.03	0.74 ± 0.03	0.73 ± 0.01	0.69 ± 0.01
Liver	6.23 ± 0.21	6.49 ± 0.27	6.59 ± 0.15	5.89 ± 0.51
Lungs	1.18 ± 0.04	1.20 ± 0.02	1.23 ± 0.03	1.08 ± 0.12
Thymus	0.45 ± 0.01	0.51 ± 0.02	0.46 ± 0.01	0.41 ± 0.06

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Organ weights are given in grams. Mean ± standard error. No data were reported for the 40 and 80 mg/kg dose groups, due to 100% mortality in these groups.

TABLE D2
Organ-Weight-to-Body-Weight Ratios[a] for Rats in the 14-Day Gavage Studies of Sodium Azide

Organ	Vehicle Control	5 mg/kg	10 mg/kg	20 mg/kg
Male				
n	5	5	5	5
Brain	8.30 ± 0.13	8.57 ± 0.14	7.98 ± 0.82	8.51 ± 0.31
Heart	3.61 ± 0.08	3.81 ± 0.09	3.75 ± 0.17	3.88 ± 0.03
R. kidney	4.93 ± 0.18	4.75 ± 0.09	4.74 ± 0.13	4.94 ± 0.12
Liver	47.0 ± 0.64	47.5 ± 1.15	44.8 ± 0.83	51.9 ± 1.07*
Lungs	6.90 ± 0.30	7.08 ± 0.19	6.72 ± 0.29	6.96 ± 0.13
Thymus	2.56 ± 0.20	2.66 ± 0.13	2.42 ± 0.15	2.54 ± 0.13
Female				
n	5	5	5	3
Brain	1.20 ± 0.02	1.21 ± 0.03	1.20 ± 0.03	1.27 ± 0.11
Heart	4.11 ± 0.10	4.48 ± 0.06	4.41 ± 0.16	4.40 ± 0.30
R. kidney	4.86 ± 0.06	4.89 ± 0.06	4.88 ± 0.11	4.93 ± 0.27
Liver	42.1 ± 0.59	43.2 ± 0.62	44.0 ± 0.54	41.7 ± 0.93
Lungs	7.98 ± 0.26	7.99 ± 0.25	8.22 ± 0.20	7.65 ± 0.41
Thymus	3.02 ± 0.10	3.44 ± 0.22	3.07 ± 0.08	2.89 ± 0.20

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Organ-weight-to-body-weight ratios are given as mg organ weight/g body weight. Mean ± standard error; n=5 for all groups except 20 mg/kg females (n=3). No data were reported for the 40 and 80 mg/kg dose groups, due to 100% mortality in these groups.

TABLE D3
Organ Weights[a] for Rats in the 13-Week Gavage Studies of Sodium Azide

Organ	Vehicle Control	1.25 mg/kg	2.5 mg/kg	5 mg/kg	10 mg/kg	20 mg/kg[b]
Male						
n	10	10	10	10	10	10
Brain	1.95 ± 0.02	1.87 ± 0.07	1.84 ± 0.06	1.91 ± 0.03	1.89 ± 0.04	2.03 ± 0.02
Heart	1.01 ± 0.02	0.99 ± 0.01	1.03 ± 0.03	1.03 ± 0.03	0.94 ± 0.02	0.98 ± 0.06
R. kidney	1.29 ± 0.02	1.34 ± 0.03	1.29 ± 0.04	1.33 ± 0.04	1.19 ± 0.03	1.38 ± 0.08
Liver	13.66 ± 0.30	13.60 ± 0.40	13.86 ± 0.43	14.41 ± 0.58	13.03 ± 0.42	13.88 ± 0.43
Lungs	1.58 ± 0.08	1.71 ± 0.05	1.66 ± 0.05	1.69 ± 0.05	1.58 ± 0.06	1.51 ± 0.11
Thymus	0.33 ± 0.01[c]	0.37 ± 0.02	0.35 ± 0.04	0.35 ± 0.02	0.32 ± 0.02[c]	0.37 ± 0.09
Female						
n	10	10	10	10	10	10
Brain	1.76 ± 0.02	1.80 ± 0.02	1.75 ± 0.05	1.73 ± 0.04	1.73 ± 0.07	–[d]
Heart	0.63 ± 0.01	0.64 ± 0.01	0.67 ± 0.02	0.64 ± 0.02	0.60 ± 0.02	–
R. kidney	0.70 ± 0.01	0.76 ± 0.02	0.75 ± 0.02	0.77 ± 0.02*	0.71 ± 0.02	–
Liver	6.67 ± 0.10	7.74 ± 0.18**	7.84 ± 0.20**	7.69 ± 0.28**	7.01 ± 0.10	–
Lungs	1.20 ± 0.07	1.23 ± 0.04	1.21 ± 0.03	1.17 ± 0.02	1.16 ± 0.03	–
Thymus	0.26 ± 0.01	0.28 ± 0.01	0.28 ± 0.01	0.27 ± 0.01	0.26 ± 0.01	–

