NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

SODIUM NITRITE

(CAS NO. 7632-00-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(DRINKING WATER STUDIES)

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

May 2001

NTP TR 495

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

FOREWORD

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

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

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

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

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

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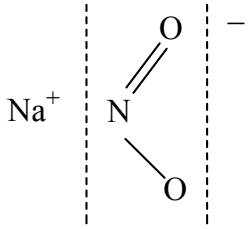
ABSTRACT



SODIUM NITRITE

CAS No. 7632-00-0

Chemical Formula: $NaNO_2$ Molecular Weight: 69.00

Synonyms: Diazotizing salts; nitrous acid, sodium salt
Trade names: Anti-Rust, Erinitrit, Filmerine

Sodium nitrite is used as a color fixative and preservative in meats and fish. It is also used in manufacturing diazo dyes, nitroso compounds, and other organic compounds; in dyeing and printing textile fabrics and bleaching fibers; in photography; as a laboratory reagent and a corrosion inhibitor; in metal coatings for phosphatizing and detinning; and in the manufacture of rubber chemicals. Sodium nitrite also has been used in human and veterinary medicine as a vasodilator, a bronchial dilator, an intestinal relaxant, and an antidote for cyanide poisoning. Sodium nitrite was nominated by the FDA for toxicity and carcinogenesis studies based on its widespread use in foods. Male and female F344/N rats and B6C3F$_1$ mice were exposed to sodium nitrite (99% pure) in drinking water for 14 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, rat and mouse bone marrow, and mouse peripheral blood.

14-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats were exposed to 0, 375, 750, 1,500, 3,000, or 5,000 ppm sodium nitrite (equivalent to average daily doses of approximately 30, 55, 115, 200, or 310 mg sodium nitrite/kg body weight to males and 40, 80, 130, 225, or 345 mg/kg to females) in drinking water for 14 weeks. Clinical pathology study groups of 15 male and 15 female rats were exposed to the same concentrations for 70 or 71 days. One female exposed to 3,000 ppm died before the end of the study. Body weights of males exposed to 3,000 or 5,000 ppm and females exposed to 5,000 ppm were significantly less than those of the controls. Water consumption by 5,000 ppm males and 3,000 and 5,000 ppm females was less than that by the controls at weeks 2 and 14. Clinical findings related to sodium nitrite exposure included brown discoloration in the eyes and cyanosis of the mouth, tongue, ears, and feet of males exposed to 3,000 or 5,000 ppm and of females exposed to 1,500 ppm or greater. Reticulocyte counts were increased in males and females exposed to 3,000 or 5,000 ppm. The erythron was decreased on day 19 but increased by week 14 in males and females exposed to 5,000 ppm. Methemoglobin concentrations were elevated in almost all exposed groups throughout the 14 week study; a no-observed-adverse-effect level was not achieved. The relative kidney and spleen weights of males and females exposed to 3,000 or 5,000 ppm were significantly greater than those of the controls. Sperm motility in 1,500 and 5,000 ppm males was significantly decreased. Increased erythropoietic

activity in the bone marrow of exposed males and females was observed. The incidences of squamous cell hyperplasia of the forestomach in 5,000 ppm males and females were significantly increased.

14-Week Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to 0, 375, 750, 1,500, 3,000, or 5,000 ppm sodium nitrite (equivalent to average daily doses of approximately 90, 190, 345, 750, or 990 mg/kg to males and 120, 240, 445, 840, or 1,230 mg/kg to females) in drinking water for 14 weeks. Body weights of males exposed to 5,000 ppm were significantly less than those of the controls. Water consumption by males exposed to 1,500 ppm or greater was slightly less than that by the controls at week 13. Relative spleen weights of 3,000 and 5,000 ppm males and absolute and relative heart, kidney, liver, and spleen weights of females exposed to 3,000 or 5,000 ppm were greater than those of the control groups. Sperm motility was decreased in 5,000 ppm males, and the estrous cycles of 1,500 and 5,000 ppm females were significantly longer than in the controls. There were increased incidences of squamous cell hyperplasia of the forestomach in 5,000 ppm males and females, extramedullary hematopoiesis of the spleen in 3,000 and 5,000 ppm males and 1,500 ppm or greater females, and degeneration of the testis in 3,000 and 5,000 ppm males.

2-Year Study in Rats

Groups of 50 male and 50 female rats were exposed to 0, 750, 1,500, or 3,000 ppm sodium nitrite (equivalent to average daily doses of approximately 35, 70, or 130 mg/kg to males and 40, 80, or 150 mg/kg to females) in drinking water for 2 years. For toxicokinetic studies of plasma nitrite and blood methemoglobin, 10 male and 10 female special study rats were exposed to the same concentrations for 12 months. Survival of exposed groups was similar to that of the controls. Mean body weights of males and females exposed to 3,000 ppm were less than those of the controls throughout the study. Water consumption by males and females exposed to 3,000 ppm was less than that by the controls throughout the study, and that by the other exposed groups was generally less after week 14.

The incidences of hyperplasia of the forestomach epithelium in males and females exposed to 3,000 ppm were significantly greater than those in the control groups. The incidence of fibroadenoma of the mammary gland was significantly increased in females exposed to 1,500 ppm, and the incidences of multiple fibroadenoma were increased in 750 ppm and 1,500 ppm females; however, these neoplasms occur with a high background incidence, and no increase was seen in the 3,000 ppm group. The incidences of mononuclear cell leukemia were significantly decreased in males and females exposed to 1,500 or 3,000 ppm.

2-Year Study in Mice

Groups of 50 male and 50 female B6C3F$_1$ mice were exposed to 0, 750, 1,500, or 3,000 ppm sodium nitrite (equivalent to average daily doses of approximately 60, 120, or 220 mg/kg to males and 45, 90, or 165 mg/kg to females) in drinking water for 2 years. Survival of exposed groups was similar to that of the controls; mean body weights of 3,000 ppm females were less than those of the controls throughout the study. Exposed groups generally consumed less water than the control groups.

The incidences of squamous cell papilloma or carcinoma (combined) in the forestomach of female mice occurred with a positive trend. The incidence of hyperplasia of the glandular stomach epithelium was significantly greater in 3,000 ppm males than in the controls.

Genetic Toxicology

Sodium nitrite was mutagenic in *Salmonella typhimurium* strain TA100, with and without Aroclor 1254-induced hamster and rat liver S9 enzymes; no mutagenicity was observed in strain TA98. Results of acute bone marrow micronucleus tests with sodium nitrite in male rats and mice by intraperitoneal injection were negative. In addition, a peripheral blood micro nucleus assay conducted with mice from the 14-week study gave negative results.

Conclusions

Under the conditions of this 2-year drinking water study, there was *no evidence of carcinogenic activity** of sodium nitrite in male or female F344/N rats

exposed to 750, 1,500, or 3,000 ppm. There was *no evidence of carcinogenic activity* of sodium nitrite in male $B6C3F_1$ mice exposed to 750, 1,500, or 3,000 ppm. There was *equivocal evidence of carcinogenic activity* of sodium nitrite in female $B6C3F_1$ mice based on the positive trend in the incidences of squamous cell papilloma or carcinoma (combined) of the forestomach.

Exposure to sodium nitrite in drinking water resulted in increased incidences of epithelial hyperplasia in the forestomach of male and female rats and in the glandular stomach of male mice.

Decreased incidences of mononuclear cell leukemia occurred in male and female rats.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report is on page 13.

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in drinking water	0, 750, 1,500, or 3,000 ppm	0, 750, 1,500, or 3,000 ppm	0, 750, 1,500, or 3,000 ppm	0, 750, 1,500, or 3,000 ppm
Body weights	3,000 ppm group less than the control group	3,000 ppm group less than the control group	Exposed groups similar to the control group	3,000 ppm group less than the control group
Survival rates	29/50, 38/50, 36/50, 36/50	33/50, 31/50, 36/50, 33/50	39/50, 45/50, 42/50, 39/50	40/50, 34/50, 37/50, 41/50
Nonneoplastic effects	Forestomach: epithelial hyperplasia (12/50, 9/50, 10/50, 44/50)	Forestomach: epithelial hyperplasia (8/50, 6/50, 8/50, 40/50)	Glandular stomach: epithelial hyperplasia (0/50, 0/50, 2/50, 10/50)	None
Neoplastic effects	None	None	None	None
Uncertain findings	None	None	None	Forestomach: squamous cell papilloma or carcinoma (1/50, 0/50, 1/50, 5/50)
Decreased incidences	Mononuclear cell leukemia: (17/50, 12/50, 7/50, 3/50)	Mononuclear cell leukemia: (15/50, 10/50, 1/50, 1/50)	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	Equivocal evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Positive in strain TA100 with and without S9; negative in strain TA98			
Micronucleated erythrocytes				
Male rat bone marrow *in vivo*:	Negative			
Male mouse bone marrow *in vivo*:	Negative			
Male and female mouse peripheral blood *in vivo*:	Negative			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on sodium nitrite on 18 May 2000 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 18 May 2000, the draft Technical Report on the toxicology and carcinogenesis studies of sodium nitrite received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. P.C. Chan, NIEHS, introduced the toxicology and carcinogenesis studies of sodium nitrite by describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic lesions in female mice, possible compound-related neoplastic lesions in female rats, and compound-related nonneoplastic lesions in male and female rats and male mice. The proposed conclusions were *no evidence of carcinogenic activity* in male F344/N rats or male B6C3F$_1$ mice, *equivocal evidence of carcinogenic activity* in female F344/N rats, and *some evidence of carcinogenic activity* in female B6C3F$_1$ mice.

Dr. F. Ye, NIEHS, presented statistical analyses and information on the toxicokinetic modeling of nitrite absorption and elimination and methemoglobinemia in rats and mice. The objectives of the analyses were to study the relationship between nitrite and methemoglobinemia by developing a toxicokinetic model to characterize the nitrite-induced methemoglobin process and to compare net absorption and elimination rates of nitrite from plasma. The studies found that nitrite is rapidly absorbed after oral exposure and may depend on dose level. The studies also found that overall clearance of nitrite may depend on species, route, and dose, and nitrite is rapidly cleared from plasma because it causes oxidation to methemoglobin by binding to hemoglobin. Dr. Ye further concluded that reduction of hemoglobin to its ferrous form is sensitive to basal methemoglobin reductase activity, strong binding of nitrite to methemoglobin, and the autocatalytic cycle.

Dr. Hecht, a principal reviewer, agreed with the proposed conclusions in regard to male rats but disagreed with the proposed conclusions in regard to female mice, for which he stated the data only supported equivocal evidence of carcinogenic activity. Dr. Hecht also stated that the NTP had ignored literature on endogenous formation of nitrosamines and that the literature should be updated and expanded.

Dr. Bus, the second principal reviewer, agreed with the proposed conclusions for male rats and mice but disagreed with the proposed conclusions for female rats and mice. For female rats, he argued that the response in the mammary glands was not exposure concentration dependent, occurred in the presence of high concurrent and historical control incidences of fibroadema, and was not accompanied by increased incidences of carcinomas, thus supporting no evidence of carcinogenic activity. Dr. J.R. Bucher, NIEHS, stated the incidence in the mid-exposure group was the highest seen, and the finding could not be dismissed. Dr. Bus emphasized that the increased incidence of forestomach squamous cell papilloma or carcinoma (combined) in 3,000 ppm female mice was not significantly different from that in the controls, and that only the trend test showed statistical significance, thus supporting equivocal evidence of carcinogenic activity. Dr. Chan agreed that the level of evidence in female mice could be debated. Due to the positive trend in the incidences of squamous cell papillomas and carcinomas (combined) and because the incidence in the 3,000 ppm females exceeded the historical range for NTP controls on NTP-2000 diet, he concluded the evidence supported some evidence of carcinogenic activity. Also, he found the two carcinomas hard to ignore.

Dr. Chatman, the third principal reviewer, disagreed with the proposed conclusions for female rats and mice. Dr. Chatman agreed with Dr. Bus that the level of evidence should be no evidence of carcinogenic activity in female rats and equivocal evidence of carcinogenic activity in female mice. Dr. Chatman questioned the use of drinking water rather than dosed feed as the route of administration.

Dr. J.R. Hailey, NIEHS, addressed a comment by Dr. Bus and by Dr. G. Williams, New York Medical College, concerning incidences of gastrointestinal neoplasms in mice on the NTP-2000 diet compared with the NIH-07 diet. Dr. Hailey stated there was an increase noted in the incidences of intestinal neoplasms but not in forestomach neoplasms. Dr. Bailer suggested that significant negative trends in the

incidences of neoplasms such as mononuclear cell leukemia in male and female rats warranted more attention than given in the report.

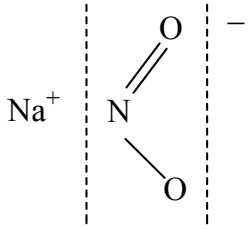
Dr. L.L. Borchert, Director of Research (Retired), Oscar Mayer Foods Corporation and Adjunct Professor, Meat Science and Muscle Biology, University of Wisconsin-Madison, representing the American Meat Science Association, provided historical background on the food industry's need to use sodium nitrite and the safety of sodium nitrite as a food additive. He stated the United States Department of Agriculture and its predecessors have permitted the use of sodium nitrite in processed meat products since 1925, when it was proven safe for human consumption. He said the industry welcomed the use of sodium nitrite because it accelerated the curing process from days and weeks to hours. He stated that in order to meet safety concerns arising in the 1970s, the food industry eliminated sodium nitrate, reduced usage levels of sodium nitrite, incorporated sodium ascorbate into all processed meat products, and monitored nitrosamine formation in fried bacon. He noted a national survey from 1996 which showed that processed meats in the United States contain about 10 ppm of sodium nitrite and no sodium nitrate.

Dr. D. Archer, Food Science and Human Nutrition Department, University of Florida, representing the Food Safety Advisory Committee of the American Meat Institute Foundation, noted some of the positive aspects of having sodium nitrite in the food supply. First, he stressed the positive physiologic role of nitric oxide and its metabolites, including nitrite. Second, he noted that nitrite is a physiologically endogenous compound. Third, he emphasized the profound effect of sodium nitrite in preventing growth of and toxin production by *Clostridium botulinum*. Fourth, he remarked on the growth retardant role that sodium nitrite plays on food pathogens as a bactericidal agent in conjunction with stomach acid.

Dr. G. Williams, New York Medical College, representing the American Meat Institute Foundation, asserted that due to several reasons, the small incidence of forestomach neoplasms seen in 3,000 ppm female mice at the end of the study is not attributable to sodium nitrite. He commented that the high pH of the female mouse forestomach and sodium nitrite solutions used were not conducive to formation of DNA-deaminating nitrous acid or of carcinogenic N-nitroso compounds, and there was no evidence for this reaction. Also, he noted that the genetic toxicology database for sodium nitrite supports the view that it is not an *in vivo* genotoxic agent. Dr. Williams further stated that the new NTP-2000 diet appears to facilitate the development of more spontaneous gastrointestinal neoplasms than the NIH-07 diet, and sodium nitrite has not been shown to be a forestomach carcinogen in rats in this bioassay or in the scientific literature.

Dr. Hecht moved that the Technical Report on sodium nitrite be accepted with revisions discussed including changes in the conclusions for female rats and mice. The proposed revised conclusions were, for male and female rats and male mice, *no evidence of carcinogenic activity* and for female mice, *equivocal evidence of carcinogenic activity*. Dr. Bus seconded the motion. The motion was accepted unanimously with six yes votes.

INTRODUCTION



SODIUM NITRITE

CAS No. 7632-00-0

Chemical Formula: $NaNO_2$ Molecular Weight: 69.00

Synonyms: Diazotizing salts; nitrous acid, sodium salt
Trade names: Anti-Rust, Erinitrit, Filmerine

CHEMICAL AND PHYSICAL PROPERTIES

Sodium nitrite is a white solid. It has a melting point of 271° C and decomposes at 320° C; its specific gravity is 2.17 at 0° C; it is very soluble in water and ammonia and soluble in methanol, ethanol, ether, and pyridine; and it slowly oxidizes to nitrate in air (*Kirk-Othmer*, 1985; *Merck Index*, 1996).

PRODUCTION, USE, AND HUMAN EXPOSURE

Industrially, sodium nitrite is produced by mixing 1 to 10 parts oxygen, 2 to 12 parts nitrogen oxide, 15 to 20 parts water, and 58 to 83 parts inert gas. The mixture is cooled from 900° C to between 300° and 350° C and then dispersed under the surface of an aqueous sodium hydroxide solution at 30° to 120° C. A 99% pure product is obtained by evaporating the solution and drying the residue.

Sodium nitrite can also be prepared by reducing sodium nitrate with lead, heat, light, or ionizing radiation (*Kirk-Othmer*, 1985). Approximately 61 million pounds of sodium nitrite were produced in the United States. More recent production information was not located.

Sodium nitrite inhibits the formation of a toxin by the anaerobic spore-forming bacteria, *Clostridium botulinum*. It imparts a pink color to nitrite-cured meats and stabilizes the flavors of stored meats. Therefore, it is used as a color fixative and preservative in meats and fish. It is also used in manufacturing diazo dyes, nitroso compounds, and other organic compounds; in dyeing and printing textile fabrics; in bleaching fibers; in photography; as a laboratory reagent and a corrosion inhibitor; in metal coatings for phosphatizing and detinning; and in the manufacture of rubber chemicals. Sodium nitrite also has been used in human and veterinary medicine as a vasodilator, a bronchial dilator, an intestinal relaxant, and an antidote for cyanide poisoning.

Humans are constantly exposed to sodium nitrite through the oral route because it is used as a food additive (21 CFR §§ 172.175, 172.177, 181.34, and 573.700). Some vegetables, such as spinach and beets, and some well water contain high concentrations of nitrates, which may be reduced to nitrites by the action of microorganisms before and after ingestion (Wolff and Wasserman, 1972; Heisler *et al.*, 1974; Ishiwata

et al., 1975; White, 1975; Tannenbaum *et al.*, 1978a,b; Archer, 1982). White (1976) estimated that a United States resident ingests 99.8 mg per day of nitrates and nitrites, Phillips (1968) estimated that Canadians consume 313 mg nitrate per meal (4.5 mg/kg), Stephany and Schuller (1980) estimated nitrate ingestion in the Netherlands as 100 mg per person per day, and Knight *et al.* (1987) reported daily intake of 95 mg nitrate and 1.4 mg nitrite from food and 13.5 mg nitrate from water per person in Britain.

Sodium nitrite is also found in human saliva. Tannenbaum *et al.* (1974, 1976) estimated that human saliva contains 6 to 10 mg/L, and the amount is directly related to nitrate intake. Nitrate and nitrite are also formed *de novo* in the intestines of humans, possibly by heterotrophic nitrification of microorganisms (Tannenbaum *et al.*, 1978a).

Nitrite exposure may occur as a result of inhaling nitrogen oxide and nitrogen dioxide, which are converted to nitrate and nitrite *in vivo*, from the polluted atmosphere (Imaizumi *et al.*, 1980; Mirvish, 1995). The National Occupational Health Survey conducted from 1972 to 1974 estimated that 69,341 workers in 1,008 plants were potentially exposed to sodium nitrite annually (NIOSH, 1976). Another survey conducted from 1981 to 1983 indicated that 54,179 workers at 2,530 sites were potentially exposed to sodium nitrite (NIOSH, 1990).