**Significantly different (P≤0.01) from the control group by Dunn's or Shirley's test
[a] Organ weights are given in grams. Mean ± standard error.
[b] n=2
[c] n=9
[d] No data reported due to 100% mortality in this group.

TABLE D4
Organ-Weight-to-Body-Weight Ratios[a] for Rats in the 13-Week Gavage Studies of Sodium Azide

Organ	Vehicle Control	1.25 mg/kg	2.5 mg/kg	5 mg/kg	10 mg/kg	20 mg/kg[b]
Male						
n	10	10	10	10	10	10
Brain	5.17 ± 0.05	4.93 ± 0.18	4.85 ± 0.17	5.09 ± 0.10	5.36 ± 0.15	5.70 ± 0.25
Heart	2.69 ± 0.05	2.61 ± 0.03	2.71 ± 0.06	2.74 ± 0.05	2.67 ± 0.05	2.75 ± 0.07
R. kidney	3.42 ± 0.04	3.52 ± 0.06	3.38 ± 0.07	3.53 ± 0.06	3.35 ± 0.03	3.88 ± 0.35
Liver	3.63 ± 0.06	3.58 ± 0.08	3.64 ± 0.07	3.82 ± 0.11	3.69 ± 0.09	3.89 ± 0.01
Lungs	4.20 ± 0.22	4.49 ± 0.11	4.36 ± 0.10	4.50 ± 0.12	4.48 ± 0.11	4.22 ± 0.16
Thymus	0.88 ± 0.03[c]	0.98 ± 0.04	0.92 ± 0.09	0.94 ± 0.03	0.09 ± 0.04[c]	1.05 ± 0.27
Female						
n	10	10	10	10	10	10
Brain	8.52 ± 0.19	8.37 ± 0.11	8.19 ± 0.22	8.26 ± 0.20	8.51 ± 0.30	–[d]
Heart	3.04 ± 0.07	3.00 ± 0.06	3.13 ± 0.09	3.06 ± 0.05	2.95 ± 0.04	–
R. kidney	3.40 ± 0.05	3.52 ± 0.07	3.53 ± 0.07	3.66 ± 0.03**	3.49 ± 0.05	–
Liver	3.21 ± 0.03	3.61 ± 0.08**	3.68 ± 0.09**	3.66 ± 0.10**	3.46 ± 0.08**	–
Lungs	5.82 ± 0.43	5.73 ± 0.15	5.69 ± 0.12	5.61 ± 0.07	5.72 ± 0.08	–
Thymus	1.23 ± 0.05	1.32 ± 0.06	1.32 ± 0.07	1.29 ± 0.04	1.29 ± 0.08	–

** Significantly different ($P \leq 0.01$) from the control group by Dunn's or Shirley's test
[a] Organ-weight-to-body-weight ratios are given as mg organ weight/g body weight. Mean ± standard error.
[b] n=2
[c] n=9
[d] No data reported due to 100% mortality in this group.

APPENDIX E
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF SODIUM AZIDE

Sodium azide was obtained from Fairmont Chemical Co. (Newark, NJ) in one lot (lot no. 32880, batch no. 02). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on analyses performed in support of the sodium azide studies are on file at the National Institute of Environmental Health Sciences.

The study chemical, a white, microcrystalline powder, was identified as sodium azide by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra of sodium azide (Figures E1 and E2) (*Sadtler Standard Spectra*).