The main concern regarding sodium nitrite exposure is that the chemical reacts readily with secondary amines and amides present in food or drugs to form carcinogenic *N*-nitroso compounds *in vivo* in the stomach under low pH conditions (Mirvish, 1975; Maekawa *et al.*, 1982). Nitrosation of amines also occurs in the presence of saliva (Ishiwata *et al.*, 1975; Tannenbaum *et al.*, 1978b), in the intestine (Tannenbaum *et al.*, 1978a), in the urinary bladder (Hill *et al.*, 1973), and via nitric oxide formation during inflammation (Mirvish, 1995). In the early 1960s, incidences of poisoning in mink and ruminants fed herring meal were traced to the formation of nitrosamine in the meal from sodium nitrite used as a preservative (Archer, 1982). Maekawa *et al.* (1982) reported that CRF-1 rat diet contained 7.5 ppb *N*-nitrosodimethylamine. Newly formed *N*-nitrosodimethylamine was found in the stomach of male (18.0-36.8 ppb) and female (13.5-15.2 ppb) F344 rats fed CRF-1 diet and given water containing 0.25% sodium nitrite. Fine *et al.* (1977) reported that 0.35 µg/L nitrosodimethylamine and 0.09 µg/L nitrosodiethylamine were present in the blood of humans. After a meal of raw spinach and tomatoes, cooked bacon, bread, and beer, the nitrosodimethylamine concentration had increased to 0.76 µg/L and the nitrosodiethylamine concentration to 0.46 µg/L. The total nitrosamine concentration in the blood was higher than that present in the food consumed and was considered to have been formed *in vivo*. Carcinogenic tobacco-specific nitrosamines are formed endogenously in rats treated with tobacco alkaloids and sodium nitrite (Carmella *et al.*, 1997).

Sodium nitrite can also act with secondary amines and amides in *in vitro* conditions, forming *N*-nitroso compounds (Aoyagi *et al.*, 1980; Maekawa *et al.*, 1982; Chen *et al.*, 1996). Approximately 300 nitrosamines and nitrosoamides have been shown to be carcinogenic in experimental animals (Hecht, 1997).

Furthermore, sodium nitrite may react with phenolic antioxidants (e.g., phenol, 3-methoxycatechol, catechol, vanillin, and butylated hydroxyanisole) under acidic conditions to form compounds with cell proliferative, hyperplastic, genotoxic, and carcinogenic activities (Kawabe *et al.*, 1994). For example, incidences of forestomach hyperplasia and papilloma in rats were significantly greater when sodium nitrite was given with catechol or 3-methoxycatechol than when catechol or 3-methoxycatechol was given alone (Kawabe *et al*., 1994).

REGULATORY STATUS

The FDA approves the use of sodium nitrite as a color fixative and preservative in smoked, cured sablefish, salmon, and shad and in meat products including poultry and wild game at concentrations not to exceed 200 ppm (21 CFR §§ 172.175, 172.177, 181.34, and 573.700). The Safe Drinking Water Act (43 USC 300f) established a maximum contaminant concentration for nitrate of 10 mg/L. The World Health Organization (1974) set the acceptable daily intake for nitrate at 3.67 mg/kg body weight and nitrite at 0.13 mg/kg body weight (expressed as nitrate and nitrite ion). The Joint FAO/WHO Expert Committee on Food Additives established an accepted daily nitrite intake of 0 to 0.06 mg/kg body weight (Speijers, 1996). The U.S. Environmental Protection Agency has

designated sodium nitrite as a hazardous substance and requires that it be notified if 100 pounds or more is released in water or on land (40 CFR Part 302). Under the Hazardous Materials Transportation Act (49 CFR §172.101), the Department of Transportation regulates sodium nitrite as an oxidizer that is subject to certain labeling and packaging requirements. Neither the American Conference of Governmental Industrial Hygienists (1999) nor the Occupational Safety and Health Administration (NIOSH, 1997) has established a workplace or permissible exposure limit for sodium nitrite.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Ingested nitrate is absorbed from the small intestine into the circulatory system. Blood nitrate is either concentrated in the salivary glands where it is reduced to nitrite by bacteria or removed by the kidney and excreted in the urine. Sodium nitrite is absorbed unchanged from the stomach of rats and mice. In blood, nitrite is rapidly and irreversibly oxidized to nitrate (Vleeming *et al.*, 1997), which is then eliminated by excretion.

Following gavage administration of 150 µg sodium nitrite in an aqueous solution, 85% of the dose disappeared from the stomach of ICR/Ha mice in 10 minutes, and 95% disappeared in 30 minutes (Friedman *et al.*, 1972). In Wistar rats, 154 µg/g sodium nitrite mixed in 5 g of food persisted in the stomach for up to 5 hours with a half-life of 1.4 hours (Mirvish *et al.*, 1975). Sodium nitrate or nitrite injected intraperitoneally or intravenously showed a mean plasma half-life of 1.54 hours in mice (Veszelovsky *et al.*, 1995). Nitrite is unstable in acid and spontaneously decomposes to nitrate and nitrogen dioxide. Under acidic conditions and in the presence of food, nitrite disappeared with a half-life of 2.2 hours at pH 4.5, 0.93 hours at pH 3.5, and 0.42 hours at pH 2.5 (Mirvish *et al.*, 1975).

Humans

No information on the absorption, distribution, metabolism, or excretion of sodium nitrite in humans was found in a review of the literature.

BIOLOGIC EFFECTS

Nitrite in blood is highly reactive with hemoglobin and causes methemoglobinemia. Ferrous iron associated with hemoglobin is oxidized by nitrite to ferric iron, leading to the formation of methemoglobin. The oxygen-carrying capacity of methemoglobin is much less than that of hemoglobin (NAS, 1981).

Following a single oral dose of 0.15 g/kg sodium nitrite to Sprague-Dawley rats, maximum methemoglobin concentrations (45%-80%) occurred within 60 minutes; the concentration returned to normal after 24 hours if the animal survived (Imaizumi *et al.*, 1980). The production of methemoglobin was preceded by the formation of nitrosyl hemoglobin. Blood concentrations of nitrate and nitrite reached a maximum 20 to 30 minutes after dosing; nitrite had a half-life of about 70 minutes while nitrate concentrations remained high for more than 5 hours. After 6 months of exposure to 0.5% sodium nitrite in drinking water, methemoglobin concentration peaked between 6:00 and 9:00 p.m. and was at a minimum around 9:00 a.m. Increased methemoglobin concentration was accompanied by marked increases in Heinz body formation in erythrocytes, anisocytosis, and hypohemoglobinemia. This study also showed that the minimum lethal concentration of methemoglobin is about 80% to 85%. The lowest concentration of methemoglobin occurred at 9:00 a.m. because of its short half-life and because 80% of a rat's daily intake of water is at night (Shuval and Gruener, 1972). Blood methemoglobin concentrations correlate positively with plasma sodium nitrite concentrations in rats (Hirneth and Classen, 1984).

The enzyme methemoglobin reductase catalyzes the reduction of methemoglobin to hemoglobin and protects red cells against oxidative damage. Along with methemoglobin concentrations, methemoglobin reductase activities increased after nitrite administration to rats (Pankow *et al.*, 1975). Calabrese *et al.* (1983) showed that 50% methemoglobin was formed when 1 mL of human whole blood was mixed with 10 µL of a 3 mM solution of sodium nitrite, whereas the same concentration of sodium nitrite induced only 14% methemoglobin formation with rat blood. The difference in sensitivity is probably due to the fivefold difference in erythrocyte methemoglobin reductase activity between the two species (Smith and Beutler, 1966).

Nitrite reacts readily with secondary amines and amides to produce carcinogenic *N*-nitroso compounds. The reaction proceeds when the pH in the stomach is acidic and at near-neutral pH in the presence of enteric bacteria in the small intestine of rats. The nitrosation rate for secondary amines is proportional to the square of the nitrite concentration (Mirvish, 1975). Nitrosation also occurs with tertiary amines and quaternary ammonium compounds.

TOXICITY

Experimental Animals

The primary acute effect of sodium nitrite in rats and mice is methemoglobinemia. Smith and Layne (1969) reported methemoglobin concentrations ranging from 9.5% to 72.1% in female CD-1 mice following intraperitoneal injection of 0.5 to 2.8 nmol/kg (35 to 193 mg/kg). Methemoglobin concentrations in Sprague-Dawley rats increased to 45% to 80% 1 hour after an oral dose of 150 mg/kg and returned to normal within 24 hours in surviving rats (Imaizumi *et al.*, 1980). Sodium nitrite administered in drinking water at 1,000 to 3,000 mg/L (1,000 to 3,000 ppm) for 2 years elevated methemoglobin concentrations in male rats (unspecified strain) throughout the 2-year period (Shuval and Gruener, 1972).

The secondary effects of acute nitrite intoxication in animals are vasodilation, relaxation of smooth muscle, and lowering of blood pressure (Gangolli *et al*., 1994) and a decrease in D-xylose absorption in the intestinal mucosa (Grudzinski and Szymanski, 1991a,b; Grudzinski *et al.*, 1991). Other nitrite-induced toxic effects include abdominal pain, diarrhea, atrophied intestinal villi, and apoptotic cell death in the intestinal crypts (Grudzinski and Szymanski, 1991a,b; Grudzinski *et al.*, 1991; Grudzinski and Law, 1998a,b). The LD_{50} values for experimental animals are given in Table 1.

Sodium nitrite administered in drinking water at 0.06%, 0.125%, 0.25%, 0.5%, or 1% (600, 1250, 2500, 5,000, or 10,000 ppm) to male and female ICR mice for 6 weeks caused slight degeneration and spotty necrosis of hepatocytes and hemosiderin deposition in the liver, spleen, and lymph nodes, indicating hemolysis. At 2% and 4% (20,000 and 40,000 ppm), mice died within 3 weeks (Inai *et al.*, 1979). In F344 rats subjected to the same exposure regimen as the ICR mice, abnormal blood and spleen colors due to methemoglobin were observed in the 0.5% and 1.0% groups (Maekawa *et al.*, 1982).

TABLE 1
LD_{50} Values of Sodium Nitrite in Experimental Animals

Species	Strain	Route	LD_{50} (mg/kg)	Reference
Rat	BD	gavage	130	Druckery *et al.*, 1963
			77 (fasted)	
		intravenous	65	
	Sprague-Dawley	oral	150 (fasted)	Imaizumi *et al.*, 1980
Mouse	White	oral	214 (male)	Riemann, 1950
			216 (female)	
	CD-1	intraperitoneal	158 (female)	Smith and Layne, 1969
Rabbit	New Zealand	oral	124	Dollahite and Rowe, 1974

Darad *et al.* (1983) reported that hepatic microsomal lipoperoxidation activity, as measured by malondialdehyde formation, was increased in male Wistar rats given 0.2% sodium nitrite in drinking water. Liver lysosomal enzyme (acid phosphatase and cathepsin) and superoxide dismutase activities were increased compared to the controls. The data suggest that sodium nitrite stimulates generation of superoxide radicals in the liver and causes damage to the cellular and subcellular membranes. Decreased plasma vitamin E and greater reduced glutathione-per-erythrocyte values were reported in male rats receiving sodium nitrite in drinking water (Chow *et al.*, 1980).

Sodium nitrite administered in feed at 10 or 25 mg/kg (10,000 or 25,000 ppm) to unilaterally ovariectomized Long-Evans rats for 21 days inhibited body weight gain and caused a decrease in the compensatory ovarian hypertrophy that follows hemicastration. Decreased uterine, liver, and kidney weights and increased spleen weights were also observed (Noel *et al.*, 1974). Hsu *et al*. (1997) demonstrated that feeding sodium nitrite to male Wistar rats at 0.3% (3,000 ppm) for 3 months did not affect relative liver weights or the expression of hepatic c-*Jun*, c-*Fos*, or c-*Myc* oncogenes.

Humans

In humans, sodium nitrite causes smooth muscle relaxation, methemoglobinemia, and cyanosis. Fatal poisonings of infants resulting from ingestion of nitrates in water or spinach have been recorded (Shuval and Gruener, 1972; Knobeloch *et al*., 2000). Long-term ingestion of water containing high levels of nitrate may increase the risk of gastric cancer (Xu *et al*., 1992; Morales-Suarez-Varela *et al*., 1995; Yang *et al*., 1998). However, prospective cohort study did not support an association between the intake of nitrate and nitrite and gastric cancer risk (Van Loon *et al*., 1998). The LD_{50} value for sodium nitrite has been estimated to be about 1 g in adults (Archer, 1982); a 17-year-old woman died after taking a single 1-g tablet (Gowans, 1990). Fatal methemoglobinemia was reported after ingestion of a laxative solution contaminated with 15 g/L sodium nitrite (Ellis *et al.*, 1992).

REPRODUCTIVE TOXICITY

There is evidence for placental transfer of sodium nitrite to rat and mouse fetuses. Sodium nitrite administered by oral intubation to pregnant mice (0.5 mg/mouse per day) did not cause fetal mortality or resorption or changes in embryo weight or incidence of skeletal malformation. The treatment did stimulate fetal hepatic erythropoiesis, probably related to fetal methemoglobinemia (Globus and Samuel, 1978). Nitrite and methemoglobin were detected in fetal blood after pregnant rats were given a single dose of 2.5 to 5.0 mg sodium nitrite/kg body weight (Shuval and Gruener, 1972).

Sodium nitrite (60 mg/kg) administered in drinking water to pregnant guinea pigs produced maternal anemia and increased the incidences of abortion and fetal mortality (Sinha and Sleight, 1971). At 0.31 g/kg in drinking water, sodium nitrite did not affect reproductive parameters of female C57BL/6 mice (Anderson *et al.*, 1985). Pregnant Swiss CD-1 mice given up to 0.24% sodium nitrite in drinking water had reduced water consumption, but body weight was not affected (Chapin and Sloane, 1997). The treatment did not affect the mean number of litters per pair, the number of pups per litter, or the pup viability or weight. Reproductive success in the F_1 generation was not affected.

Administration of 2,000 or 3,000 mg/L of sodium nitrite in drinking water to pregnant rats (exposure period and rat strain not specified) caused 30% or 53% fetal mortality, respectively; fetal mortality in the controls was 6% (Shuval and Gruener, 1972). In rat dams given 0.025% to 0.5% in feed, sodium nitrite caused increases in fetal and pup mortality and decreases in preweanling body weights (Vorhees *et al.*, 1984). However, oral intubation of up to 120 mg/kg on gestation day 13 had no effect on dams or pups (Khera, 1982). Reproductive performance was not affected in male or female rats given up to 0.05% in feed before and during breeding (Vorhees *et al.*, 1984).

NEUROTOXICITY

After a single subcutaneous dose of 55 mg sodium nitrite/kg body weight, locomotor, exploratory, and grooming activities were suppressed in 3-month-old male rats; complete recovery was observed after 24 hours (Hlinak *et al.*, 1990). Exposure of rats to sodium nitrite at 100 to 2,000 mg/L in drinking water for 2 months produced changes in the pattern of brain electrical activity (Shuval and Gruener, 1972, 1977).

The electroencephalogram pattern of four dosed rats differed from those for controls and remained different after sodium nitrite withdrawal (Behroozi *et al.*, 1972).

CARCINOGENICITY

Experimental Animals

Conflicting results were reported in sodium nitrite studies with rats. Rats exposed to sodium nitrite in drinking water at 2 g/L (Taylor and Lijinsky, 1975), 3 g/L (Shuval and Gruener, 1972), or 0.25% (2.5 g/L) (Maekawa *et al.*, 1982) for 2 years did not have increased tumor incidences compared to the controls. Rats given 390 mg/kg sodium nitrite in feed for life (2.5 years) had tumor incidences (incidences not given) similar to those in the controls (cited in Rubenchik *et al.*, 1990); however, liver tumors (incidences 5/19 or 26%) were induced in Wistar rats given 1,600 ppm in pelleted feed (Aoyagi *et al.*, 1980). Mirvish *et al.* (1980) administered 3 g/L in drinking water to Wistar rats for life and reported increased incidences (18% versus 2% in controls) of forestomach squamous papilloma in males and females. Lijinsky (1984a) reported that 2,000 ppm administered in drinking water to F344 rats increased the incidences of liver tumors in females but not males. Newberne (1979) gave Sprague-Dawley rats 250 to 2,000 ppm in an agar diet, 1,000 to 2,000 ppm in a commercial diet, 1,000 ppm in a casein diet, or 1,000 to 2,000 ppm (20-30 mg/day) in drinking water; exposure began during pregnancy and continued for life (up to 26 months) for dams and pups. Incidences of malignant lymphoma were significantly increased in all exposed groups compared to the controls, and immunoblastic cell proliferation was observed in some animals in each exposed group. However, these results were not confirmed by a committee specially formed to review the data (FDA, 1980). In an earlier study, Shank and Newberne (1976) reported that Sprague-Dawley rats fed 1 g sodium nitrite/kg body weight in feed developed a higher incidence (27%) of lymphoreticular tumors than did the controls (6%).

Sodium nitrite may react *in vivo* with secondary amines to form carcinogenic nitrosamines in the stomach. In a number of interaction studies, concurrent administration of sodium nitrite in drinking water and secondary amines in feed induced a variety of tumors in rats and mice. Sodium nitrite was given in water and the amines in feed in order to avoid any chemical reaction before ingestion (Table 2); the studies demonstrated that carcinogenic *N*-nitroso compounds are formed *in vivo* as a result of sodium nitrite reacting with secondary amines. Carcinogenesis studies have also been conducted by exposing animals to sodium nitrite and amines together in feed or in drinking water (Table 3).

Sodium nitrite in drinking water appears to be nontumorigenic in mice. Male and female outbred ICR mice administered 7 mg/kg daily by gavage for 10 weeks and allowed to live without treatment for up to 18 months did not have increased tumor incidences (Yoshida *et al.*, 1993). Inai *et al.* (1979) reported that tumor incidence, latency period, and tumor type were not different between exposed and control groups of male and female ICR mice exposed to 0%, 0.125%, 0.25%, or 0.5% sodium nitrite in drinking water for 109 weeks. Sodium nitrite in drinking water at 1.0 g/L for 20 to 34 weeks did not induce lung tumors in Swiss or A-strain mice (Greenblatt *et al.*, 1971; Greenblatt and Lijinsky, 1972; Greenblatt and Mirvish, 1973). Anderson *et al.* (1985) did not observe increased tumors in female C57BL/6 or $B6C3F_1$ mice at 1.84 g/L in drinking water; however, from conception through gestation, lactation, and life, sodium nitrite at 0.184 g/L (but not at 1.84 g/L) enhanced the incidences of lymphomas and lung tumors in male $B6C3F_1$ mice. Negative findings were reported in male $(C57BL\times C3H)F_1$ mice given a single intragastric dose of 50 mg sodium nitrite/kg body weight at 15 days of age and sacrificed at 70 weeks (Rijhsinghani *et al.,* 1982). Male and female C57BL/6 mice given 0.5% sodium nitrite in feed for 1 year did not exhibit higher tumor incidences than did the controls (Krishna Murthy *et al.*, 1979). No 2-year dosed feed studies in mice have been reported.

Sodium nitrite can also promote carcinogenesis. In drinking water, 5, 50, 500, and 2,000 ppm sodium nitrite accelerated leukemia development induced by the Rauscher, Mazurenko, and Gross leukemia viruses in Balb/c mice (Ilnitsky and Kolpakova, 1997). At 0.3% in drinking water, sodium nitrite promoted forestomach carcinogenesis in male Fisher rats pretreated with *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (Yoshida *et al.*, 1994). In a multi-organ model in

TABLE 2
Neoplasms in Rats and Mice Concurrently Exposed to Sodium Nitrite in Drinking Water and Secondary Amines in Feed

Strain and Species	Amine	Neoplasm Site	Reference
MRC-Wistar rats (males)	Morpholine	Liver	Montesano and Magee, 1971; Mirvish *et al.*, 1983
Wistar rats	Bis(2-hydroxy-propyl)amine	Nasal cavity, esophagus, liver, lung, and urinary bladder	Yamamoto *et al.*, 1989
Swiss mice	Piperazine, morpholine, and *N*-methylaniline	Lung	Greenblatt *et al.*, 1971
	Methylurea and morpholine	Lung	Mirvish *et al.*, 1972, 1975
(C57BL×C3H)F_1 mice	Diethylamine hydrochloride	Liver	Rijhsinghani *et al.*, 1982

TABLE 3
Neoplasms in Rodents Concurrently Exposed to Sodium Nitrite and Secondary Amines in Feed or Drinking Water

Strain and Species	Amine	Neoplasm Site	Reference
Rats (strain not specified)	Aminopyrine, disulfiram, and thiram	Esophagus, tongue, forestomach, nasal cavity, and liver	Lijinsky, 1980, 1984a,b; Lijinsky and Reuber, 1980
	N,N-dimethyl-dodecylamine-N-oxide	Liver (males)	Lijinsky, 1984a
	Methylurea	Neurogenic and lymphoid	Koestner and Denlinger, 1975
F344 rats (males)	Diphenhydramine and chlorpheniramine	Liver	Lijinsky, 1984a
	Allantoin	Forestomach	Lijinsky, 1984a
Sprague-Dawley rats	Heptamethyleneimine	Respiratory and alimentary canal	Taylor and Lijinsky, 1975
Wistar rats	Sarcosine ethyl ester hydrochloride	Esophagus	Xiang *et al.*, 1995
Balb/c mice	Ethambutol	Lung and hematopoietic system	Biancifiori *et al.*, 1975
Strain A mice	Piperazine	Lung	Greenblatt and Mirvish, 1973
B6C3F_1 mice (males)	Cimetidine	Lung and hematopoietic system	Anderson *et al.*, 1985
Syrian golden hamsters	Morpholine	Liver and lung	Shank and Newberne, 1976

which rats were initiated with various carcinogens, 0.3% sodium nitrite in drinking water strongly enhanced the development of forestomach lesions but inhibited the development of glandular stomach lesions when these animals were given catechol or 3-methoxycatechol, with or without prior carcinogen exposure (Hirose *et al*., 1993). In addition, the carcinogenesis-promoting effects of catechol were evident only in combination with sodium nitrite.