The purity of lot no. 32880 was determined by elemental analysis, Karl Fischer water analysis, titration with excess 0.1 N ammonium hexanitratocerate, followed by back-titration with 0.1 N ferrous sulfate, using *o*-phenanthroline ferrous complex as an indicator, and spark source mass spectrometry.

Results of elemental analysis for sodium and nitrogen were in agreement with the theoretical values. Karl Fischer analysis indicated the presence of 0.051% water. Titration indicated a purity of 100.0%. Spark source mass spectrometry indicated elemental impurities totaling less than 500 ppm. The impurity occurring in the largest concentration was silicon, detected at 370 ppm, followed by magnesium, calcium, and chlorine, detected at 18, 17, and 16 ppm, respectively. The concentration of all other elemental impurities totaled less than 100 ppm. The overall analyses indicated a purity greater than 99%.

Stability studies performed by titration with the system described above indicated that sodium azide, when protected from light, was stable as a bulk chemical for at least two weeks at temperatures up to 60° C. During all the studies, the stability of the bulk chemical was monitored by infrared spectroscopy and by titration. No change in the study material was detected.

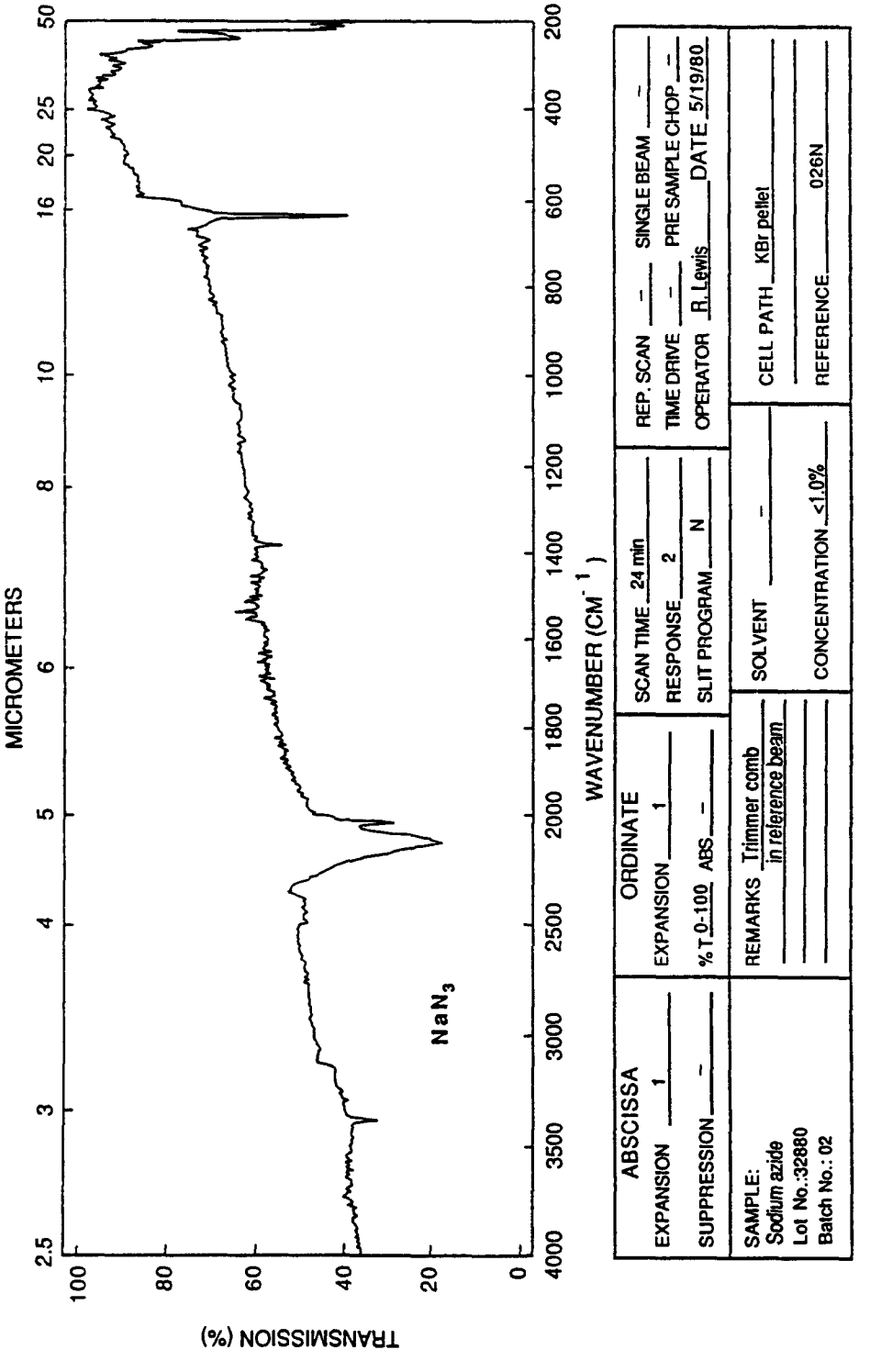

FIGURE E1
Infrared Spectrum of Sodium Azide

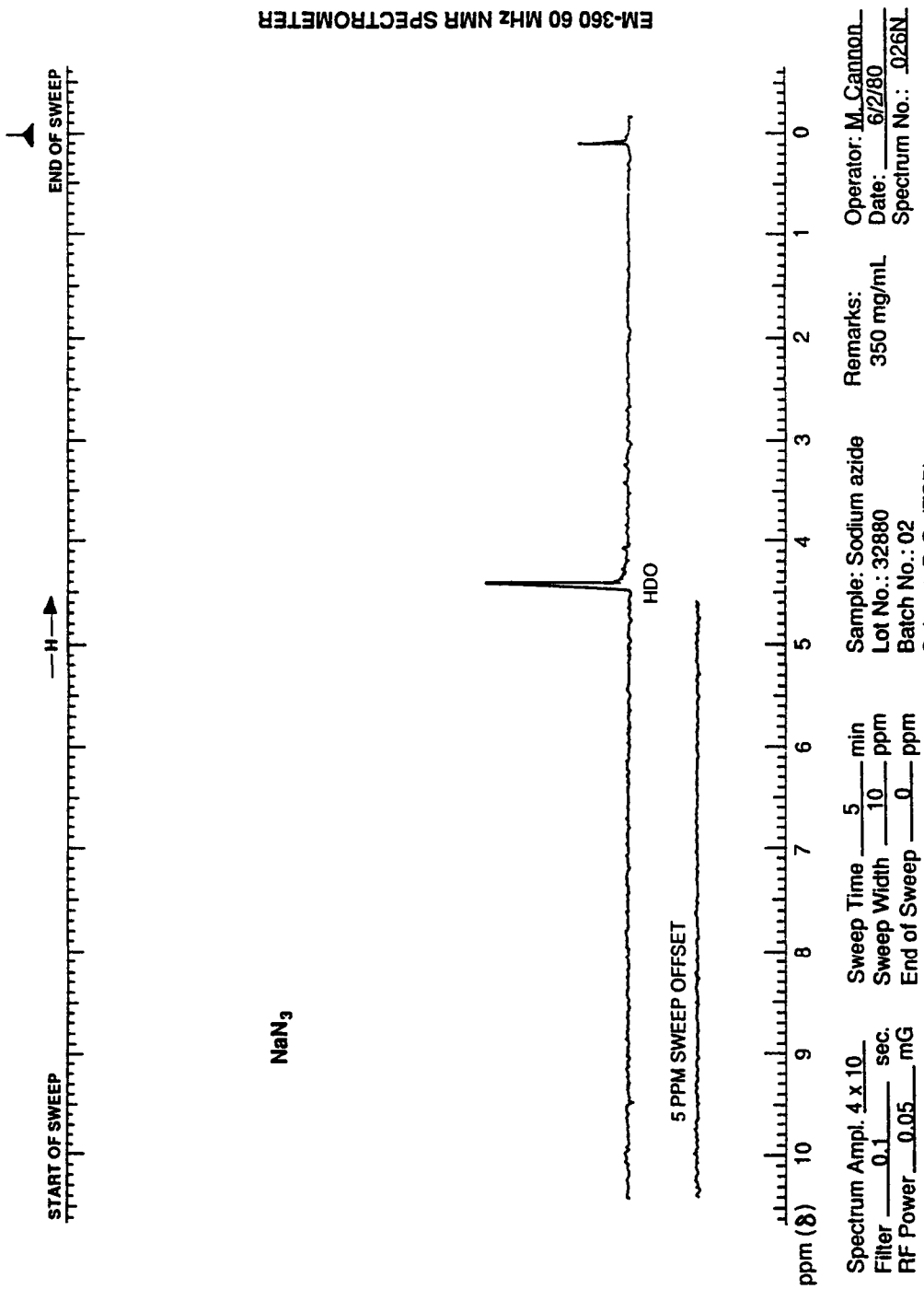

FIGURE E2
Nuclear Magnetic Resonance Spectrum of Sodium Azide