Humans

No adequate epidemiology studies of sodium nitrite and human cancer were found in the literature. Rogers *et al.* (1995) reported no associations between nitrite intake and risk of laryngeal or oral cancer. In epidemiological studies, Risch *et al.* (1985) reported a direct association between nitrite intake and stomach cancer risk. La Vecchia *et al.* (1995, 1997) compared subjects with low methionine (<1.5 mg/day) and low nitrite (<2.7 mg/day) intake with subjects with high methionine (>1.9 mg/day) and high nitrite (>2.7 mg/day) intake and reported an association between nitrite intake and stomach cancer risk. Boeing *et al*. (1991) reported a significantly elevated risk for stomach cancer for users of well water compared with those who used central water supplies in Germany. The study did not report measurements of nitrate in the water but assumed that well water contained considerable amounts of nitrate. An increased death rate from gastric cancer among the residents of the English town of Worsop was thought to be related to the high concentration of nitrate (90 mg/L) in the public water supply (Hill *et al.*, 1973). In Columbia, where gastric cancer is common, the high intake of nitrate is reflected in the high urinary excretion rate of nitrate (Tannenbaum *et al.*, 1979). Patients with precancerous gastric lesions had high nitrite concentrations in their gastric juice (Ruddell *et al.*, 1976).

Vermeer *et al.* (1998) demonstrated that nitrate intake resulted in a significant rise in mean salivary nitrate and nitrite concentrations and that *N*-nitrosodimethylamine and *N*-nitrosopiperidine were detected in the urine samples.

GENETIC TOXICITY

Sodium nitrite is a direct-acting, base-pair substitution mutagen in organisms ranging from bacteria to mammals. It also has been shown to induce chromosomal effects in mammalian cells *in vitro* and *in vivo*. In an acidic environment, sodium nitrite reacts with amines to form nitrosamines or with amides to form nitrosamides. These compounds are mutagenic in a variety of systems. Nitrosamines require metabolic activation for expression of mutagenic activity, but nitrosamides do not. Positive results have been reported for sodium nitrite, with and without S9 metabolic activation enzymes, in *Salmonella* gene mutation studies with strains that revert by base-pair substitution (Ehrenberg *et al.*, 1980; Katz *et al.*, 1980; De Flora, 1981; Ishidate *et al.*, 1984; Brams *et al.*, 1987; Zeiger *et al.*, 1992; Balimandawa *et al.*, 1994). Genotoxicity of sodium nitrite is not often detected in strains of *S. typhimurium* that mutate via frameshift mechanisms (Zeiger *et al.*, 1992; Balimandawa *et al.*, 1994). Gene reversion (Kosako and Nishioka, 1982) and DNA damage (De Flora *et al.*, 1984) were also observed in *Escherichia coli* WP tester strains after exposure to sodium nitrite in the presence of S9. Furthermore, sodium nitrite-induced gene mutations were reported in *Saccharomyces cerevisiae* (Lemontt, 1977; Fahrig, 1979), *Candida utilis* (Grimmelikhuijzen and Slater, 1973), and *C. albicans* (Kakar and Magee, 1982).

In cultured mammalian cells, sodium nitrite was reported to induce gene mutations (Tsuda *et al.*, 1973; Kodama *et al.*, 1976), chromosomal aberrations (Kodama *et al.*, 1976; Ishidate and Odashima, 1977; Tsuda and Kato, 1977; Ishidate *et al.*, 1981; Tsuda *et al.*, 1981), and sister chromatid exchanges (SCEs) (Abe and Sasaki, 1977; Tsuda *et al.*, 1981; Inoue *et al.*, 1985); in none of these experiments was S9 required for the positive response. HeLa cells incubated for 1 to 36 hours had increased levels of unscheduled DNA synthesis (DNA repair) at concentrations above 1 mM sodium nitrite (Lynch *et al.*, 1983).

In vivo, increased frequencies of micronuclei and 8-azaguanine- and ouabain-resistant mutations, but not chromosomal aberrations, were seen in cells of Syrian golden hamster embryos 24 hours after oral administration of 125, 250, or 500 mg/kg sodium nitrite to the dams (Inui *et al.*, 1979a). No increases in chromosomal aberrations were noted in lymphocytes of Wistar rats 48 hours after a single gavage treatment of 300 mg/kg sodium nitrite (Lilly *et al.*, 1979). However, positive results were reported for induction of chromosomal aberrations in bone marrow cells of pregnant female albino rats exposed to 210 mg/kg per day in

drinking water for 13 days (El Nahas *et al.*, 1984). In this same study, the liver cells of embryos exposed trans- placentally for the first 13 days of gestation also showed increased numbers of chromosomal aberrations. SCE induction increased with increasing dose in bone marrow cells of Swiss albino mice treated with 2.5 to 200 mg/kg sodium nitrite by intraperitoneal injection (Giri *et al.*, 1986). In addition to the demonstrated genotoxicity of sodium nitrite, concerns about the effects of the compound arise from its ability to transform primary and secondary amines into *N*-nitroso compounds, which are generally mutagenic after S9 activation (Whong *et al.*, 1983). Acid conditions facilitate the reaction of nitrite with amines (Ehrenberg *et al.*, 1980), and this reaction is further catalyzed by alcohols and aldehydes (Ehrenberg *et al.*, 1980; Törnqvist *et al.*, 1983; Valin *et al.*, 1985), ultimately producing the actual nitrosating agent, nitrous anhydride (Brambilla *et al.*, 1983).

There are numerous reports of mutagenic activity detected after combined administration of sodium nitrite with amino compounds. For example, sodium nitrite combined with the dye metanil yellow induced dose-related increases in SCEs in the bone marrow of Swiss mice; the increase was significantly greater than the increase in SCEs induced by sodium nitrite alone (Giri *et al.*, 1986). Amino acid derivatives in food stuffs (Amadori compounds, <1 μM), when reacted with sodium nitrite (>1 mM) under acidic conditions at normal body temperatures (37° C), produced mutagenic nitrosated products and induced high levels of unscheduled DNA synthesis in HeLa cells when present in culture medium for 1 to 36 hours (Lynch *et al.*, 1983).

Transplacental exposure of cells of Syrian golden hamster embryos to a combination of aminopyrine plus sodium nitrite, administered to dams via gavage on days 11 or 12 of gestation, induced a significant increase in 8-azaguanine-resistant mutations compared to either compound administered individually (Inui *et al.*, 1980). In a similar study, transplacental exposure to sodium nitrite plus morpholine, administered simultaneously by gavage to pregnant Syrian golden hamsters on days 11 or 12 of gestation, induced significant increases in 8-azaguanine- and ouabain-resistant mutations, as well as micronuclei, in embryonic fibroblasts (Inui *et al.*, 1979b).

STUDY RATIONALE

Sodium nitrite was nominated by the FDA for toxicity and carcinogenesis studies based on its widespread use in foods and the fact that many nitroso compounds are carcinogenic. Studies were performed to evaluate the toxic and carcinogenic potential of sodium nitrite given to rats and mice in 14-week and 2-year drinking water studies. Tests for mutagenicity in *S. typhimurium* and induction of micronuclei in rat and mouse bone marrow and mouse peripheral blood were employed to characterize the genetic toxicity of sodium nitrite.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF SODIUM NITRITE

Sodium nitrite was obtained from J.T. Baker, Inc. (Phillipsburg, NJ), in two lots (A42340 and H05714). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix J). Reports on analyses performed in support of the sodium nitrite studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a white crystalline solid, was identified as sodium nitrite by infrared and ultraviolet/visible spectroscopy. Purity of both lots was determined by elemental analyses, weight loss on drying, spark source mass spectrometry, and high-performance liquid chromatography (HPLC). The purity of lot A42340 was also analyzed by differential scanning calorimetry, a United States Pharmacopeia (USP) XXI titrimetric assay, and American Chemical Society tests for chloride and sulfate. Elemental analyses for sodium and nitrogen were in agreement with the theoretical values for sodium nitrite. For lot A42340, weight loss on drying indicated 0.006% ± 0.002% water. HPLC of lot A42340 revealed a major peak and a single impurity with an area of 0.2% of the major peak area. HPLC of lot H05714 revealed a major peak and a single impurity with an area of 0.15% of the major peak. The overall purity was determined to be 99% or greater.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using permanganate titration. These studies indicated that sodium nitrite was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at 5° C, protected from light, in closed containers under an inert atmosphere during the 14-week study and in Nalgene® containers at room temperature, protected from light, during the 2-year studies. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared every 2 weeks (14-week studies) or approximately every 4 weeks (2-year studies) by mixing sodium nitrite with water (Table J2). Stability studies of a 0.075 mg/mL dose formulation were performed by the analytical chemistry laboratory using ultraviolet/visible spectrophotometry by measuring absorbance at 347 nm of an aliquot of the sample treated with a salt solution (sodium sulfate and sodium acetate) and a color reagent (hydrochloric acid, resorcinol and zinconyl chloride). Stability was confirmed for at least 35 days for dose formulations stored at 5° C or at room temperature in the dark.

Periodic analyses of the dose formulations of sodium nitrite were conducted by the study laboratory using ultraviolet/visible spectroscopy as described for the stability study. During the 14-week studies, the dose formulations were analyzed at the beginning, midpoint, and end of the studies; animal room samples of these dose formulations were also analyzed (Table J3). During the 2-year studies, the dose formulations were analyzed approximately every 8 to 12 weeks; animal room samples were also analyzed periodically (Table J4). All 32 dose formulations analyzed during the 14-week studies were within 10% of the target concentrations. All 39 dose formulations analyzed during the 2-year studies were within 10% of the target concentrations. Results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table J5).

14-WEEK STUDIES

The 14-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to sodium nitrite and to determine the appropriate doses to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms, Germantown, NY. On receipt, the rats and mice were 5 weeks old. Rats were quarantined for 14 or 15 days and mice for 11 days; animals were 6 (mice) or 7 (rats) weeks old on the first day of the studies. Before initiation of the studies, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female sentinel rats using the protocols of the NTP Sentinel Animal Program (Appendix M).

Groups of 10 male and 10 female rats and mice were exposed to 0, 375, 750, 1,500, 3,000 and 5,000 ppm sodium nitrite in drinking water for 14 weeks. Clinical pathology study groups of 15 male and 15 female rats were given the same exposure concentrations for 70 to 71 days. Feed and water were available *ad libitum*. Rats were housed five per cage, and mice were housed individually. Feed consumption was measured weekly, and water consumption was recorded daily by cage. Animal room feed samples were monitored for total nitrosamine content (rats: 3.8 to 6.1 ppb; mice: 3.6 to 13.4 ppb). Core study animals were weighed and clinical findings were recorded initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 4.

Blood was collected from the retroorbital sinus of up to 10 clinical pathology study rats on days 5 and 19 and from all core study rats at the end of the study for hematology and clinical chemistry analyses. Blood samples for hematology analyses were placed in tubes containing potassium EDTA or acid-citrate-dextrose as the anticoagulant. All automated hematology measurements were performed on a Serono-Baker 9000 automated cell counter using reagents supplied by the manufacturer (Serono-Baker Diagnostics, Allentown, PA). Leukocyte differentials were counted on slides stained with a modified Wright's stain using an Ames Hema-Tek II slide stainer (Miles Laboratory, Ames Division, Elkhart, IN). Smears made from preparations of equal volumes of new methylene blue and whole blood and incubated for at least 20 minutes at room temperature were examined microscopically for the quantitative determination of reticulocytes and Heinz bodies. Methemoglobin assays were performed using an Instrumentation Laboratory CO-Oximeter 282 with reagents from the manufacturer (Instrumentation Laboratory, Inc., Lexington, MA). Blood for clinical chemistry determinations was placed into tubes and allowed to clot. All clinical chemistry analyses were performed with a Serono-Baker Centrifichem 600 Analyzer and System 400 pipette. Reagents for bile acids were obtained from Nyconed Diagnostics (Oslo, Norway), and reagents for sorbitol dehydrogenase were obtained from Sigma Diagnostics (St. Louis, MO). Determination of erythrocyte glutathione concentration was performed using a spectrophotometric assay on whole, acid-citrate-dextrose-anticoagulated blood (Fairbanks and Klee, 1987). The hematology parameters measured and the clinical chemistry assays performed are listed in Table 4.

On day 70 (2000 or 2200 hours) or 71 (0900 hours), two blood samples each were collected from up to five male and five female clinical pathology study rats at three time points. Samples for methemoglobin analyses were collected from the retroorbital sinus under CO_2 anesthesia and placed in tubes containing potassium EDTA. Samples for nitrosamine analyses were collected from the abdominal aorta and placed in tubes containing acid-citrate-dextrose. Using vacutainers with no rubber parts, the samples for nitrosamine analyses were transferred to glass culture tubes with Teflon®-lined caps (Baxter Healthcare Corp., McGraw Park, IL) containing 0.3 g sulfamic acid (J.T. Baker Chemical Co., Phillipsburg, NJ) and frozen until analysis. After blood samples were obtained from special study animals on day 70 or 71, the stomachs were removed; stomach contents were extruded through an anterior incision into wide-mouth borosilicate glass vials with Teflon®-lined caps, washed with 10 mL of saline, and frozen with 0.3 g sulfamic acid until analysis for gastric nitrosamines. Serum and stomach nitrosamine concentrations were determined using the Thermal Energy Analyzer at Thermedics, Inc., (Woburn, MA), as described by Fine and Rounbehler (1975).

At the end of the 14-week studies, samples were collected for sperm motility and vaginal cytology evaluations on male rats and male and female mice exposed to 0, 375, 1,500 or 5,000 ppm and female rats

exposed to 0, 375, 750, or 3,000 ppm. The parameters evaluated are listed in Table 4. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1987). For 12 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm morphology, count, and motility. The left testis and epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer.

Necropsies were performed on all core study animals at the end of the studies. The heart, right kidney, liver, lung, spleen, right testis and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 6 µm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on core study animals in the control and 5,000 ppm groups. The forestomach of rats and mice, testis of male mice, and spleen of female mice were examined to a no-effect level. Table 4 lists the tissues and organs routinely examined.

2-YEAR STUDIES

Study Design

Groups of 50 male and 50 female rats and mice were given 0, 750, 1,500 or 3,000 ppm sodium nitrite in drinking water for 105 weeks (rats) or 104 to 105 weeks (mice). Groups of 10 male and 10 female special study rats and mice were exposed to the same concentrations for 12 months for toxicokinetic studies (plasma nitrite and blood methemoglobin concentrations) and then discarded. Additional groups of 15 male and 15 female sentinel rats and mice were given a single gavage dose of sodium nitrite (40 mg/kg for rats and 62.5 mg/kg for mice) for toxicokinetic studies at 18 months.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services, Germantown, NY, for use in the 2-year studies. Rats were quarantined for 11 or 12 days and mice for 13 or 14 days before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix M).

Animal Maintenance

Male rats were housed two or three per cage and females three or five per cage; male mice were housed individually and females three or five per cage. Water and feed were available *ad libitum*. Water consumption was measured over a 1-week period at 4-week intervals, beginning during the first week of the study. Cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 4. Information on feed composition and contaminants is provided in Appendix L.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded on days 8 and 36, at 4-week intervals thereafter, and at necropsy for core study animals. Body weights were recorded at the beginning of the study, on days 8 and 36, at 4-week intervals thereafter, and at necropsy for core study animals. Special study rats were weighed at 2 weeks and 3 months, special study mice at 12 months, and aged sentinel rats and mice prior to gavage dosing at 18 months. Blood was taken from the retroorbital sinus of special study rats at 2 weeks and 3 months, from special study mice at 12 months, and from aged sentinel rats and mice at 18 months. Blood was placed in tubes and mixed with potassium EDTA. Samples for plasma nitrite determinations were separated by centrifugation and nitrite concentrations were determined by ultraviolet spectroscopy. Whole blood samples were analyzed for methemoglobin using

Instrumentation Laboratory CO-Oximeter 282 with reagents from the manufacturer. The sample times and the parameters measured are listed in Table 4.

Necropsies were performed on core study animals and five male and five female aged sentinel rats and mice. Microscopic examinations were performed on all core study animals. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 4.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated.

For the 2-year studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the adrenal gland, clitoral gland, rectum, kidney (males), liver, lung, mammary gland, pancreas (males), pituitary gland, spleen, skin, stomach (forestomach and glandular), testis (and epididymis and seminal vesicle), and thyroid gland of rats and the adrenal gland, small intestine (males), kidney (males), liver, lung, mesentery (females), skin, spleen, and stomach [forestomach and glandular (males)] of mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al*. (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al*. (1986).