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing appropriate quantities of sodium azide and distilled water to give the required concentrations (w/v) (Table E1). Stability studies were performed at the study laboratory by titration. The method utilized involved determination of the sodium azide content by reaction of a known quantity of potassium permanganate in sulfuric acid solution with the dose formulation sample. The amount of potassium permanganate consumed by the sodium azide present was determined by titration of the iodine liberated from reaction of potassium iodide with the excess permanganate, using sodium thiosulfate and a starch indicator solution. Sodium azide in water (1 mg/mL) was found to be stable for up to 2 weeks when stored protected from light at room temperature and at 5° C and for 3 hours when stored under simulated animal dosing conditions (open to air and light). During the 2-year studies, the dose formulations were stored at 5° C for no longer than 3 weeks, and new dose formulations were prepared every 2 to 3 weeks, as needed.

Periodic analyses of the dose formulations of sodium azide were conducted at the study laboratory by the titration method described above. Dose formulations were analyzed once during the 14-day studies and twice during the 13-week studies. The results were within ± 10% of the target concentrations during the 14-day studies and were within specifications approximately 93% (13/14) of the time during the 13-week studies (Tables E2 and E3). During the 2-year studies, dose formulations were analyzed at approximately 8-week intervals and were within ± 10% of the target concentrations 100% (27/27) of the time throughout the 2-year studies (Table E4). Results of periodic referee analysis performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory (Table E5).

TABLE E1