TABLE 4
Experimental Design and Materials and Methods in the Drinking Water Studies of Sodium Nitrite

14-Week Studies	2-Year Studies
Study Laboratory	
Microbiological Associates, Inc. (Bethesda, MD)	Battelle Columbus Laboratories (Columbus, OH)
Strain and Species	
Rats: F344/N Mice: B6C3F$_1$	Rats: F344/N Mice: B6C3F$_1$
Animal Source	
Taconic Farms (Gemantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)
Time Held Before Studies	
Rats: 14 days (males) or 15 days (females) Mice: 11 days	Rats: 11 days (males) or 12 days (females) Mice: 13 days (males) or 14 days (females)
Average Age When Studies Began	
Rats: 7 weeks Mice: 6 weeks	6 weeks
Date of First Exposure	
Rats: 10 August 1989 (males) and 11 August 1989 (females) Mice: 7 August 1989	Rats: 14 August 1995 (males) and 15 August 1995 (females) Mice: 2 August 1995 (males) and 3 August 1995 (females)
Duration of Exposure	
14 weeks	Rats: 105 weeks Mice: 104 to 105 weeks
Date of Last Exposure	
Rats: 9 November 1989 (males) and 10 November 1989 (females) Mice: 6 November 1989 (males) and 7 November 1989 (females)	Rats: 11-13 August 1997 (males) and 13-15 August 1997 (females) Mice: 28-30 July 1997 (males) and 30-31 July 1997 and 1 August 1997 (females)
Necropsy Dates	
Rats: 9 November 1989 (males) and 10 November 1989 (females) Mice: 6 November 1989 (males) and 7 November 1989 (females)	Rats: 11-13 August 1997 (males) and 13-15 August 1997 (females) Mice: 28-30 July 1997 (males) and 30-31 July 1997 and 1 August 1997 (females)
Average Age at Necropsy	
Rats: 20 weeks Mice: 19 weeks (males) and 20 weeks (females)	110 weeks
Size of Study Groups	
Rats: core study, 10 males and 10 females; clinical pathology study, 15 males and 15 females Mice: 10 males and 10 females	Core study: 50 males and 50 females; special study, 10 males and 10 females; aged sentinel animal study, 15 males and 15 females
Method of Distribution	
Animals were distributed randomly into groups of approximately equal initial mean body weights	Animals were distributed randomly into groups of approximately equal initial mean body weights
Animals per Cage	
Rats: 5 Mice: 1	Rats: core study, 2 or 3 (males) or 5 (females); special study, 2 or 3 (males) or 5 (females); aged sentinel animal study, 3 Mice: core and special studies, 1 (male) or 5 (females); aged sentinel animal study, 1 (male) or 3 (females)

TABLE 4
Experimental Design and Materials and Methods in the Drinking Water Studies of Sodium Nitrite

14-Week Studies	2-Year Studies
Method of Animal Identification Tail tattoo	Tail tattoo
Diet NIH-07 open formula powdered diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, changed weekly	Rats: NTP-2000 pelleted diet, irradiated beginning 22 July 1996, changed weekly Mice: NTP-2000 pelleted diet, irradiated beginning 16 July 1996, changed weekly (males), or twice weekly (females)
Water Charcoal-filtered deionized water via amber glass bottles with stainless steel sipper tubes, available *ad libitum* and changed twice weekly	Tap water (Columbus, OH, municipal supply) via amber glass bottles with stainless steel sipper tubes, available *ad libitum* and changed twice weekly (rats and female mice) or weekly (male mice)
Cages Solid-bottom polycarbonate (Lab Products, Inc., Rochelle Park, NJ), changed twice weekly (rats) or weekly (mice); rotated every 2 weeks	Solid-bottom polycarbonate (Lab Products, Inc., Maywood, NJ), changed twice weekly (rats and female mice) or weekly (male mice); rotated every 2 weeks
Bedding Sani-Chips® (P.J. Murphy Forest Products Corp., Montville, NJ), changed twice weekly (rats) or once weekly (mice)	Sani-Chips® (P.J. Murphy Forest Products Corp., Montville, NJ), changed twice weekly (rats and female mice) or once weekly (male mice)
Cage Filters DuPont 2024 spun-bonded polyester filter (Snow Filtration Co., Cincinnati, OH), changed every 2 weeks.	DuPont 2024 spun-bonded polyester filter (Snow Filtration Co., Cincinnati, OH), changed twice weekly (rats and female mice) or weekly (male mice)
Racks Stainless steel (Lab Products, Inc., Rochelle Park, NJ), rotated and changed every 2 weeks	Stainless steel, drawer-type (Lab Products, Inc., Maywood, NJ), rotated every 2 weeks
Animal Room Environment Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: ≥10/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: ≥10/hour
Exposure Concentrations 0, 375, 750, 1,500, 3,000, or 5,000 ppm in drinking water, available *ad libitum*	0, 750, 1,500, or 3,000 ppm in drinking water, available *ad libitum*
Type and Frequency of Observation Rats and mice were observed twice daily. Core study animals were weighed and clinical findings were recorded initially, weekly, and at the end of the studies. Drinking water consumption was measured daily.	All rats and mice were observed twice daily. Core study animals were weighed initially and clinical findings and body weights were recorded on day 8, day 36, at 4-week intervals thereafter, and at necropsy. Special study rats were weighed at 2 weeks and 3 months, special study mice were weighed at 12 months, and aged sentinel animal rats and mice were weighed at 18 months. Drinking water consumption by the core study animals was measured over a 1-week period at 4-week intervals, beginning during the first week of the study.

TABLE 4
Experimental Design and Materials and Methods in the Drinking Water Studies of Sodium Nitrite

14-Week Studies	2-Year Studies
Method of Sacrifice CO_2 asphyxiation	CO_2 asphyxiation
Necropsy Necropsy was performed on all core study rats and mice. Organs weighed were heart, right kidney, liver, lung, spleen, right testis, and thymus.	Necropsy was performed on all core study rats and mice and five male and five female aged sentinel rats and mice.
Clinical Pathology Blood for hematology and clinical chemistry was collected from the retroorbital sinus of anesthetized clinical pathology study rats on days 5 and 19 and from core study rats at the end of the study. Two blood samples each were collected from the abdominal aorta of 15 male and 15 female clinical pathology study rats on day 70 (2000 or 2200 hours) or 71 (0900 hours) for hemoglobin, methemoglobin and nitrosamine concentrations; stomach contents were also collected for nitrosamine concentrations. Blood and stomach contents were collected from five males and five females at each time point. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; leukocyte count and differentials; erythrocyte and platelet morphologic assessments; methemoglobin concentration; reduced glutathione concentration in erythrocytes; and Heinz body count. ***Clinical chemistry:*** urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, and bile acids ***Nitrosamine concentrations:*** serum and gastric nitrosamine	None
Histopathology Complete histopathology was performed on 0 and 5,000 ppm core study animals. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone and marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland (except male mice), muscle, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, skin, stomach (forestomach and glandular), testis (and epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus. The forestomach of 750 (males), 1,500, and 3,000 ppm rats and the forestomach, testis, and spleen of all remaining mice were also examined.	Complete histopathology was performed on all core study animals. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone and marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland (except male mice), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, skin, stomach (forestomach and glandular), testis (and epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus.

TABLE 4
Experimental Design and Materials and Methods in the Drinking Water Studies of Sodium Nitrite

14-Week Studies	2-Year Studies
Sperm Motility and Vaginal Cytology At the end of the studies, samples were collected for sperm motility or vaginal cytology evaluations from male rats and male and female mice in the 0, 375, 1,500, and 5,000 ppm groups and female rats in the 0, 375, 750, and 3,000 ppm groups. The left cauda, epididymis, and testis were weighed. The following parameters were evaluated: spermatid heads per gram testis, spermatid heads per testis, spermatid count, motility, and concentration. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies for vaginal cytology evaluations. The length of the estrous cycle and the length of time spent in each stage of the cycle were evaluated.	None
Plasma Nitrite and Blood Methemoglobin Concentrations None	Blood was collected from the retroorbital sinus of 10 male and 10 female special study rats at 2 weeks and 3 months and from 10 male and 10 female mice at 12 months. Blood was collected from two animals per group per time point (0600, 1200, 2100, 2400, and 0300 hours). Blood was collected from the retroorbital sinus of 15 male and 15 female aged sentinel rats and mice after a single gavage dose of 40 mg/kg (rats) or 62.5 mg/kg (mice) at 18 months. Two or three animals were sampled at each time point (2, 5, 10, 30, or 60 minutes after dosing). Plasma nitrite and blood methemoglobin concentrations were determined.

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. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, B5, C1, C4, D1, and D5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animalswith that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the

fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

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

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

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. Values of P greater than 0.5 are presented as 1−P with the letter N added to indicate a lower incidence or negative trend in neoplasm occurrence relative to the control group (e.g., P=0.99 is presented as P=0.01N).

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which historically have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Clinical pathology, blood and plasma concentration, toxicokinetic, spermatid, and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across the exposure concentrations.

Historical Control Data

The concurrent control group represents the most valid comparison to the treated groups and is the only control group analyzed statistically in NTP bioassays. However, historical control data are often helpful in interpreting potential treatment-related effects, particularly for uncommon or rare neoplasm types. For

meaningful comparisons, the conditions for studies in the historical database must be generally similar. Until recently, the NTP historical control database consisted of animals fed NIH-07 diet. In 1995, the NTP changed the diet fed to animals used in toxicity and carcinogenesis studies conducted by the NTP. This new diet (NTP-2000) contains less protein and more fiber and fat than the NIH-07 diet previously used (Rao, 1996, 1997). This dietary change was instituted primarily to increase longevity and decrease the incidence and/or severity of some spontaneous neoplasms and nonneoplastic lesions in the rats and mice used in NTP studies. This study of sodium nitrite is one of the first in which the animals on study were fed the NTP-2000 diet. Because the incidence of some neoplastic and nonneoplastic lesions are affected by the dietary change, use of the existing historical control database (NIH-07) diet is not appropriate for all neoplasm types.

Currently, the number of studies in which the NTP-2000 diet was used is limited. This diet was used in four studies (indium phosphide, sodium nitrite, *p,p′*-dichlorodiphenyl sulfone, and naphthalene) reported at the May 18, 2000, peer review and in two others (methacrylonitrile and *p*-nitrotoluene) not yet reported. Therefore, a database of incidences of neoplastic lesions was created for this group of six studies. Four routes of administration were used in these six studies: *p*-nitrotoluene and *p,p′*-dichlorodiphenyl sulfone were administered by dosed feed; sodium nitrite was administered in the drinking water; methacrylonitrile was administered by gavage using deionized water; and naphthalene and indium phosphide were administered via whole body inhalation. Based on the extensive NTP historical database using the NIH-07 diet, incidences of the vast majority of spontaneous neoplasms are not significantly different between control groups irrespective of the route of administration. There is no reason to expect this to be different with the NTP-2000 diet. Clearly, control animals from dosed feed and dosed water studies are treated no differently and no differences in incidence of neoplasms are expected. There are some exceptions, and if comparisons are necessary for these neoplasm types, only studies with similar routes of administration will be used.

The set of six studies using the NTP-2000 diet will be the primary historical control group used for comparison. However, where appropriate, the larger historical database (NIH-07 diet) may be used to augment the smaller NTP-2000 database.

QUALITY ASSURANCE METHODS

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

GENETIC TOXICOLOGY

The genetic toxicity of sodium nitrite was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and micronucleated erythrocytes in rat and mouse bone marrow and mouse peripheral blood. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of sodium nitrite are part of a larger effort by the NTP to develop a comprehensive database that would permit a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). These short-term genetic toxicity tests were originally developed to clarify mechanisms of chemical-induced DNA damage growing out of the earlier electrophilicity/mutagenicity relationship proposed by Miller and Miller (1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). Therefore, the information obtained from these tests applies only to mutagenic carcinogens.

For mutagenic carcinogens, the combination of DNA reactivity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in multiple species and genders of rodents and at multiple tissue sites (Ashby and Tennant, 1991). Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) and that there is no

complementarity among the *in vitro* genetic toxicity tests (Tennant *et al*., 1987; Zeiger *et al*., 1990). That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. Although other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity compared with the *Salmonella* test, these other tests can provide useful information on the types of DNA and chromosomal effects induced by the chemical under investigation.

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

RESULTS

RATS

14-WEEK STUDY

Except for one female exposed to 3,000 ppm sodium nitrite, all rats survived until the end of the study (Table 5). Final mean body weights and body weight gains of males exposed to 3,000 or 5,000 ppm and females exposed to 5,000 ppm were significantly less than those of the controls. Water consumption by the 5,000 ppm male group and the 3,000 and 5,000 ppm female groups was less than that by the controls at weeks 2 and 14. Drinking water concentrations of 375, 750, 1,500, 3,000, or 5,000 ppm sodium nitrite resulted in average daily doses of approximately 30, 55, 115, 200, or 310 mg sodium nitrite/kg body weight to males and 40, 80, 130, 225, or 345 mg/kg to females. Clinical findings related to sodium nitrite exposure included brown discoloration in the eyes and cyanosis of the mouth, tongue, ears, and feet of males exposed to 3,000 or 5,000 ppm and of females exposed to 1,500 ppm or greater. Males in the 5,000 ppm group were hypoactive, and a few females exposed to 375 ppm or greater developed alopecia.

TABLE 5
Survival, Body Weights, and Water Consumption of Rats in the 14-Week Drinking Water Study of Sodium Nitrite

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Water Consumption[c]	
		Initial	Final	Change		Week 2	Week 14
Male							
0	10/10	153 ± 5	366 ± 4	213 ± 4		23.3	16.8
375	10/10	155 ± 4	347 ± 6	192 ± 5	95	18.6	18.6
750	10/10	155 ± 4	351 ± 8	196 ± 7	96	21.7	19.2
1,500	10/10	150 ± 4	360 ± 4	211 ± 3	98	24.5	17.0
3,000	10/10	160 ± 5	344 ± 6*	184 ± 4**	94	19.5	16.6
5,000	10/10	150 ± 3	310 ± 8**	160 ± 8**	85	13.1	14.4
Female							
0	10/10	128 ± 4	202 ± 4	75 ± 2		18.9	14.7
375	10/10	127 ± 4	207 ± 3	80 ± 3	102	22.0	14.4
750	10/10	125 ± 4	198 ± 3	73 ± 4	98	18.6	15.5
1,500	10/10	130 ± 3	206 ± 3	76 ± 4	102	17.2	14.1
3,000	9/10[d]	133 ± 4	195 ± 3	63 ± 5*	96	14.5	9.3
5,000	10/10	135 ± 4	191 ± 3*	56 ± 3**	94	11.0	8.7

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 14 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 study.
[c] Water consumption is expressed as grams per animal per day.
[d] Week of death: 4

The hematology and clinical chemistry data for rats are presented in Tables 6 and F1. In general, methemoglobin concentrations were increased in all exposed groups of male and female rats throughout the study. Increases in the numbers of erythrocytes containing Heinz bodies, another marker of oxidative red cell injury, occurred on day 5 in the 5,000 ppm male and female groups; this alteration was transient and numbers returned to control levels by day 19. Alterations in other variables evaluating the red cell mass occurred at all time points. On day 5, an increase in erythropoietic activity was evidenced by increased reticulocyte counts in the 3,000 and 5,000 ppm males and females. Reticulocyte count increases continued on day 19 and were accompanied by increases in nucleated erythrocyte counts in 3,000 and 5,000 ppm males and 5,000 ppm females. Also, on day 19, there was an apparent decrease in the erythron, evidenced by decreases in the hemoglobin concentration in the 5,000 ppm males and females; the hematocrit values for these animals were also consistent with, but not statistically significant for, a decrease in the erythron. However, the erythrocyte counts did not support a decreased erythron and were in fact increased for the 3,000 and 5,000 ppm rats on day 19. There were decreases in the mean cell volumes for 5,000 ppm males and females on day 19, suggesting the presence of smaller erythrocytes in the circulation. The mean cell hemoglobin values in these rats were decreased at this time point and would be consistent with the decreased mean cell volume. Also, on day 19, the mean cell hemoglobin concentrations were decreased in 3,000 and 5,000 ppm males and females. The apparent decrease in the erythron was transient and, by week 14, was replaced by an increased erythron, evidenced by increased hemoglobin concentrations (3,000 and 5,000 ppm males and females), hematocrit values (3,000 ppm females and 5,000 ppm males and females) and erythrocyte counts (5,000 ppm females). Reticulocyte counts were still increased in 3,000 and 5,000 ppm males and 5,000 ppm females at week 14, but the magnitude of the increase in nucleated erythrocyte counts had lessened. The decreases in mean cell volumes, mean cell hemoglobin values, and mean cell hemoglobin concentrations on day 19 disappeared and, by study termination, mean cell volumes and mean cell hemoglobin values were increased in 3,000 ppm males and females and 5,000 ppm females.

Platelet counts were increased on day 5 in 3,000 ppm females and 5,000 ppm males and females and on day 19 in 5,000 ppm males and females but fell to control levels by week 14.

Increases in urea nitrogen concentrations occurred on day 19 in 5,000 ppm males and females and at week 14 in all exposed groups of males and 1,500 ppm or greater females. Creatinine concentrations, another marker of renal function, were increased on day 5 in 3,000 and 5,000 ppm females and on day 19 in females exposed to 1,500 ppm or greater but had returned to control levels by week 14; male rats were not affected. On day 5, there was a decrease in the serum activity of alkaline phosphatase in various male and female exposed groups; this effect disappeared with time in most groups.

N-Nitrosodimethylamine and *N*-nitrosopyrrolidine were not detected in the blood of male or female exposed groups (levels of detection were less than 2.0 ppb for the highest level of sensitivity). Total nitrosamine concentrations in the blood of exposed males and females at different time points (9 a.m., 8 p.m., and 10 p.m.) were not significantly different from control values (Table F2). *N*-Nitrosodimethylamine and *N*-nitrosopyrrolidine were not detected in the stomach contents of exposed males or females.

TABLE 6
Selected Hematology and Clinical Chemistry Data for Rats in the 14-Week Drinking Water Study of Sodium Nitrite[a]

	0 ppm	375 ppm	750 ppm	1,500 ppm	3,000 ppm	5,000 ppm
Male						
Hematology						
n						
Day 5	9	6	10	7	8	9
Day 19	10	10	9	10	10	9
Week 14	10	10	10	9	10	10
Hematocrit (%)						
Day 5	41.6 ± 0.5[b]	41.1 ± 0.6[c]	39.2 ± 0.6*	40.0 ± 0.4[d]	41.0 ± 0.7[b]	39.5 ± 0.6[b]
Day 19	43.5 ± 0.2	43.9 ± 0.4	44.3 ± 0.4[b]	42.8 ± 1.0	46.3 ± 1.1	37.7 ± 1.3[b]
Week 14	43.8 ± 0.6	44.1 ± 0.5	42.0 ± 0.6	42.2 ± 0.6	45.5 ± 0.5	46.5 ± 0.7*
Hemoglobin (g/dL)						
Day 5	14.5 ± 0.2[b]	14.2 ± 0.2[c]	13.6 ± 0.2*	13.8 ± 0.1[d]	14.2 ± 0.2[b]	13.8 ± 0.2[b]
Day 19	14.9 ± 0.1	15.0 ± 0.1	15.1 ± 0.1[b]	14.7 ± 0.3	15.3 ± 0.3	12.5 ± 0.4**[b]
Week 14	15.0 ± 0.2	15.2 ± 0.1	14.7 ± 0.2	14.7 ± 0.2	15.7 ± 0.1*	16.0 ± 0.3**
Erythrocytes (10^6/µL)						
Day 5	7.08 ± 0.08[b]	6.95 ± 0.13[c]	6.90 ± 0.10	6.79 ± 0.08[d]	6.94 ± 0.13[b]	6.89 ± 0.12[b]
Day 19	7.61 ± 0.05	7.65 ± 0.10	7.90 ± 0.08*[b]	7.54 ± 0.17	8.44 ± 0.15**	8.10 ± 0.21**[b]
Week 14	8.30 ± 0.12	8.39 ± 0.08	7.97 ± 0.13	7.91 ± 0.10	8.29 ± 0.08	8.92 ± 0.25
Reticulocytes (10^6/µL)						
Day 5	0.45 ± 0.03	0.47 ± 0.05	0.72 ± 0.05**	0.51 ± 0.05	0.67 ± 0.06**	0.69 ± 0.03**[d]
Day 19	0.21 ± 0.02	0.19 ± 0.01	0.21 ± 0.02	0.23 ± 0.03	0.37 ± 0.02**	0.58 ± 0.05**
Week 14	0.22 ± 0.02	0.22 ± 0.03	0.26 ± 0.02	0.18 ± 0.02	0.30 ± 0.03*	0.37 ± 0.04**
Nucleated erythrocytes (10^3/µL)						
Day 5	1.00 ± 0.33	3.00 ± 0.45	2.80 ± 0.65	1.57 ± 0.69	2.75 ± 1.03	2.78 ± 0.49
Day 19	0.60 ± 0.22	0.90 ± 0.23	0.89 ± 0.35	1.20 ± 0.44	2.70 ± 0.52**	5.33 ± 1.12**
Week 14	0.70 ± 0.30	0.70 ± 0.21	0.60 ± 0.27	0.89 ± 0.20	1.10 ± 0.41	1.70 ± 0.50
Mean cell volume (fL)						
Day 5	58.8 ± 0.3[b]	59.2 ± 0.3[c]	56.9 ± 0.2**	59.0 ± 0.4[d]	59.1 ± 0.4[b]	57.4 ± 0.3[b]
Day 19	57.1 ± 0.4	57.4 ± 0.5	56.2 ± 0.5[b]	56.9 ± 0.5	54.9 ± 0.9	46.4 ± 0.5**[b]
Week 14	52.8 ± 0.2	52.5 ± 0.2	52.8 ± 0.1	53.3 ± 0.3	55.0 ± 0.2**	52.4 ± 1.2**
Mean cell hemoglobin (pg)						
Day 5	20.4 ± 0.1[b]	20.5 ± 0.1[c]	19.8 ± 0.1*	20.3 ± 0.1[d]	20.5 ± 0.2[b]	20.0 ± 0.1[b]
Day 19	19.6 ± 0.1	19.6 ± 0.2	19.1 ± 0.2*[b]	19.6 ± 0.2	18.1 ± 0.3**	15.4 ± 0.2**
Week 14	18.1 ± 0.1	18.1 ± 0.1	18.5 ± 0.1*	18.5 ± 0.1*	18.9 ± 0.1**	18.1 ± 0.5**
Mean cell hemoglobin concentration (g/dL)						
Day 5	34.7 ± 0.2[b]	34.6 ± 0.1[c]	34.7 ± 0.1	34.5 ± 0.2[d]	34.7 ± 0.2[b]	34.9 ± 0.2[b]
Day 19	34.3 ± 0.2	34.1 ± 0.2	34.0 ± 0.2[b]	34.4 ± 0.3	33.0 ± 0.2**	33.1 ± 0.3**[b]
Week 14	34.4 ± 0.2	34.4 ± 0.2	35.1 ± 0.2	34.8 ± 0.1	34.5 ± 0.1	34.4 ± 0.3
Platelets (10^3/µL)						
Day 5	999.9 ± 23.9[b]	1,028.6 ± 43.3[c]	1,140.8 ± 31.1*	966.3 ± 51.6[d]	1,008.7 ± 23.2[b]	1,166.4 ± 42.0*[b]
Day 19	763.6 ± 17.9	753.9 ± 24.5	827.4 ± 23.7[b]	777.3 ± 45.5	759.1 ± 30.6	1,815.2 ± 129.0**[b]
Week 14	577.7 ± 21.4	608.0 ± 13.0	597.9 ± 15.1	588.3 ± 18.3	606.1 ± 16.3	673.4 ± 56.4
Methemoglobin (g/dL)						
Day 5	0.03 ± 0.02	0.04 ± 0.02	4.36 ± 0.78**[c]	0.08 ± 0.03**	1.37 ± 0.41**[e]	3.97 ± 0.75**
Day 19	0.09 ± 0.05	0.06 ± 0.02	0.28 ± 0.12*	0.38 ± 0.12**	1.25 ± 0.37**	3.26 ± 0.36**
Week 14	0.03 ± 0.01	0.08 ± 0.01**	0.12 ± 0.02**	0.25 ± 0.07**	0.71 ± 0.20**	3.38 ± 0.80**
Heinz bodies (10^6/µL)[f]						
Day 5	0.002 ± 0.001	0.005 ± 0.001	0.009 ± 0.002*	0.010 ± 0.004	0.007 ± 0.002	0.013 ± 0.004**[d]
Day 19	0.004 ± 0.002	0.004 ± 0.002	0.003 ± 0.001	0.004 ± 0.002	0.006 ± 0.002	0.006 ± 0.002
Week 14	0.170 ± 0.114	0.170 ± 0.114	0.470 ± 0.128	0.267 ± 0.133	0.240 ± 0.122	0.350 ± 0.144