Preparation and Storage of Dose Formulations in the Gavage Studies of Sodium Azide

14-Day Studies	13-Week Studies	2-Year Studies
Preparation The required amount of sodium azide for each concentration was transferred to the appropriately sized volumetric flask. The flask was filled to approximately 3/4 volume with distilled water, stoppered and shaken until thoroughly mixed. The flask was then filled to volume with water, using a pipette to carefully add the last few milliliters, stoppered, mixed and transferred to the appropriate dosing bottles.	Similar to 14-day studies	Similar to 14-day studies
Concentration of Dose Formulations 1.0, 2.0, 4.0, 8.0, 16.0 mg/mL	0.25, 0.5, 1.0, 2.0, 4.0 mg/mL	1.0 and 2.0 mg/mL
Volume Administered 5 mL/kg	Same as 14-day studies	Same as 14-day studies
Dose Administered 0, 5, 10, 20, 40, 80 mg/kg	0, 1.25, 2.5, 5, 10, 20 mg/kg	0, 5 or 10 mg/kg
Maximum Storage Time for Dose Formulations 3 weeks	2 weeks	3 weeks
Storage Conditions for Dose Formulations Refrigeration at 4°-8° C	Refrigeration at 4°-8° C	Refrigeration at 5° C
Study Laboratory Microbiological Associates, Inc., Bethesda, MD	Same as 14-day studies	Same as 14-day studies
Referee Laboratory Midwest Research Institute, Kansas City, MO	Same as 14-day studies	Same as 14-day studies

TABLE E2
Results of Analysis of Dose Formulations in the 14-Day Gavage Studies of Sodium Azide

Date Mixed	Concentration of Sodium Azide in Gavage Solutions (mg/mL)		Determined as a Percent of Target
	Target	Determined[a]	
16 February 1981	1.0	0.95	95
	2.0	2.06	103
	4.0	4.03	101
	8.0	8.41	105
	16.0	16.64	104

[a] Results of duplicate analyses.
[b] Only one sample analyzed.

TABLE E3
Results of Analysis of Dose Formulations in the 13-Week Gavage Studies of Sodium Azide

Date Mixed	Concentration of Sodium Azide in Gavage Solutions (mg/mL)		Determined as a Percent of Target
	Target	Determined[a]	
2 July 1981	0.063	0.061	97
	0.125	0.130	104
	0.25	0.251	101
	0.5	0.520	104
	1.0	1.040	104
	2.0	1.994	100
	4.0	4.378	109
25 August 1981	0.063	0.052	83
	0.125	0.130	104
	0.25	0.260	104
	0.5	0.477	95
	1.0	0.976	98
	2.0	1.951	98
	4.0	4.118	103

[a] Results of duplicate analyses.

TABLE E4
Results of Analysis of Dose Formulations in the 2-Year Gavage Studies of Sodium Azide

Date Mixed	Concentration of Sodium Azide in Gavage Solutions for Target Concentration[a] (mg/mL)	
	1.0	2.0
3 June 1982	1.045	2.077
29 July 1982	1.019	2.028
9 September 1982	–[b]	2.064
23 September 1982	1.060	1.970
23 September 1982[c]	1.010	1.950
18 November 1982	0.960	1.985
13 January 1983	0.957	1.896
10 March 1983	0.970	2.085
3 May 1983	0.932	1.988
29 June 1983	1.013	2.050
24 August 1983	1.031	2.046
24 August 1983[c]	1.031	2.080
19 October 1983	1.014	2.021
14 December 1983	0.971	2.109
8 February 1984	1.033	1.976
8 February 1984[c]	1.033	1.993
21 March 1984	0.999	2.100
Mean (mg/mL)	1.000	2.028
Standard deviation	0.039	0.060
Coefficient of variation (%)	3.9	3.0
Range	0.932 - 1.060	1.896 - 2.109
Number of samples	13	14

[a] Results of duplicate analyses
[b] Not analyzed
[c] Animal room samples; not included in the mean

TABLE E5
Results of Referee Analysis of Dose Formulations in the 13-Week and 2-Year Gavage Studies of Sodium Azide

Date Mixed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory[a]	Referee Laboratory[b]
13-Week			
2 July 1981	0.125	0.130	0.112
2-Year			
3 June 1982	1.0	1.045	1.013
13 January 1983	2.0	1.896	1.990
24 August 1983	2.0	2.048	2.020
21 March 1984	1.0	0.999	1.010

[a] Results of duplicate analyses
[b] Results of triplicate analyses

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

TABLE F1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

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

TABLE F2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE F3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.21 ± 1.06	21.3–26.3	26
Crude fat (% by weight)	5.10 ± 0.54	3.3–5.7	26
Crude fiber (% by weight)	3.46 ± 0.51	2.9–5.6	26
Ash (% by weight)	6.58 ± 0.41	5.7–7.3	26
Amino Acids (% of total diet)			
Arginine	1.320 ± 0.072	1.310–1.390	5
Cystine	0.319 ± 0.088	0.218–0.400	5
Glycine	1.146 ± 0.063	1.060–1.210	5
Histidine	0.571 ± 0.026	0.531–0.603	5
Isoleucine	0.914 ± 0.030	0.881–0.944	5
Leucine	1.946 ± 0.056	1.850–1.990	5
Lysine	1.280 ± 0.067	1.200–1.370	5
Methionine	0.436 ± 0.165	0.306–0.699	5
Phenylalanine	0.938 ± 0.158	0.655–1.050	5
Threonine	0.855 ± 0.035	0.824–0.898	5
Tryptophan	0.277 ± 0.221	0.156–0.671	5
Tyrosine	0.618 ± 0.086	0.564–0.769	5
Valine	1.108 ± 0.043	1.050–1.170	5
Essential Fatty Acids (% of total diet)			
Linoleic	2.290 ± 0.313	1.830–2.520	5
Linolenic	0.258 ± 0.040	0.210–0.308	5
Vitamins			
Vitamin A (IU/kg)	12,638 ± 4,501	4,100–24,000	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000–6,300	4
α–Tocopherol (ppm)	43.58 ± 6.92	31.1–48.0	5
Thiamine (ppm)	17.12 ± 3.51	12.0–27.0	26
Riboflavin (ppm)	7.60 ± 0.85	6.10–8.20	5
Niacin (ppm)	97.80 ± 31.68	65.0–150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0–34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60–8.80	5
Folic acid (ppm)	2.62 ± 0.89	1.80–3.70	5
Biotin (ppm)	0.254 ± 0.053	0.19–0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6–38.0	5
Choline (ppm)	3,122 ± 416.8	2,400–3,430	5
Minerals			
Calcium (%)	1.28 ± 0.11	1.11–1.54	26
Phosphorus (%)	0.97 ± 0.05	0.89–1.10	26
Potassium (%)	0.900 ± 0.098	0.772–0.971	3
Chloride (%)	0.513 ± 0.114	0.380–0.635	5
Sodium (%)	0.323 ± 0.043	0.258–0.371	5
Magnesium (%)	0.167 ± 0.012	0.151–0.181	5
Sulfur (%)	0.304 ± 0.064	0.268–0.420	5
Iron (ppm)	410.3 ± 94.04	262.0–523.0	5
Manganese (ppm)	90.29 ± 7.15	81.70–99.40	5
Zinc (ppm)	52.78 ± 4.94	46.10–58.20	5
Copper (ppm)	10.72 ± 2.76	8.090–15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52–3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44–2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490–0.780	4