TABLE 6
Selected Hematology and Clinical Chemistry Data for Rats in the 14-Week Drinking Water Study of Sodium Nitrite

	0 ppm	375 ppm	750 ppm	1,500 ppm	3,000 ppm	5,000 ppm
Male (continued)						
Clinical Chemistry						
n						
Day 5	10	10	10	9	10	10
Day 19	10	10	10	9	10	10
Week 14	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 5	20.4 ± 0.5	18.3 ± 0.7	21.7 ± 0.5	19.7 ± 1.0	19.9 ± 0.6	21.3 ± 0.6
Day 19	21.0 ± 0.7	21.4 ± 0.4	20.8 ± 0.5	22.3 ± 0.5	22.0 ± 0.3	24.9 ± 0.7**
Week 14	17.8 ± 0.5	20.5 ± 0.9*	21.2 ± 0.7**	20.4 ± 0.8*	22.3 ± 1.4**	22.0 ± 0.8**
Alkaline phosphatase (IU/L)						
Day 5	570 ± 12	586 ± 14	445 ± 8**	544 ± 11*	504 ± 8**	441 ± 5**
Day 19	448 ± 8	455 ± 8	450 ± 8	423 ± 13[b]	402 ± 6**	333 ± 11**
Week 14	216 ± 6	233 ± 9	231 ± 9	209 ± 6	213 ± 6	210 ± 7
Female						
Hematology						
n						
Day 5	9	8	9	9	8	9
Day 19	10	10	10	10	10	10
Week 14	10	10	10	10	9	10
Hematocrit (%)						
Day 5	45.6 ± 1.4	44.3 ± 1.2	46.0 ± 0.9[b]	46.0 ± 0.7	45.1 ± 1.0[c]	44.8 ± 0.6
Day 19	46.8 ± 0.5	46.0 ± 0.6	45.2 ± 0.5	46.6 ± 0.8	48.5 ± 1.3	42.7 ± 1.8
Week 14	43.8 ± 0.4	43.5 ± 0.4	42.1 ± 0.4	43.0 ± 0.4	47.1 ± 0.4**	51.3 ± 0.6**
Hemoglobin (g/dL)						
Day 5	15.3 ± 0.4	14.8 ± 0.3	15.4 ± 0.2[b]	15.4 ± 0.2	15.3 ± 0.2[c]	15.2 ± 0.1
Day 19	15.7 ± 0.1	15.3 ± 0.1	15.2 ± 0.2	15.6 ± 0.2	15.9 ± 0.4	13.9 ± 0.6*
Week 14	15.2 ± 0.1	15.0 ± 0.1	14.7 ± 0.1	15.0 ± 0.1	16.2 ± 0.1**	17.5 ± 0.1**
Erythrocytes (10^6/µL)						
Day 5	7.62 ± 0.26	7.27 ± 0.21	7.64 ± 0.13[b]	7.56 ± 0.13	7.44 ± 0.20[c]	7.49 ± 0.09
Day 19	7.87 ± 0.12	7.72 ± 0.13	7.54 ± 0.08	7.83 ± 0.17	8.36 ± 0.11*	8.71 ± 0.20**
Week 14	7.64 ± 0.07	7.61 ± 0.05	7.31 ± 0.06	7.35 ± 0.07	7.74 ± 0.05	8.49 ± 0.15**
Reticulocytes (10^6/µL)						
Day 5	0.29 ± 0.03	0.34 ± 0.02	0.36 ± 0.03	0.44 ± 0.05*	0.63 ± 0.03**	0.73 ± 0.07**
Day 19	0.14 ± 0.01	0.17 ± 0.01*	0.14 ± 0.01	0.20 ± 0.02**	0.41 ± 0.05**	0.65 ± 0.07**
Week 14	0.21 ± 0.02	0.15 ± 0.02	0.18 ± 0.02	0.23 ± 0.03	0.28 ± 0.03	0.40 ± 0.03**
Nucleated erythrocytes (10^3/µL)						
Day 5	1.80 ± 0.44[b]	1.13 ± 0.35	1.44 ± 0.48	1.56 ± 0.53	2.40 ± 0.43[b]	2.22 ± 0.36
Day 19	0.60 ± 0.22	0.40 ± 0.16	0.90 ± 0.48	1.10 ± 0.38	0.60 ± 0.27	3.00 ± 0.78*
Week 14	1.00 ± 0.30	0.60 ± 0.22	0.80 ± 0.25	1.60 ± 0.34	1.00 ± 0.37	1.70 ± 0.42
Mean cell volume (fL)						
Day 5	59.9 ± 0.4	60.9 ± 0.3	60.3 ± 0.4[b]	60.8 ± 0.3	60.7 ± 0.5[c]	59.8 ± 0.3
Day 19	59.5 ± 0.5	59.6 ± 0.6	60.0 ± 0.4	59.5 ± 0.5	58.0 ± 1.0	48.9 ± 1.0**
Week 14	57.2 ± 0.1	57.2 ± 0.3	57.6 ± 0.2	58.6 ± 0.2**	60.8 ± 0.2**	60.5 ± 0.7**
Mean cell hemoglobin (pg)						
Day 5	20.1 ± 0.2	20.3 ± 0.2	20.1 ± 0.2[b]	20.3 ± 0.1	20.7 ± 0.3[c]	20.3 ± 0.1
Day 19	19.9 ± 0.2	19.9 ± 0.2	20.1 ± 0.1	19.9 ± 0.3	19.0 ± 0.4	15.8 ± 0.3**
Week 14	19.9 ± 0.1	19.7 ± 0.1	20.1 ± 0.1	20.5 ± 0.1**	20.9 ± 0.1**	20.7 ± 0.3**

TABLE 6
Selected Hematology and Clinical Chemistry Data for Rats in the 14-Week Drinking Water Study of Sodium Nitrite

	0 ppm	375 ppm	750 ppm	1,500 ppm	3,000 ppm	5,000 ppm
Female (continued)						
Hematology (continued)						
n						
Day 5	9	8	9	9	8	9
Day 19	10	10	10	10	10	10
Week 14	10	10	10	10	9	10
Mean cell hemoglobin concentration (g/dL)						
Day 5	33.6 ± 0.3	33.3 ± 0.2	33.4 ± 0.3[b]	33.4 ± 0.2	34.0 ± 0.3[c]	33.9 ± 0.3
Day 19	33.5 ± 0.2	33.4 ± 0.2	33.6 ± 0.1	33.4 ± 0.3	32.9 ± 0.2*	32.4 ± 0.2**
Week 14	34.7 ± 0.2	34.4 ± 0.1	34.9 ± 0.2	34.9 ± 0.2	34.3 ± 0.2	34.2 ± 0.2
Platelets (10^3/μL)						
Day 5	794.6 ± 41.0	891.1 ± 27.6	847.3 ± 35.4[b]	866.9 ± 16.3	995.3 ± 34.5**[c]	931.8 ± 43.9**
Day 19	701.8 ± 24.7	703.4 ± 22.4	698.4 ± 30.7	709.4 ± 16.3	726.7 ± 61.2	1,631.0 ±171.7**
Week 14	656.6 ± 17.0	611.5 ± 10.8	668.7 ± 21.3	613.6 ± 11.3	645.3 ± 21.9	617.5 ± 14.9
Methemoglobin (g/dL)						
Day 5	0.02 ± 0.01	0.10 ± 0.05*	0.05 ± 0.01	0.21 ± 0.08**	2.41 ± 0.76**	4.95 ± 0.92**
Day 19	0.03 ± 0.01	0.11 ± 0.03*	0.18 ± 0.04**	2.01 ± 0.49**	3.78 ± 0.79**	6.66 ± 0.36**
Week 14	0.06 ± 0.02	0.14 ± 0.02**	0.16 ± 0.02**	0.48 ± 0.05**[c]	0.99 ± 0.20**	2.27 ± 0.54**
Heinz bodies (10^6/μL)						
Day 5	0.002 ± 0.001	0.001 ± 0.001	0.002 ± 0.001	0.002 ± 0.001	0.006 ± 0.002	0.010 ± 0.002**
Day 19	0.002 ± 0.001	0.002 ± 0.001	0.001 ± 0.001	0.003 ± 0.002	0.002 ± 0.002	0.002 ± 0.001
Week 14	0.300 ± 0.123	0.230 ± 0.117	0.350 ± 0.117	0.210 ± 0.107	0.178 ± 0.118	0.240 ± 0.122
Clinical Chemistry						
n						
Day 5	10	9	9	9	10	10
Day 19	10	10	10	10	10	10
Week 14	10	10	10	10	9	10
Urea nitrogen (mg/dL)						
Day 5	22.1 ± 1.1	21.2 ± 0.6	21.3 ± 0.6	20.3 ± 0.7[d]	21.0 ± 0.5	22.5 ± 0.6 .
Day 19	24.4 ± 1.0[c]	24.2 ± 0.7	23.2 ± 0.5	23.9 ± 0.5	24.1 ± 0.6	30.6 ± 0.8**
Week 14	17.8 ± 0.6	19.0 ± 0.4	19.0 ± 0.7	21.7 ± 0.4**	22.3 ± 0.7**	21.5 ± 0.5**
Creatinine (mg/dL)						
Day 5	0.63 ± 0.03[c]	0.62 ± 0.03	0.70 ± 0.04	0.65 ± 0.02[d]	0.71 ± 0.01*[c]	0.73 ± 0.03*[c]
Day 19	0.58 ± 0.04[d]	0.65 ± 0.03*	0.60 ± 0.02	0.69 ± 0.03**	0.73 ± 0.04**	0.81 ± 0.03**
Week 14	0.66 ± 0.02	0.68 ± 0.03	0.67 ± 0.02	0.68 ± 0.03	0.68 ± 0.03	0.69 ± 0.02
Alkaline phosphatase (IU/L)						
Day 5	424 ± 21	423 ± 15	415 ± 14[b]	377 ± 13	345 ± 11**	315 ± 12**
Day 19	350 ± 10	299 ± 22*	340 ± 5	315 ± 16*	288 ± 16**	257 ± 4**
Week 14	178 ± 5	176 ± 8	180 ± 5	167 ± 3	164 ± 3	142 ± 5**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=10
[c] n=9
[d] n=8
[e] n=7
[f] Total number of erythrocytes with Heinz bodies

The relative kidney weights of males and females exposed to 3,000 and 5,000 ppm were significantly increased. The relative spleen weights of males exposed to 1,500 ppm or greater and females exposed to 3,000 or 5,000 ppm were significantly greater than those of the controls (Table G1).

Sperm motility in 1,500 and 5,000 ppm males was significantly decreased relative to the controls (Table H1). There were no significant differences in vaginal cytology parameters between exposed and control females (Table H2).

Microscopically, no abnormal changes were seen in the kidney or spleen. Microscopic examination of the bone marrow demonstrated increases in the incidences of erythropoietic activity in males (5/10, 5/10, 5/10, 8/10, 8/10, 9/10) and females (1/10, 0/10, 1/10, 3/10, 7/10, 10/10). The increased incidences of erythropoiesis were consistent with the hematologic findings of regenerative anemia.

All the 5,000 ppm males and females had squamous cell hyperplasia of the forestomach; none was seen in the controls or 3,000 ppm animals. The average severity of forestomach hyperplasia was minimal in males and mild in females. Hyperplastic lesions were focal and were primarily observed near the limiting ridge between the forestomach and the glandular stomach. Hyperplasia was characterized by thickening of the squamous epithelium, and hyperkeratosis was often a component of the lesion.

Exposure Concentration Selection Rationale: Based on decreased final mean body weights and body weight gains of males and females exposed to 5,000 ppm and increased incidences of squamous cell hyperplasia of the forestomach in 5,000 ppm males and females, the sodium nitrite concentrations selected for the 2-year drinking water study in rats were 750, 1,500, and 3,000 ppm.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 7 and in the Kaplan-Meier survival curves (Figure 1). Survival of exposed groups was similar to that of the control groups.

Body Weights, Water and Compound Consumption, and Clinical Findings

Mean body weights of males and females exposed to 3,000 ppm were less than those of the control groups throughout the study (Figure 2 and Tables 8 and 9). Water consumption by males and females exposed to 3,000 ppm was less than that by the controls throughout the study, and that by the other exposed groups was generally less after week 14 (Tables K1 and K2). Drinking water concentrations of 750, 1,500, or 3,000 ppm sodium nitrite resulted in average daily doses of approximately 35, 70, or 130 mg/kg body weight to males and 40, 80, or 150 mg/kg to females. There were no clinical findings related to exposure to sodium nitrite; the brown discoloration and cyanosis seen in the 14-week studies were not observed.

TABLE 7
Survival of Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	16	4	12	8
Natural deaths	5	8	2	6
Animals surviving to study termination	29	38[c]	36	36
Percent probability of survival at end of study[a]	58	76	72	72
Mean survival (days)[b]	665	697	703	702
Survival analysis[d]	P=0.215N	P=0.075N	P=0.128N	P=0.137N
Female				
Animals initially in study	50	50	50	50
Moribund	11	6	10	15
Natural deaths	6	13	4	2
Animals surviving to study termination	33	31	36	33
Percent probability of survival at end of study	66	62	72	66
Mean survival (days)	695	693	698	694
Survival analysis	P=0.853N	P=0.890	P=0.657N	P=1.000N

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

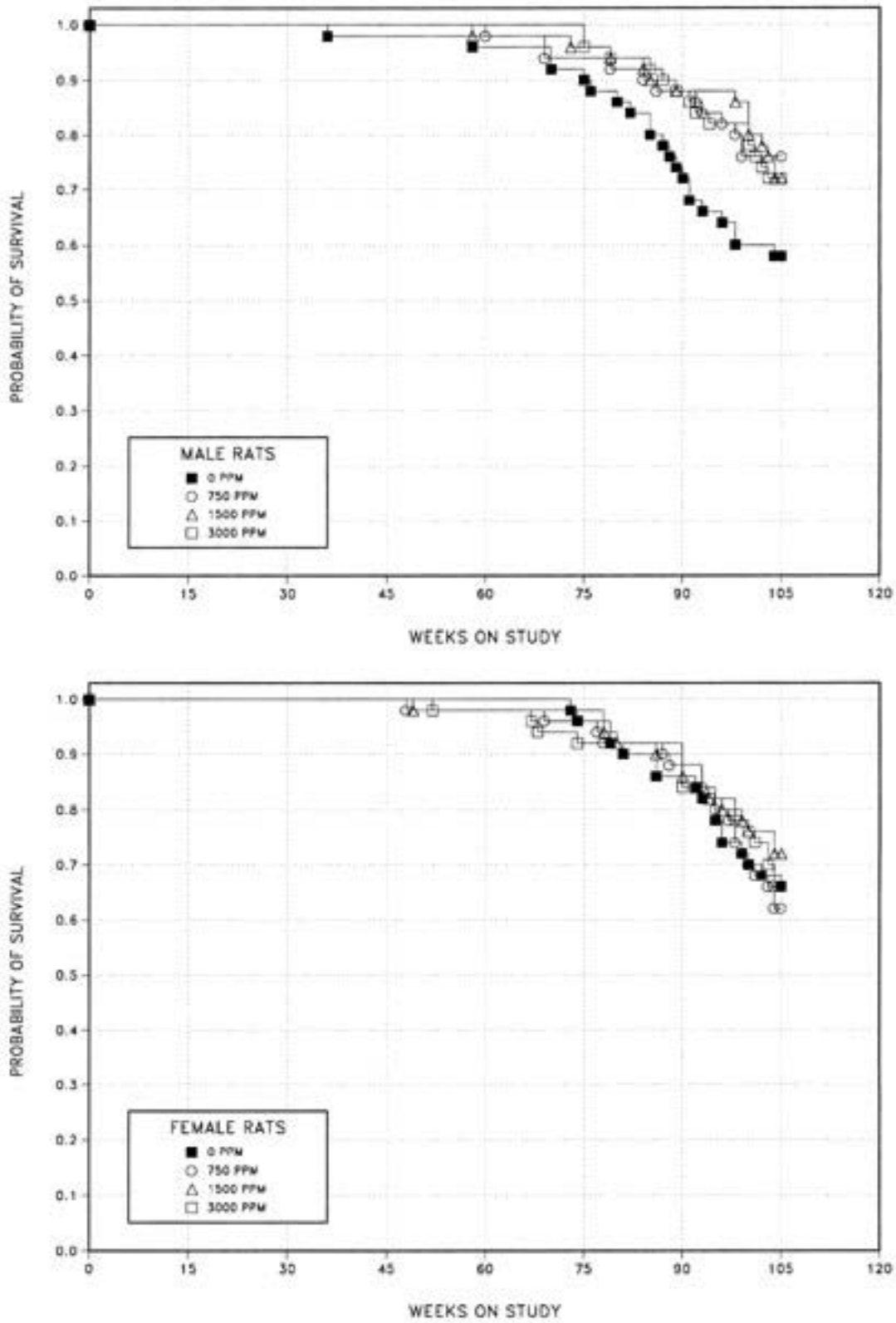


FIGURE I
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Sodium Nitrite in Drinking Water for 2 Years

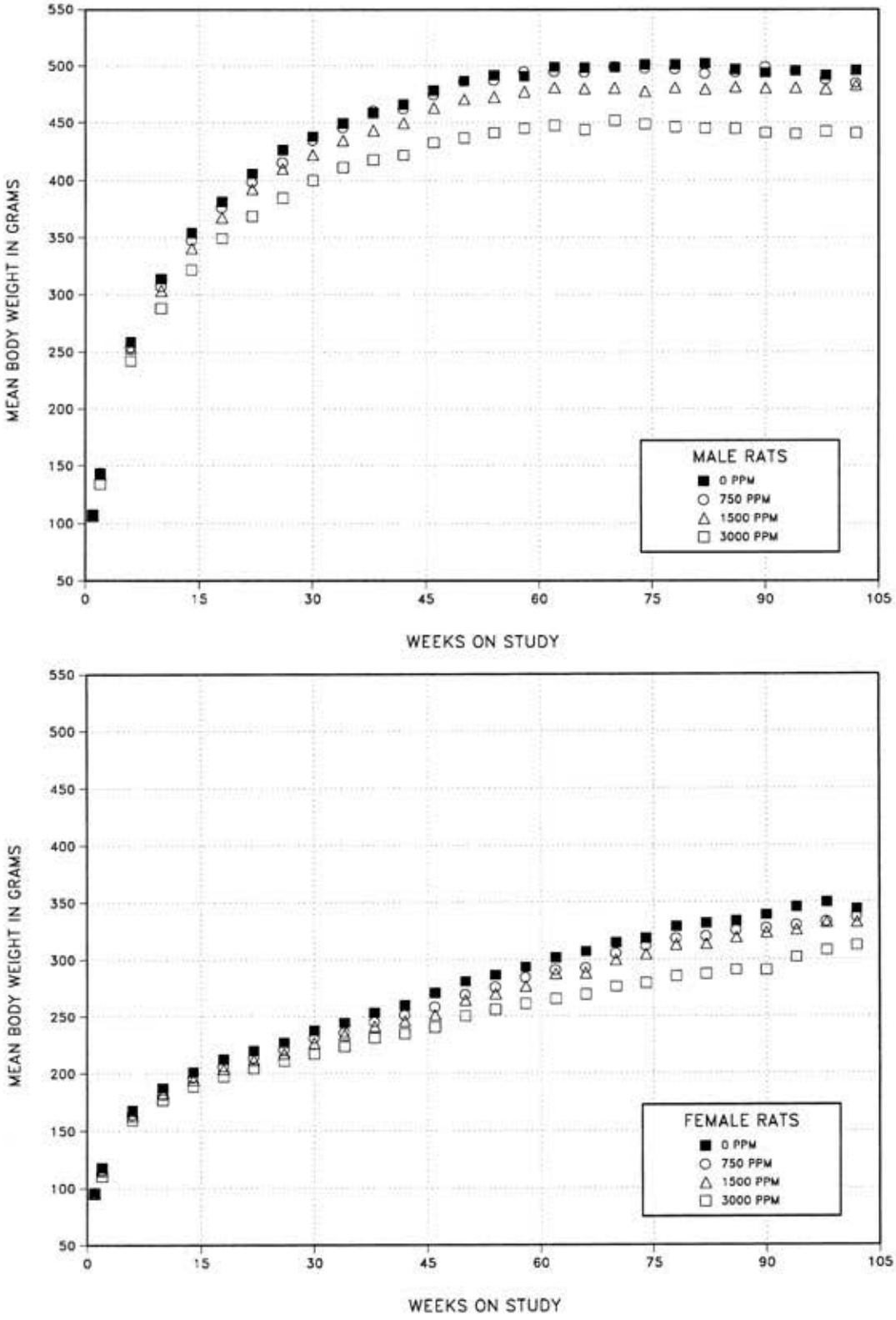


FIGURE 2
Growth Curves for Male and Female Rats Exposed to Sodium Nitrite in Drinking Water for 2 Years

TABLE 8
Mean Body Weights and Survival of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	750 ppm Av. Wt. (g)	750 ppm Wt. (% of controls)	750 ppm No. of Survivors	1,500 ppm Av. Wt. (g)	1,500 ppm Wt. (% of controls)	1,500 ppm No. of Survivors	3,000 ppm Av. Wt. (g)	3,000 ppm Wt. (% of controls)	3,000 ppm No. of Survivors
1	107	50	107	100	50	107	100	50	107	101	50
2	144	50	144	100	50	143	99	50	134	93	50
6	259	50	254	98	50	254	98	50	242	94	50
10	314	50	307	98	50	304	97	50	288	92	50
14	354	50	348	98	50	341	96	50	322	91	50
18	381	50	376	99	50	367	96	50	349	92	50
22	406	50	399	98	50	392	97	50	369	91	50
26	426	50	416	97	50	410	96	50	385	90	50
30	438	50	435	99	50	423	97	50	400	91	50
34	450	50	446	99	50	435	97	50	412	92	50
38	458	49	460	100	50	443	97	50	418	91	50
42	466	49	462	99	50	450	97	50	422	91	50
46	478	49	474	99	50	463	97	50	433	91	50
50	487	49	486	100	50	470	97	50	437	90	50
54	492	49	487	99	50	473	96	50	441	90	50
58	491	49	495	101	50	477	97	50	445	91	50
62	499	48	495	99	49	481	96	49	448	90	50
66	499	48	494	99	49	480	96	49	444	89	50
70	499	48	499	100	47	481	96	49	452	91	50
74	501	46	498	99	47	477	95	48	449	90	50
78	501	44	497	99	47	481	96	48	446	89	48
82	502	43	493	98	46	479	95	47	445	89	47
86	497	40	495	100	45	481	97	45	445	90	46
90	494	36	499	101	44	480	97	44	441	89	44
94	495	33	496	100	42	481	97	44	440	89	42
98	492	31	488	99	40	480	98	43	442	90	41
102	496	30	485	98	38	483	97	39	441	89	38
Mean for weeks											
1-13	206		203	99		202	98		193	94	
14-52	434		430	99		419	97		395	91	
53-102	497		494	99		480	97		445	90	

TABLE 9
Mean Body Weights and Survival of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	750 ppm Av. Wt. (g)	750 ppm Wt. (% of controls)	750 ppm No. of Survivors	1,500 ppm Av. Wt. (g)	1,500 ppm Wt. (% of controls)	1,500 ppm No. of Survivors	3,000 ppm Av. Wt. (g)	3,000 ppm Wt. (% of controls)	3,000 ppm No. of Survivors
1	96	50	95	99	50	96	100	50	95	99	50
2	118	50	116	98	50	115	98	50	111	94	50
6	168	50	164	98	50	164	97	50	159	95	50
10	187	50	182	97	50	183	98	50	177	94	50
14	201	50	196	98	50	195	97	50	188	94	50
18	212	50	206	97	50	204	96	50	197	93	50
22	220	50	214	97	50	212	96	50	204	93	50
26	227	50	221	97	50	218	96	50	211	93	50
30	238	50	231	97	50	227	95	50	217	91	50
34	245	50	236	97	50	234	96	50	224	91	50
38	254	50	245	97	50	241	95	50	231	91	50
42	260	50	251	97	50	246	95	50	235	90	50
46	271	50	259	96	50	252	93	50	241	89	50
50	281	50	269	96	49	264	94	49	250	89	50
54	286	50	276	96	49	270	94	49	256	90	49
58	293	50	284	97	49	276	94	49	261	89	49
62	302	50	291	96	49	287	95	49	265	88	49
66	307	50	293	95	49	288	94	49	269	88	49
70	315	50	305	97	48	299	95	49	276	88	47
74	319	49	312	98	48	305	96	49	279	88	47
78	329	48	319	97	47	313	95	49	285	87	46
82	332	45	320	97	46	314	95	46	287	87	46
86	333	45	325	98	46	319	96	46	291	87	46
90	339	43	327	97	44	323	95	45	290	86	46
94	346	41	330	96	42	326	94	42	302	87	42
98	350	37	333	95	38	332	95	40	308	88	39
102	344	35	337	98	34	332	97	38	312	91	37
Mean for weeks											
1-13	142		139	98		140	99		136	96	
14-52	241		233	97		229	95		220	91	
53-102	323		312	97		306	95		283	88	

Determination of Plasma Nitrite and Blood Methemoglobin Concentrations

At 2 weeks and 3 months, no nitrite was detected in the plasma of control male or female rats. Plasma nitrite concentrations tended to increase with increasing exposure concentrations of sodium nitrite. Generally, plasma nitrite concentrations were high at night when the rats were actively feeding and drinking, and were low during the day when the rats were less active (Tables I1 through I4). Blood methemoglobin concentrations followed the same pattern (Figures I1 and I2).

In 18-month-old male and female rats administered a single dose of 40 mg/kg sodium nitrite by gavage, plasma nitrite and blood methemoglobin concentrations peaked at 30 minutes (Tables I5 and I6).

Pathology and Statistical Analyses

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

Forestomach: The incidences of hyperplasia of the squamous epithelium were significantly increased in males and females exposed to 3,000 ppm (Tables 10, A5, and B5). Hyperplasia was generally a minimal change affecting the epithelium of the limiting ridge at the junction of the forestomach and glandular stomach (Plates 1 and 2). In a few cases, severe hyperplasia was seen both at and away from the limiting ridge. Hyperplasia was characterized primarily by variable degrees of folding of the squamous epithelium and was usually accompanied by a variable degree of thickening of the overlying keratin layer (hyperkeratosis). No forestomach neoplasms were observed following exposure to sodium nitrite.

TABLE 10
Incidences of Epithelial Hyperplasia of the Forestomach in Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm		750 ppm		1,500 ppm		3,000 ppm	
Male								
Number Examined Microscopically	50		50		50		50	
Epithelium, Hyperplasia[a]	12	(1.5)[b]	9	(1.4)	10	(1.3)	44**	(1.2)
Female								
Number Examined Microscopically	50		50		50		50	
Epithelium, Hyperplasia	8	(1.8)	6	(1.5)	8	(1.5)	40**	(1.2)

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

Mammary Gland: The incidence of fibroadenoma was significantly increased in females exposed to 1,500 ppm sodium nitrite and exceeded the historical range for NTP controls given NTP-2000 diet (all routes) (Tables 11, B3, and B4a) or NIH-07 diet (drinking water route) (24%-58%; Table B4a). The incidences in the 750 and 3,000 ppm groups also exceeded the range for the NTP controls given NTP-2000 diet; the incidence in the control group was greater than in these exposed groups and equaled the highest incidence in the NTP-2000 historical control database. Also, when combined with adenomas, there were no significant increases in the incidences of these neoplasms. The incidences of carcinoma were not increased in the exposed groups. The incidences of multiple fibroadenoma were greater in females exposed to 750 ppm and 1,500 ppm than in controls. Fibroadenomas are the most common benign neoplasms that occur in the mammary gland of female F344/N rats. However, unlike benign neoplasms in other tissues that usually progress to malignancy, fibroadenomas are generally considered to represent an end-stage lesion, and progression to carcinoma is rare. Microscopically, fibroadenomas in exposed rats were similar to those in the controls and were characterized by collections of glandular epithelium arranged in acini and ducts and surrounded by fibrous connective tissue. The relative amounts of glandular and fibrous elements varied among neoplasms. Epithelial cells were well differentiated and arranged in a single layer of cuboidal epithelium, which was often vacuolated.

TABLE 11
Incidences of Neoplasms of the Mammary Gland in Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Number Necropsied	50	50	50	50
Fibroadenoma, Multiple[a]	7	13	13	5
Fibroadenoma (includes multiple)[b]				
Overall rate[c]	21/50 (42%)	27/50 (54%)	31/50 (62%)	25/50 (50%)
Adjusted rate[d]	45.7%	58.5%	66.7%	54.4%
Terminal rate[e]	15/33 (46%)	17/31 (55%)	26/36 (72%)	16/33 (49%)
First incidence (days)	547	541	541	626
Poly-3 test[f]	P=0.268	P=0.149	P=0.029	P=0.263
Adenoma (includes multiple)	2	1	0	3
Fibroadenoma or Adenoma	23	27	31	28
Carcinoma	1	1	2	2

[a] Number of animals with lesion
[b] Historical incidence for 2-year studies with control groups given NTP-2000 diet (mean ± standard deviation): 108/299 (36.1% ± 6.2%); range 28%-42%
[c] Number of animals with neoplasm per number of animals necropsied
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.

Liver: There were significant increases in the incidences of chronic active inflammation in 1,500 and 3,000 ppm males (0 ppm, 13/50; 750 ppm, 19/50; 1,500 ppm, 25/50, 3,000 ppm, 24/50; Table A5). This was generally a minor lesion, characterized by a few to several scattered aggregates of mixed mononuclear inflammatory cells, mainly lymphocytes and macrophages. Chronic active inflammation of the liver is a common spontaneous lesion in F344/N rats and may be obscured in rats with mononuclear cell leukemia. Because of the lower incidences of mononuclear cell leukemia, this common background lesion was more easily observed microscopically. The marginally increased incidences of chronic active inflammation in 1,500 and 3,000 ppm males were not considered to be related to sodium nitrite exposure.

Kidney: The incidence of nephropathy was marginally increased in females exposed to 3,000 ppm (14/50, 16/50, 20/50, 23/50; Table B5). It is unclear whether the slightly increased incidences of nephropathy were directly related to sodium nitrite exposure. Nephropathy is a common spontaneous renal lesion in F344/N rats.

Skin: The incidence of fibroma of the subcutis was significantly increased in males exposed to 1,500 ppm (0/50, 1/50, 6/50, 3/50; Table A3). The incidence in this group slightly exceeded the historical range for NTP controls (all routes) given NTP-2000 diet (Table A4a). The lack of a dose response for fibroma or a significant increase in the incidences of fibrosarcomas (1/50, 0/50, 0/50, 2/50) and the fact that the combined incidences of fibroma or fibrosarcoma (1/50, 1/50, 6/50, 5/50) are within the historical range for NTP controls given NTP-2000 diet (Table A4a) suggest that these neoplasms were not related to sodium nitrite exposure. Fibromas and fibrosarcomas are the most common neoplasms that occur in the skin of F344/N rats.

Mononuclear Cell Leukemia: The incidences of mononuclear cell leukemia were significantly decreased in males and females exposed to 1,500 or 3,000 ppm and were less than the historical ranges for NTP controls (all routes) given NTP-2000 diet (Tables 12, A3, A4b, B3, and B4b). These findings indicate that sodium nitrite reduced the incidence of mononuclear cell leukemia in F344/N rats, thereby resulting in increased survival.

TABLE 12
Incidences of Mononuclear Cell Leukemia in Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Male				
Mononuclear Cell Leukemia[a]				
Overall rate[b]	17/50 (34%)	12/50 (24%)	7/50 (14%)	3/50 (6%)
Adjusted rate[c]	37.9%	25.7%	15.0%	6.6%
Terminal rate[d]	7/29 (24%)	7/38 (18%)	1/36 (3%)	1/36 (3%)
First Incidence (days)	486	552	620	698
Poly-3 test[e]	P<0.001N	P=0.151N	P=0.010N	P<0.001N
Female				
Mononuclear Cell Leukemia[f]				
Overall rate	15/50 (30%)	10/50 (20%)	1/50 (2%)	1/50 (2%)
Adjusted rate	32.1%	21.9%	2.2%	2.2%
Terminal rate	8/33 (24%)	4/31 (13%)	0/36 (0%)	1/33 (3%)
First incidence (days)	513	616	638	730 (T)
Poly-3 test	P<0.001N	P=0.191N	P<0.001N	P<0.001N

(T)Terminal sacrifice
[a] Historical incidence for 2-year studies with control groups given NTP-2000 feed (mean ± standard deviation): 130/299 (43.5% ± 9.6%); range 32%-54%
[b] Number of animals with neoplasm per number of animals necropsied
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[f] Historical incidence: 87/299 (29.1% ± 8.5%); range 16%-42%

MICE

14-WEEK STUDY

All mice survived until the end of the study (Table 13). Final mean body weight and body weight gain of 5,000 ppm males and body weight gain of 3,000 ppm males were significantly less than those of the controls. Water consumption by the 1,500, 3,000, and 5,000 ppm male groups was slightly less than that by the controls at week 13. Drinking water concentrations of 375, 750, 1,500, 3,000, or 5,000 ppm sodium nitrite resulted in average daily doses of approximately 90, 190, 345, 650, or 990 mg/kg to males and 120, 240, 445, 840, or 1,230 mg/kg to females. There were no chemical-related clinical findings; no cyanosis or brownish discoloration was observed.

Relative spleen weights of 3,000 and 5,000 ppm males and absolute and relative heart, kidney, liver, and spleen weights of females exposed to 3,000 or 5,000 ppm were greater than those of the control groups (Table G2).

Sperm motility in 5,000 ppm males was decreased relative to the controls (Table H3), and the estrous cycles of 1,500 and 5,000 ppm females were significantly longer than that of the controls (Table H4).

TABLE 13
Survival, Body Weights, and Water Consumption of Mice in the 14-Week Drinking Water Study of Sodium Nitrite

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Water Consumption[c]	
		Initial	Final	Change		Week 2	Week 13
Male							
0	10/10	21.4 ± 0.4	33.6 ± 0.9	12.2 ± 0.7		6.8	5.4
375	10/10	21.3 ± 0.4	33.9 ± 0.8	12.6 ± 0.5	101	10.4	4.9
750	10/10	21.3 ± 0.4	33.0 ± 0.6	11.7 ± 0.4	98	9.4	5.7
1,500	10/10	21.4 ± 0.4	33.1 ± 1.0	11.7 ± 0.6	99	10.1	5.1
3,000	10/10	21.5 ± 0.3	31.6 ± 1.0	10.1 ± 0.7*	94	8.4	4.9
5,000	10/10	21.5 ± 0.4	30.3 ± 0.7**	8.8 ± 0.3**	90	7.1	5.0
Female							
0	10/10	18.0 ± 0.2	29.9 ± 0.9	12.0 ± 0.7		9.5	6.7
375	10/10	18.0 ± 0.4	30.7 ± 1.1	12.7 ± 0.9	103	10.1	5.9
750	10/10	17.7 ± 0.3	30.3 ± 1.2	12.6 ± 1.0	101	10.1	6.7
1,500	10/10	18.0 ± 0.4	30.8 ± 1.1	12.8 ± 0.9	103	9.6	6.1
3,000	10/10	18.0 ± 0.4	30.4 ± 1.0	12.4 ± 0.7	102	8.4	6.7
5,000	10/10	18.1 ± 0.4	27.3 ± 0.6	9.2 ± 0.5	91	6.8	6.6

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Water consumption is expressed as grams per animal per day.

Compared to the controls, there were increased incidences of microscopic lesions of the forestomach, spleen, and testis in exposed mice (Table 14). The incidences of squamous cell hyperplasia (focal) of the forestomach at the limiting ridge in 5,000 ppm males and females were significantly greater than those in the control groups. The severity of forestomach hyperplasia ranged from minimal to mild. The lesion was characterized by a focal increase in the thickness of all cell layers of the squamous epithelium. Minimal hyperkeratosis was associated with the hyperplasia and was characterized by thickening of the cornified layer and fraying of the outermost portion.

The incidences of extramedullary hematopoiesis in the spleen of 3,000 and 5,000 ppm males and females exposed to 1,500 ppm or greater were significantly greater than those in the control groups (Table 14). The severity of extramedullary hematopoiesis was minimal to mild, and the lesion was characterized by larger and more numerous clusters of small, dark hematopoietic cells in the red pulp.

The incidences of degeneration of the testis in 3,000 and 5,000 ppm males were significantly greater than that in the control group (Table 14). Testicular degeneration was minimal to mild and was characterized by an increase in the size of residual bodies within the lumen of seminiferous tubules. Compared to the controls, in which the residual bodies were generally small, dark-staining cytoplasmic fragments, the residual bodies in exposed mice were typically large and spherical with glassy, eosinophilic staining and a smudged, basophilic core. The significance of the testicular degeneration was uncertain; degeneration may have been the result of a Sertoli cell defect in the processing of residual bodies.