TABLE F4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.51 ± 0.14	0.17–0.77	26
Cadmium (ppm)[a]	<0.10		26
Lead (ppm)	0.75 ± 0.63	0.33–3.37	26
Mercury (ppm)[a]	<0.05		26
Selenium (ppm)	0.32 ± 0.07	0.13–0.42	26
Aflatoxins (ppb)[a]	<5.0		26
Nitrate nitrogen (ppm)	9.02 ± 4.66	0.10–22.0	26
Nitrite nitrogen (ppm)	1.86 ± 2.01	0.10–7.20	26
BHA (ppm)[b]	4.04 ± 4.67	2.00–17.00	26
BHT (ppm)[b]	2.62 ± 2.52	1.00–12.00	26
Aerobic plate count (CFU/g)[c]	43,615 ± 32,607	4,900–130,000	26
Coliform (MPN/g)[d]	47.65 ± 122.37	3.00–460	26
E. coli (MPN/g)[d]	3.00		26
Total nitrosamines (ppb)[e]	5.30 ± 5.78	1.80–30.00	26
N-Nitrosodimethylamine (ppb)[e]	4.26 ± 5.77	0.80–30.00	26
N-Nitrosopyrrolidine (ppb)[e]	1.03 ± 0.25	0.81–1.00	26
Pesticides (ppm)			
α-BHC[af]	<0.01		26
β-BHC[a]	<0.02		26
γ-BHC[a]	<0.01		26
δ-BHC[a]	<0.01		26
Heptachlor[a]	<0.01		26
Aldrin[a]	<0.01		26
Heptachlor epoxide[a]	<0.01		26
DDE[a]	<0.01		26
DDD[a]	<0.01		26
DDT[a]	<0.01		26
HCB[a]	<0.01		26
Mirex[a]	<0.01		26
Methoxychlor[a]	<0.05		26
Dieldrin[a]	<0.01		26
Endrin[a]	<0.01		26
Telodrin[a]	<0.01		26
Chlordane[a]	<0.05		26
Toxaphene[a]	<0.1		26
Estimated PCBs[a]	<0.2		26
Ronnel[a]	<0.01		26
Ethion[a]	<0.02		26
Trithion[a]	<0.05		26
Diazinon[a]	<0.1		26
Methyl parathion[a]	<0.02		26
Ethyl parathion[a]	<0.02		26
Malathion[g]	0.10 ± 0.09	0.05–0.45	26
Endosulfan I[a]	<0.01		26
Endosulfan II[a]	<0.01		26
Endosulfan sulfate[a]	<0.03		26

[a] All values were less than the detection limit, given in the table as the mean.
[b] Source of contamination: soy oil and fish meal
[c] CFU = colony forming unit
[d] MPN = most probable number
[e] All values were corrected for percent recovery.
[f] BHC = hexachlorocyclohexane or benzene hexachloride
[g] Fourteen lots contained more than 0.05 ppm

APPENDIX G
FEED CONSUMPTION BY RATS IN THE 2-YEAR GAVAGE STUDIES

TABLE G1
Feed Consumption by Male Rats in the 2-Year Gavage Study of Sodium Azide