Exposure Concentration Selection Rationale: Based on decreased body weights of males exposed to 5,000 ppm, increased incidences and severities of forestomach hyperplasia and spleen extramedullary hematopoiesis in males and females exposed to 5,000 ppm, and increased incidences of testicular degeneration in males exposed to 3,000 or 5,000 ppm, the sodium nitrite exposure concentrations selected for use in the 2-year drinking water study in mice were 750, 1,500, and 3,000 ppm.

TABLE 14
Incidences of Selected Nonneoplastic Lesions in Mice in the 14-Week Drinking Water Study of Sodium Nitrite

	0 ppm	375 ppm	750 ppm	1,500 ppm	3,000 ppm	5,000 ppm
Male						
Forestomach[a]	10	10	10	10	10	10
Focal Hyperplasia[b]	0	—[c]	—	—	0	8** (1.3)[d]
Spleen	10	10	10	10	10	10
Extramedullary Hematopoiesis	0	—	—	0	5* (1.0)	10** (1.8)
Testis	10	10	10	10	10	10
Degeneration	0	—	—	0	9** (1.0)	9** (1.4)
Female						
Forestomach	10	10	10	10	10	10
Focal Hyperplasia	0	—	—	—	0	6** (1.5)
Spleen	10	10	10	10	10	10
Extramedullary Hematopoiesis	0	—	0	10** (1.0)	9** (1.6)	10** (1.8)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals necropsied
[b] Number of animals with lesion
[c] Organ not examined microscopically
[d] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 15 and in the Kaplan-Meier survival curves (Figure 3). Survival of exposed groups was similar to that of the controls.

Body Weights, Water and Compound Consumption, and Clinical Findings

Mean body weights of exposed groups were generally similar to those of the controls throughout the study, except mean body weights of 3,000 ppm females were consistently less than those of the controls (Figure 4 and Tables 16 and 17). Water consumption by the exposed groups was generally less than that by the control groups (Tables K3 and K4). Drinking water concentrations of 750, 1,500, or 3,000 ppm resulted in average daily doses of approximately 60, 120, or 220 mg/kg for males and 45, 90, or 165 mg/kg for females. There were no clinical findings related to exposure to sodium nitrite.

TABLE 15
Survival of Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	3	2	3	1
Natural deaths	8	3	5	10
Animals surviving to study termination	39	45	42	39
Percent probability of survival at end of study[a]	78	90	84	78
Mean survival (days)[b]	708	713	713	699
Survival analysis[c]	P=0.659	P=0.199N	P=0.616N	P=1.000
Female				
Animals initially in study	50	50	50	50
Moribund	1	7	2	4
Natural deaths	9	9	11	5
Animals surviving to study termination	40	34	37	41
Percent probability of survival at end of study	80	68	74	82
Mean survival (days)	702	704	709	705
Survival analysis	P=0.537N	P=0.340	P=0.721	P=0.963N

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A negative trend or lower mortality in an exposure group is indicated by **N**.

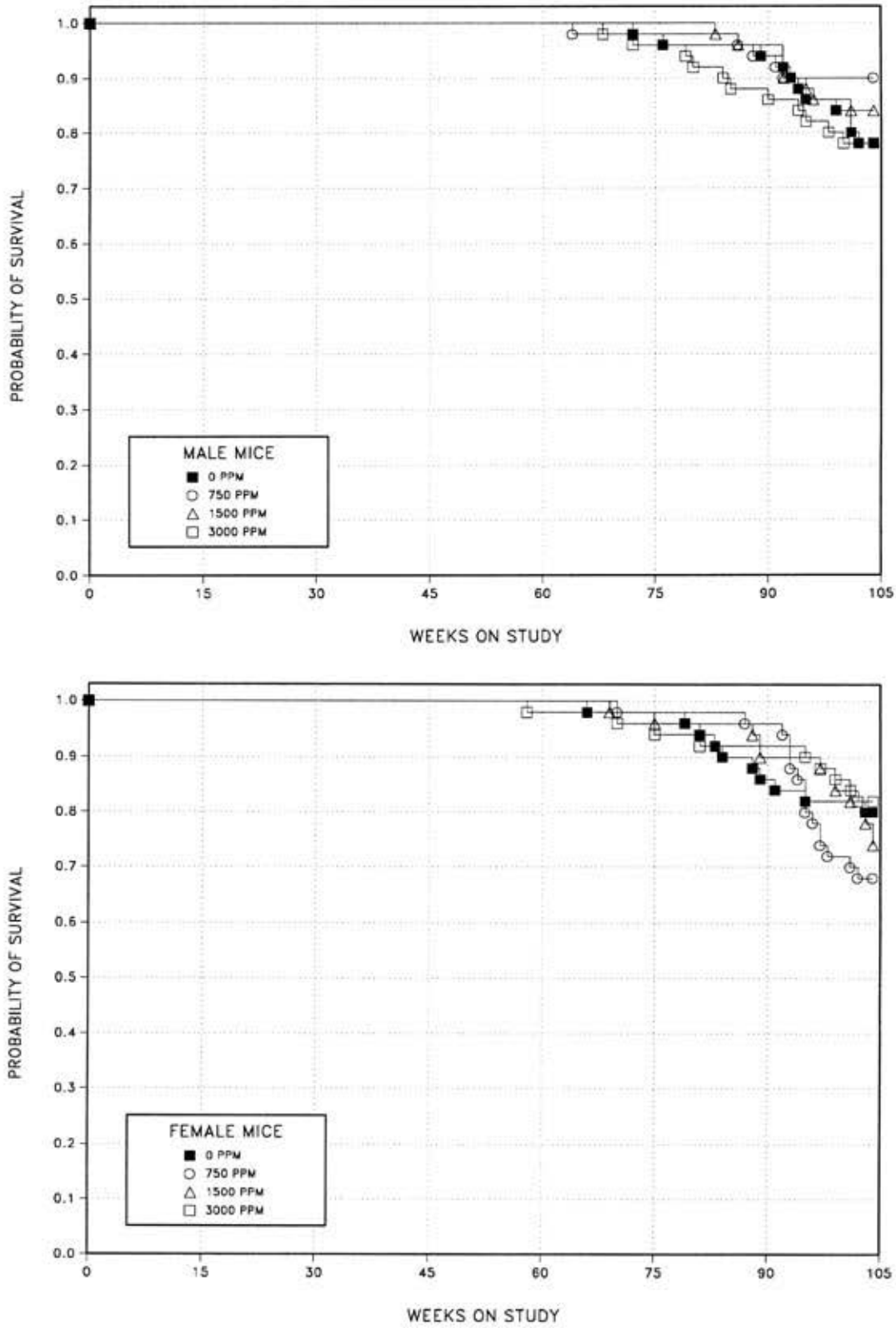


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Sodium Nitrite in Feed for 2 Years

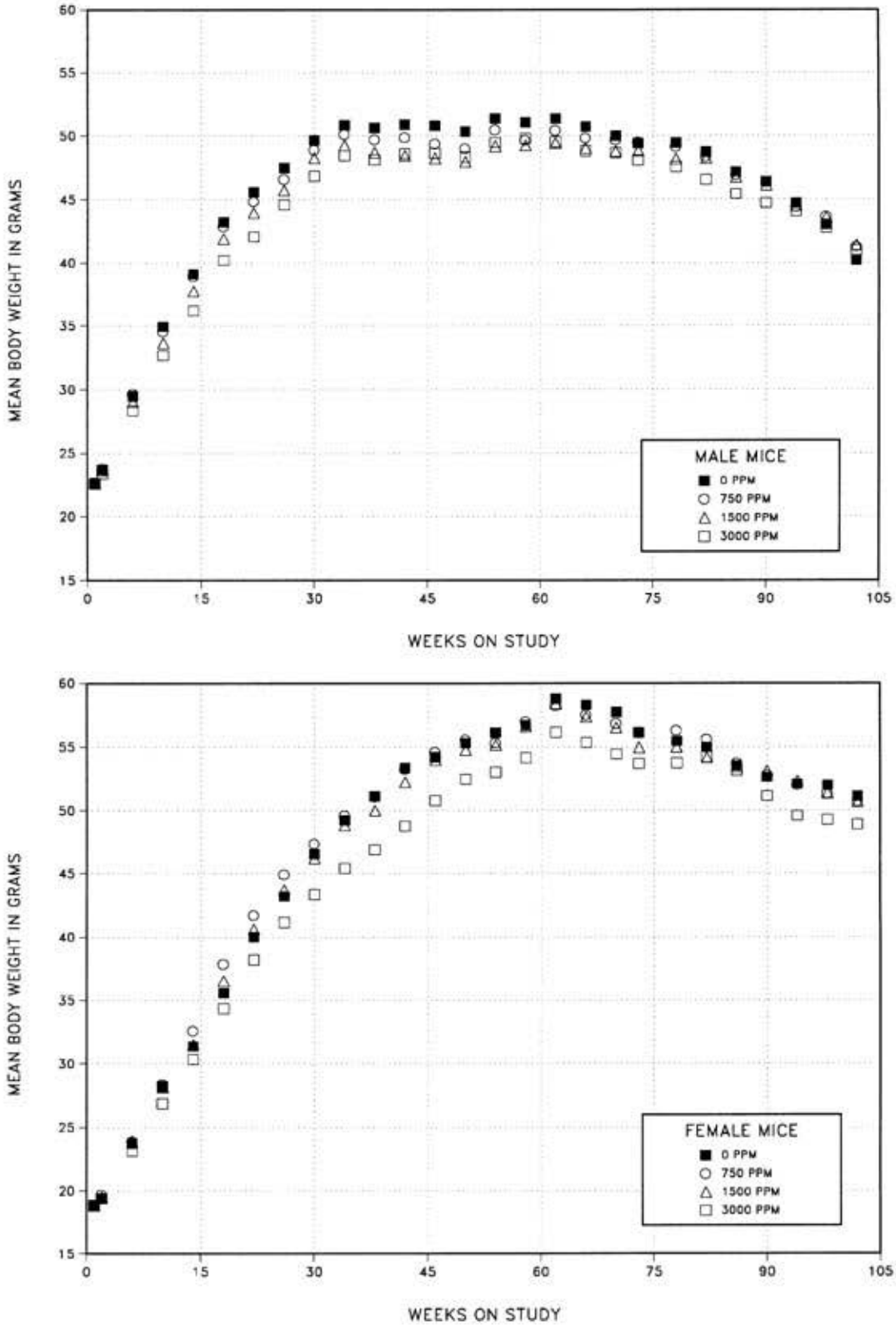


FIGURE 4
Growth Curves for Male and Female Mice Exposed to Sodium Nitrite in Feed for 2 Years

TABLE 16
Mean Body Weights and Survival of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite

Weeks on Study	0 ppm		750 ppm			1,500 ppm			3,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	22.6	50	22.7	100	50	22.6	100	50	22.6	100	50
2	23.7	50	23.7	100	50	23.6	100	50	23.4	99	50
6	29.5	50	29.6	100	50	29.1	99	50	28.3	96	50
10	34.9	50	34.5	99	50	33.7	97	50	32.7	94	50
14	39.1	50	38.9	100	50	37.7	96	50	36.2	93	50
18	43.2	50	42.9	99	50	41.9	97	50	40.2	93	50
22	45.6	50	44.9	99	50	44.0	97	50	42.1	92	50
26	47.5	50	46.6	98	50	45.7	96	50	44.6	94	50
30	49.6	50	48.9	99	50	48.3	97	50	46.9	95	50
34	50.8	50	50.1	99	50	49.2	97	50	48.4	95	50
38	50.6	50	49.7	98	50	48.7	96	50	48.1	95	50
42	50.9	50	49.9	98	50	48.4	95	50	48.6	96	50
46	50.8	50	49.4	97	50	48.3	95	50	48.6	96	50
50	50.3	50	49.0	97	50	48.0	95	50	48.3	96	50
54	51.3	50	50.5	98	50	49.2	96	50	49.5	97	50
58	51.1	50	49.6	97	50	49.3	97	50	49.8	98	50
62	51.4	50	50.4	98	50	49.4	96	50	49.5	96	50
66	50.7	50	49.8	98	49	49.0	97	50	48.8	96	50
70	50.0	50	49.7	99	49	48.8	98	50	48.7	97	49
73	49.4	49	49.5	100	49	48.8	99	50	48.1	97	48
78	49.4	48	49.1	99	49	48.2	98	50	47.6	96	48
82	48.7	48	48.4	99	49	48.2	99	50	46.6	96	46
86	47.2	48	46.9	99	49	46.8	99	48	45.4	96	44
90	46.4	47	46.4	100	47	46.1	99	48	44.7	96	44
94	44.7	45	44.4	99	45	44.5	100	45	44.1	99	43
98	43.0	43	43.7	102	45	43.6	101	43	42.8	100	41
102	40.2	40	41.3	103	45	41.4	103	42	41.0	102	39
Mean for weeks											
1-13	27.7		27.6	100		27.3	99		26.8	97	
14-52	47.8		47.0	98		46.0	96		45.2	95	
53-102	48.0		47.7	99		47.2	98		46.7	97	

TABLE 17
Mean Body Weights and Survival of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite

Weeks on Study	0 ppm		750 ppm			1,500 ppm			3,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	18.9	50	18.9	100	50	18.8	100	50	18.9	100	50
2	19.4	50	19.7	102	50	19.5	101	50	19.4	100	50
6	23.7	50	23.9	101	50	23.9	101	50	23.2	98	50
10	28.2	50	28.4	101	50	28.2	100	50	26.9	95	50
14	31.4	50	32.6	104	50	31.5	100	50	30.3	97	50
18	35.6	50	37.8	106	50	36.5	103	50	34.4	97	50
22	40.0	50	41.7	104	50	40.6	102	50	38.2	96	50
26	43.2	50	44.9	104	50	43.7	101	50	41.1	95	50
30	46.6	50	47.4	102	50	46.2	99	50	43.3	93	50
34	49.2	50	49.6	101	50	48.8	99	50	45.4	92	50
38	51.1	50	51.1	100	50	50.0	98	50	46.9	92	50
42	53.4	50	53.3	100	50	52.3	98	50	48.8	91	50
46	54.2	50	54.6	101	50	54.0	100	50	50.8	94	50
50	55.3	50	55.6	101	50	54.8	99	50	52.5	95	50
54	56.1	50	55.3	99	50	55.2	98	50	53.0	95	50
58	56.7	50	57.0	101	50	56.6	100	50	54.2	96	50
62	58.8	50	58.2	99	50	58.4	99	50	56.1	95	49
66	58.3	49	57.5	99	50	57.4	99	50	55.4	95	49
70	57.7	49	56.8	98	49	56.5	98	49	54.4	94	48
73	56.1	49	56.1	100	49	55.0	98	49	53.7	96	48
78	55.5	49	56.3	101	49	55.0	99	48	53.8	97	47
82	55.0	47	55.6	101	49	54.2	99	48	54.2	99	46
86	53.5	45	53.7	100	49	53.5	100	48	53.2	99	46
90	52.6	43	52.8	100	48	53.1	101	45	51.2	97	46
94	52.1	42	52.1	100	43	52.3	100	45	49.6	95	46
98	52.0	41	51.4	99	37	51.4	99	44	49.3	95	44
102	51.1	41	50.7	99	35	50.7	99	41	48.9	96	41
Mean for weeks											
1-13	22.6		22.7	100		22.6	100		22.1	98	
14-52	46.0		46.9	102		45.8	100		43.2	94	
53-102	55.0		54.9	100		54.6	99		52.8	96	

Determinations of Plasma Nitrite and Blood Methemoglobin Concentrations

At 12 months, no nitrite was detected in the plasma of control or 750 ppm male mice (Table I7) or in any group of female mice (data not shown). In general, there was an exposure concentration-related increase in plasma nitrite in the 1,500 and 3,000 ppm male mice; peak plasma nitrite concentrations occurred around midnight. Blood methemoglobin concentrations were similar among exposed groups of males and females (Tables I7 and I8).

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the forestomach, glandular stomach, lung, and skin. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Forestomach: The incidences of squamous cell papilloma or carcinoma (combined) in female mice occurred with a positive trend, and the incidence in 3,000 ppm females exceeded the historical range for NTP controls given NTP-2000 diet (all routes) (Tables 18, D3, and D4) or NIH-07 diet (drinking water route) (range 0%-4%; Table D4). Because both of these historical databases are rather small, the historical incidences of forestomach squamous cell papilloma or carcinoma (combined) in NTP controls given NIH-07 diet in studies with other routes of chemical administration were evaluated, such as feed controls and inhalation controls (Table D4). The incidence of squamous cell papilloma or carcinoma (combined) in the 3,000 ppm females exceeded these historical incidences with the exception of corn oil gavage studies, where as many as five papillomas, but no carcinomas, were observed in one control group. Hyperplasia of the squamous epithelium was observed more frequently in 3,000 ppm females than in the controls (Table 18). Forestomach neoplasms were not observed in male mice exposed to sodium nitrite. Proliferative lesions involving the squamous epithelium represent a continuum, progressing from focal hyperplasia to papilloma to squamous cell carcinoma. Hyperplasia was generally a mild change affecting the squamous epithelium of the limiting ridge at the junction of the forestomach and glandular stomach. Papillomas (Plate 3) consisted of a solitary stalk of lamina propria protruding into the lumen with multiple finger-like projections arising from the stalk. The epithelium covering the projections was hyperplastic. In carcinomas, there was a focal invasion of the squamous epithelium into the lamina propria; however, there was no infiltration of neoplastic cells through the serosa of the forestomach, and there was no metastasis.

TABLE 18
Incidences of Neoplasms and Nonneoplastic Lesions of the Forestomach and Glandular Stomach in Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Female				
Forestomach[a]	50	50	50	50
Epithelium, Hyperplasia[b]	2 (2.5)[c]	3 (2.0)	3 (2.0)	6 (2.5)
Squamous Cell Papilloma	1	0	1	3
Squamous Cell Carcinoma	0	0	0	2
Squamous Cell Papilloma or Carcinoma[d]				
Overall rate[e]	1/50 (2%)	0/50 (0%)	1/50 (2%)	5/50 (10%)
Adjusted rate[f]	2.2%	0.0%	2.1%	10.7%
Terminal rate[g]	1/40 (3%)	0/34 (0%)	1/37 (3%)	4/41 (10%)
First incidence (days)	728 (T)	—[i]	728 (T)	708
Poly-3 test[h]	P=0.011	P=0.500N	P=0.756N	P=0.106
Male				
Glandular Stomach	50	50	50	50
Epithelium, Hyperplasia	0	0	2 (1.5)	10** (2.0)

** Significantly different ($P \leq 0.01$) from the control group by the Poly-3 test
(T)Terminal sacrifice
[a] Number of animals necropsied
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked.
[d] Historical incidence for 2-year studies with control groups given NTP-2000 feed (mean ± standard deviation): 2/250 (0.8% ± 1.1%); range, 0%-2%
[e] Number of animals with neoplasm per number of animals necropsied
[f] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[g] Observed incidence at terminal kill
[h] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposure group is indicated by **N**.
[i] Not applicable; no neoplasms in animal group

Glandular Stomach: The incidence of epithelial hyperplasia was significantly greater in 3,000 ppm males than in the controls (Table 18). Hyperplasia of the glandular stomach epithelium was focally extensive and was characterized by a distorted and irregular arrangement of the glandular elements of the gastric mucosa. In the hyperplastic areas, the proportion of the gastric glands with mucus-secreting cells was reduced to 25% compared to 50% in the normal area (Plates 4 and 5). In addition, the parietal cells in the mid portion of the gastric glands were less distinct in the hyperplastic areas. Instead of large, cuboidal cells with eosinophilic cytoplasm (characteristic of normal parietal cells), the parietal cell area tended to be composed of smaller, elongated, basophilic cells with vesiculated, fusiform nuclei and relatively scant cytoplasm consistent with chief cells (Plate 6). There were no neoplasms of the glandular stomach.