Week	Control		5 mg/kg		10 mg/kg	
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)[a]	Body Weight (g)
4	–[b]	251	–	247	–	244
8	–	319	–	309	–	304
12	–	350	–	341	–	343
16	18	361	17	342	16	343
20	17	396	16	373	15	363
24	16	417	15	392	15	377
28	17	437	16	408	15	389
32	16	450	16	420	15	398
36	16	454	16	430	15	405
40	18	455	17	441	15	418
44	17	477	17	450	14	426
48	15	484	17	454	15	429
52	15	487	16	460	13	443
56	15	489	16	460	14	445
60	16	495	16	466	12	449
64	17	496	16	468	16	444
68	17	494	16	463	15	442
72	17	497	15	466	15	441
76	17	495	16	465	16	433
80	16	483	15	465	15	432
84	17	491	16	461	16	433
88	17	485	13	462	17	432
92	16	473	14	453	14	421
96	18	486	16	446	15	409
100	17	462	15	444	16	391
104	17	461	16	439	19	394
Mean	16		16		15	
% of control value			100		94	

[a] Grams of feed removed from feed per animal per day. Not corrected for scatter.
[b] Food consumption was not measured until week 16, following amendment of the protocol on 29 November 1982.

TABLE G2
Feed Consumption by Female Rats in the 2-Year Gavage Study of Sodium Azide

Week	Control		5 mg/kg		10 mg/kg	
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)[a]	Body Weight (g)
4	–[b]	161	–	159	–	157
8	–	190	–	187	–	182
12	–	198	–	196	–	195
16	11	203	10	200	6	192
20	11	215	11	207	7	193
24	11	224	10	215	8	195
28	11	230	11	221	8	196
32	12	236	11	227	8	198
36	12	245	11	235	8	205
40	12	247	12	239	9	209
44	13	260	12	246	9	218
48	13	267	12	254	8	224
52	12	273	12	263	7	227
56	11	280	11	265	9	231
60	12	290	11	272	9	238
64	12	300	12	282	10	243
68	13	309	12	287	10	246
72	12	316	12	297	10	248
76	13	320	12	299	12	246
80	13	320	12	306	11	259
84	13	326	13	310	11	255
88	14	334	13	310	11	255
92	13	335	12	312	11	257
96	14	338	11	311	10	245
100	13	336	11	308	12	250
104	13	338	11	305	13	257
Mean	12		11		9	
% of control value			92		75	

[a] Grams of feed removed from feed per animal per day. Not corrected for scatter.
[b] Food consumption was not measured until week 16, following amendment of the protocol on 29 November 1982.

APPENDIX H
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 are untreated, and 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.

Upon arrival, 5 male and 5 female rats were sacrificed and their blood collected for the evaluation of the health status of the animals. Fifteen F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Data from animals surviving 24 months were collected from 5/50 randomly selected control animals of each sex. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Complement Fixation	
RCV (rat coronavirus)	Preinitiation and 6 months
ELISA	
RCV/SDA (sialodacryoadenitis virus)	12, 17, 18, and 24 months
Mycoplasma pulmonis	Preinitiation, 6, 12, 17, 18, and 24 months
Hemagglutination Inhibition	
PVM (pneumonia virus of mice)	Preinitiation, 6, 12, 17, 18, and 24 months
KRV (Kilham rat virus)	Preinitiation, 6, 12, 17, 18, and 24 months
H-1 (Toolan's H-1 virus)	Preinitiation, 6, 12, 17, 18, and 24 months
Sendai	Preinitiation, 6, 12, 17, 18, and 24 months

RESULTS

The serology results for sentinel animals are presented in Table H1.

TABLE H1
Murine Virus Antibody Determinations for Rats in the 2-Year Gavage Studies of Sodium Azide

Interval (months)	Number of Animals	Positive Serologic Reaction for
0	0/10	None
6	3/10	PVM
	1/10	*M. pulmonis* (equivocal)
12	5/9	*M. pulmonis* (positive)
	3/9	*M. pulmonis* (equivocal)
17[a]	0/2	None
18	2/9	*M. pulmonis*
24	0/10	None

[a] Two animals found moribund were evaluated for murine virus antibodies.

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201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichloroethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	1,3-Dichloropropane (Telone II®)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3
336	Penicillin VK
337	Nitrofurazone

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338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	*a*-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3'-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
386	Tetranitromethane
387	Amphetamine Sulfate
390	3,3'-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
393	Sodium Fluoride

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