Lung: The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in exposed groups of females were slightly greater than that in the control group. (1/50, 6/50, 5/50, 6/50; Table D3). However, the incidences of these lesions were within the historical range for controls (all routes) given NTP-2000 diet [17/250 (6.8% ± 5.6%), range 0%-12%]. The increased incidences were not statistically significant or exposure concentration related and were not accompanied by increased incidences of preneoplastic lesions; therefore, the lung neoplasms in exposed females were not

considered to be related to sodium nitrite exposure.

Skin: The incidence of fibrosarcoma in 750 ppm females was significantly greater than that in the controls (0 ppm, 0/50; 750 ppm, 5/50; 1,500 ppm, 1/50; 3,000 ppm, 2/50; Table D3). The incidence exceeded the historical range for NTP controls (all routes) given NTP-2000 diet [3/250 (1.2% ± 1.8%), range 0%-4%]. The lack of a dose response for fibrosarcomas and the fact that the combined incidence of fibroma or fibrosarcoma (0/50, 5/50, 1/50, 3/50) fell within the historical range for NTP controls given NTP-2000 diet suggest that these neoplasms were not related to sodium nitrite exposure. The most frequent spontaneous mesenchymal neoplasms of the subcutaneous skin in female mice in the order of occurrence were fibrosarcomas, sarcomas, and lipomas.

GENETIC TOXICOLOGY

Sodium nitrite (100-10,000 µg/plate) was mutagenic in *Salmonella typhimurium* strain TA100, with and without Aroclor 1254-induced hamster and rat liver S9 enzymes; no mutagenicity was observed in strain TA98 (Table E1; Zeiger *et al.*, 1992). When sodium nitrite was administered by intraperitoneal injection at 6.25 to 200 mg/kg to male rats three times at 24-hour intervals, no significant increase in the frequency of micronucleated polychromatic erythrocytes was observed in any of the dose groups (Table E2). The initial trial was judged to be positive, based on the trend test (P=0.001); however, results of a repeat trial, in which 50 mg/kg was the highest nonlethal dose tested, were negative, and the rat bone marrow micronucleus test with sodium nitrite was judged to be negative overall. A similar study in which male mice were administered 7.81 to 250 mg/kg also gave negative results (Table E3). A third *in vivo* study, a peripheral blood micronucleus test in male and female mice administered sodium nitrite (375 to 5,000 ppm) for 14 weeks, showed no significant increase in the frequency of micronucleated normochromatic erythrocytes in either males or females (Table E4). Thus, sodium nitrite demonstrated mutagenic activity in a strain of *S. typhimurium* that mutates via base-pair substitution, but no indication of chromosomal damage was observed in three micronucleus studies conducted in rats and mice *in vivo*.

DISCUSSION AND CONCLUSIONS

Sodium nitrite is used as a color fixative and preservative in meats and fish. It is also used in manufacturing diazo dyes, nitroso compounds, and other organic compounds; in dyeing and printing textile fabrics; and in bleaching fibers; in photography; as a laboratory reagent and a corrosion inhibitor; in metal coatings for phosphatizing and detinning; and in the manufacture of rubber chemicals. Sodium nitrite also has been used in human and veterinary medicine as a vasodilator, a bronchial dilator, an intestinal relaxant, and an antidote for cyanide poisoning. Sodium nitrite was nominated for toxicity and carcinogenesis studies by the FDA based on its widespread use and because many nitroso compounds are carcinogenic.

In the 14-week studies, survival of rats exposed to sodium nitrite was not affected. Rats exposed to 3,000 or 5,000 ppm showed reduced body weight gains and water consumption. It is likely that animals that do not drink do not eat; therefore, reduced water consumption may have contributed to the reduction in body weight gains through decreased feed consumption. The possibility of decreased feed consumption is supported by the transient decreases in the serum activities of alkaline phosphatase. It has been demonstrated that the intestinal alkaline phosphatase isoenzyme is a major component of rat serum alkaline phosphatase activity (Righetti and Kaplan, 1971) and that fasting or feed restriction causes decreases in serum alkaline phosphatase activity (Jenkins and Robinson, 1975; Imai *et al*., 1991). Thus, the decreases in alkaline phosphatase activity could be related to a loss of the normal circulating intestinal fraction as a result of decreased feed consumption early in the study. In another study, Til *et al.* (1997) administered sodium nitrite in drinking water to male and female Wistar rats at 81 or 2,432 mg/L (81 or 2,432 ppm) for 13 weeks. The authors reported reduced water consumption in the 2,432 mg/L group but reported no changes in body weights or feed consumption. Apparently, the drinking water became unpalatable with high sodium nitrite content.

A treatment-related increase in methemoglobin concentrations was a prominent finding in the sodium nitrite-exposed rats. This effect occurred by day 5 and continued throughout the study; a no-observed-adverse-effect level was not determined for methemoglobin formation in male or female animals. Development of methemoglobinemia has been reported for rats (Chow *et al.,* 1980; Til *et al.,* 1997) and other species (Bruning-Fann and Kaneene, 1993) administered sodium nitrite. The production of methemoglobin would be consistent with oxidative injury to erythrocytes (Smith and Beutler, 1966) and could account for the increased numbers of Heinz bodies observed on day 5 in 5,000 ppm male and female rats. It has been demonstrated that as the glutathione concentration is depleted in the cell, globin sulfhydryl groups become susceptible to oxidation (Berzofsky *et al*., 1971; Rachmilewitz, 1974). Thus, the maintenance of adequate red cell glutathione concentrations in the exposed animals' erythrocytes in this study may account for the lack of a stronger Heinz body effect.

Cyanosis or brownish discoloration of mucous membranes and skin occurred in the 1,500 ppm female and 3,000 and 5,000 ppm male and female rats in the 14-week study; this finding was considered to be consistent with sodium nitrite exposure and methemoglobin formation. In studies with pigs, it has been reported that clinical findings become apparent when the methemoglobin concentration reaches 20% of the total hemoglobin content, but fatalities do not occur until a concentration of greater than 75% methemoglobin is achieved (London *et al.*, 1967). In the present study, depending on the gender and sampling time, the percentage of methemoglobin varied from approximately 0.5% to 13% for the 1,500 ppm groups, 5% to 24% for the 3,000 ppm groups and 13% to 50% for the 5,000 ppm groups. This suggests that biologically significant exposure concentration-related increases in methemoglobin concentration were induced, but the percentages of methemoglobin did not achieve lethal levels. In general, female rats had higher methemoglobin concentrations than male rats, which may be related to a higher sodium nitrite consumption by the females. There were increased erythrocyte counts on day 19 and an increased erythron at week 14 in the 3,000 and 5,000 ppm male and female rats. Because methemoglobin cannot bind oxygen, a

consequence of increased methemoglobin formation would include hypoxia (Jain, 1986a; Harvey, 1989). A secondary polycythemia may result from increased erythropoiesis as a compensatory physiological response to tissue hypoxia and the resultant increased production of erythropoietin (Jain, 1986b). The elevated reticulocyte and nucleated erythrocyte counts and bone marrow erythroid hyperplasia observed would be consistent with increased erythropoietic activity related to hypoxia and would account for the increased erythron.

Because reticulocytes are larger than mature red cells, the increased mean cell volume and mean cell hemoglobin values that occurred at week 14 would be consistent with reticulocytosis. This explanation, however, would suggest that the mean cell volumes and mean cell hemoglobin values also should have increased for affected animals on days 5 and 19. This did not happen, and the mean cell volume and mean cell hemoglobin values for the 5,000 ppm animals decreased on day 19. This suggests that more than one mechanism affected red cell size, that the factor(s) resulting in small cells had more influence at the early time points, and that this effect abated with time. Additionally, while the magnitude of methemoglobinemia remained fairly constant for the 5,000 ppm groups, the magnitude of the erythropoietic response appeared to diminish with time. The mechanism for this amelioration is unknown but may reflect an acclimation of the animals to lower tissue oxygen concentrations. Additionally, it has been reported that nitrate administration has goitrogenic activity in rats (Bruning-Fann and Kaneene, 1993). If nitrite administration had a similar action in the present study, it may have altered the basal metabolic rate of rats through altered thyroid gland function.

A transient increase in platelet counts occurred in 5,000 ppm male and female rats in the 14-week study. The mechanism for the platelet count alterations is unknown. However, it has been reported that nitric oxide, nitrate, and peroxynitrites inhibit platelet aggregation (Torfgoard and Ahlner, 1994; Brown *et al.*, 1998) and that nitric oxide administration may cause increased platelet counts in humans (Mellgren *et al.*, 1998).

Nitrite and nitrate are end-products of nitric oxide metabolism. Thus, administration of nitrite may have altered nitric oxide metabolism, which may have contributed to the increase in platelet counts.

In the 14-week study, survival of exposed mice was not affected. Male mice exposed to 5,000 ppm had reduced body weight gains. The brownish discoloration and cyanosis seen in rats were not observed in mice. Mice may have a higher erythrocyte methemoglobin reductase activity than do rats (Smith and Beutler, 1966), and this may, in part, help explain the observed difference between rats and mice. Increased relative spleen weights occurred in the 3,000 and 5,000 ppm male and female mice, and increased splenic extramedullary hematopoiesis was observed. Since the spleen is an erythropoietically active tissue in adult mice (Brodsky *et al.*, 1966), the splenic extramedullary hematopoiesis observed in mice would be consistent with methemoglobin formation and tissue hypoxia. In another study, Inai *et al*. (1979) reported hemosiderin deposition in the liver, spleen, and lymph nodes of ICR mice exposed to sodium nitrite in drinking water and suggested that a hemolytic event had occurred. No hemosiderin deposition was observed in the present studies.

In the 14-week studies, increased incidences of focal forestomach hyperplasia occurred in the 5,000 ppm male and female rats and mice. *N*-Nitroso compounds were not detected in the stomach contents of exposed rats. Evidence of cytotoxicity (necrosis or inflammation) of the forestomach was not observed. Yoshida *et al*. (1994) also observed that male Fischer rats administered sodium nitrite at 0.3% (3,000 ppm) in drinking water for 4 weeks had significantly increased incidences of hyperplasia of the mucosa in the forestomach and increased BrdU-labeling indices of the forestomach and glandular stomach. The mechanism of action of sodium nitrite in inducing forestomach hyperplasia is unknown.

In the 14-week studies, exposure to 3,000 or 5,000 ppm induced testicular degeneration in male mice; exposure to 5,000 ppm reduced sperm motility in male rats and mice and increased estrous cycle lengths in female mice. Further investigation by continuous breeding studies in Swiss mice showed no reproductive toxicity of sodium nitrite (NTP, unpublished data).

In the 2-year studies, survival of exposed rats was similar to that of the controls. Body weights were less than those of the controls in male and female rats exposed to 3,000 ppm. This finding agrees with that of Maekawa *et al*. (1982), who reported lower body weight gains in F344 rats exposed to 0.25% (2,500 ppm) sodium nitrite in drinking water for

2 years. The reduced body weights were probably related to lower water consumption as in the 14-week studies.

Exposure to 3,000 ppm sodium nitrite for 2 years induced hyperplasia of the forestomach epithelium in male and female rats. The results agree with Maekawa *et al*. (1982) who reported no increased neoplasm incidences in F344 rats given 0.25% (2,500 ppm) sodium nitrite for 2 years, and Garcia and Lijinsky (1973) reported no tumor induction in MRC Wistar rats exposed to 2 g/L (2,000 ppm) sodium nitrite in drinking water for 2 years. In contrast, Mirvish *et al*. (1980) reported that MRC Wistar rats exposed to 3.0 g/L (3,000 ppm) sodium nitrite in drinking water for life developed squamous papillomas of the forestomach, and Lijinsky *et al*. (1983) reported induction of hepatocellular neoplasms in female F344 rats exposed to 2,000 ppm in drinking water for 104 weeks and sacrificed at 127 to 130 weeks. It should be noted that the animals in the latter studies were kept longer than 2 years. In a multi-organ carcinogenesis model, male F344 rats pretreated with carcinogens and then given 0.3% (3,000 ppm) sodium nitrite in drinking water until week 28 exhibited an increased incidence of neoplasms in the forestomach (Hirose *et al.,* 1993). The authors concluded that sodium nitrite promoted the development of forestomach neoplasms. Together, the data appear to indicate that sodium nitrite is a weak carcinogen, requiring more than a 2-year exposure period to express fully its carcinogenic activity in rats.

There was a significant increase in the incidence of fibroadenomas in the mammary gland of female rats exposed to 1,500 ppm sodium nitrite for 2 years. However, no increase occurred in the 3,000 ppm group and no concomitant increase in the incidences of adenomas or carcinomas was observed. Given the high background incidence (concurrent and historical control incidences) of fibroadenomas, the incidence in the 1,500 ppm group was not considered treatment related.

Maekawa *et al.* (1982) reported that F344 rats administered 0.125% (1,250 ppm) or 0.25% (2,500 ppm) sodium nitrite in drinking water for 2 years had lower incidences of mononuclear cell leukemia than the controls. The authors attributed the reduced incidences of mononuclear cell leukemia to a slight atrophy of the hematopoietic organs. Lijinsky *et al*. (1983) also reported a reduction in the incidences of mononuclear cell leukemia in F344 rats exposed to 2,000 ppm sodium nitrite in drinking water. Dietary administration of sodium nitrite at 0.2% (2,000 ppm) or 0.5% (5,000 ppm) to male F344 rats also induced exposure-related decreases in the incidences and lengthened the time of onset of lymphomas, leukemias, and testicular interstitial cell tumors (Grant and Butler, 1989). Body weights of rats exposed to sodium nitrite were also lower than those of the controls. Elwell *et al*. (1996) cited splenic toxicity, methemoglobinemia, and Heinz body formation as factors that may be related to the reduced incidences of mononuclear cell leukemia in F344 rats. The present studies showed significant increases in methemoglobin concentrations (14-week studies) and decreased incidences of mononuclear cell leukemia (2-year studies) in male and female rats exposed to 1,500 or 3,000 ppm sodium nitrite; toxic injury or atrophy of the spleen was not detected. Microscopic examination at 14 weeks showed treatment-related hematopoietic activity in the bone marrow of male and female rats. The increased methemoglobin concentrations and lower body weights of the exposed rats may be factors in the reduced incidences of mononuclear cell leukemia.

Exposure to 3,000 ppm sodium nitrite for 2 years was associated with a positive trend in the incidences of squamous cell papilloma or carcinoma (combined) in the forestomach of female mice which may have been related to exposure to sodium nitrite. The 10% incidence of squamous cell papilloma or carcinoma (combined) in the 3,000 ppm group fell outside the upper end of the historical range of 4% for forestomach neoplasms. In addition, the finding of two squamous cell carcinomas in the 3,000 ppm group was supportive of a chemical-related effect because forestomach carcinomas are rarely observed in controls in drinking water studies. In NTP drinking water studies, no forestomach carcinomas were seen in 340 female mice given NIH-07 diet; forestomach carcinoma was observed in 1 of 250 control females given NTP-2000 diet. Although increased incidences of forestomach neoplasms were not observed in exposed rats or male mice, the forestomach was clearly a target organ because hyperplasia was observed in both rats and mice in the 14-week studies and in rats in the 2-year study. Interestingly, although forestomach hyperplasia was not observed in male mice in the 2-year study, hyper-plasia of the glandular epithelium of the stomach was seen in 3,000 ppm males. In contrast, Inai *et al*. (1979) reported no increase in the incidence of forestomach

tumors in ICR mice exposed to sodium nitrite at up to 0.5% (5,000 ppm) in drinking water for 109 weeks.

Genotoxic carcinogens such as methylnitrosourea and 7,12-dimethylbenz[a]anthracene reportedly interact directly with DNA in forestomach carcinogenesis (Kroes and Wester, 1986; Doi *et al*., 1994; Masui *et al*., 1997). Cytotoxicity and sustained cell proliferation have been suggested to play a role in the induction of forestomach neoplasms by nongenotoxic carcinogens such as butylated hydroxyanisole and ethyl acrylate (Ghanayem *et al*., 1986; Clayson *et al.*, 1991; Ito *et al*., 1993; Benford *et al.*, 1994). Sodium nitrite is mutagenic in *Salmonella* assays, but evidence of cytotoxicity (necrosis or inflammation) of the forestomach at earlier time points in this study was not observed. The mechanism of action of sodium nitrite in the development of forestomach neoplasms in 3,000 ppm mice is unclear and needs to be investigated further.

Mirvish (1995) reported that ingested sodium nitrite is converted to nitrous acid (HNO_2) by gastric acid, which dimerizes (with loss of water) to give dinitrogentrioxide (N_2O_3). This intermediate reacts with secondary amines and amides, producing carcinogenic *N*-nitroso compounds. The rate-limiting factor for nitrosation is the concentration of secondary amines or amides (Greenblatt and Mirvish, 1973). The NTP-2000 diet contains about 13.8% protein by weight, of which 4% is fish meal. Previously, NTP studies used NIH-07 diet containing 22.8% protein by weight, of which 10% was fish meal. It should be noted that fish meal is reported to contain high amounts of amines (Singer and Lijinsky, 1976; Groenen *et al.*, 1982). No *N*-nitrosocompounds were detected in the stomach contents in the present studies. The lower protein and fish meal content in the NTP-2000 diet may have limited the production of the carcinogenic *N*-nitroso compounds in the stomach. The assumption was supported by Furukawa *et al*. (2000), who reported increased renal carcinogenicity in F344 rats given a diet containing 32% and 64% fish meal together with 0.12% sodium nitrite in drinking water. No increased carcinogenicity was found in rats fed 8% fish meal and 0.12% sodium nitrite in drinking water. Mirvish (1975) estimated that the intragastric nitrosation rate is proportional to the square of the nitrite concentration. Accordingly, doubling the nitrite concentration in drinking water, as in the present studies (750, 1,500 and 3,000 ppm), should not lead to a dramatic increase in nitrosation. In addition, because *in vivo* nitrosation can be inhibited by vitamins C and E (Tannenbaum, 1988; Hecht, 1997), the roles of these vitamins in the rodent bioassay system are not known.

Sodium nitrite was mutagenic in *Salmonella typhimurium* strain TA100, with and without Aroclor 1254-induced hamster and rat liver S9 enzymes; no mutagenicity was observed in strain TA98. The results of acute bone marrow micronucleus tests in male rats and mice with sodium nitrite administered by intraperitoneal injection were negative. In addition, a peripheral blood micronucleus assay conducted using mice from the 14-week study gave negative results.

CONCLUSIONS

Under the conditions of this 2-year drinking water study, there was *no evidence of carcinogenic activity** of sodium nitrite in male or female F344/N rats exposed to 750, 1,500, or 3,000 ppm. There was *no*

evidence of carcinogenic activity of sodium nitrite in male B6C3F$_1$ mice exposed to 750, 1,500, or 3,000 ppm. There was *equivocal evidence of carcinogenic activity* of sodium nitrite in female B6C3F$_1$ mice based on the positive trend in the incidences of squamous cell papilloma or carcinoma (combined) of the forestomach.

Exposure to sodium nitrite in drinking water resulted in increased incidences of epithelial hyperplasia in the forestomach of male and female rats and in the glandular stomach of male mice.

Decreased incidences of mononuclear cell leukemia occurred in male and female rats.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report is on page 13.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF SODIUM NITRITE

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TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite[a]

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	16	4	12	8
Natural deaths	5	8	2	6
Survivors				
Died last week of study		1		
Terminal sacrifice	29	37	36	36
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Intestine large, colon	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)		
Leiomyosarcoma				1 (2%)
Schwannoma malignant, metastatic, heart	1 (2%)			
Intestine large, cecum	(50)	(50)	(50)	(49)
Intestine small, duodenum	(49)	(50)	(50)	(50)
Intestine small, jejunum	(50)	(48)	(50)	(49)
Intestine small, ileum	(50)	(49)	(50)	(49)
Liver	(50)	(50)	(50)	(50)
Hepatocellular adenoma			1 (2%)	
Histiocytic sarcoma		1 (2%)		1 (2%)
Leiomyosarcoma, metastatic, intestine large, colon				1 (2%)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Schwannoma malignant, metastatic, heart	1 (2%)			
Mesentery	(11)	(7)	(5)	(8)
Fat, leiomyosarcoma, metastatic, intestine large, colon				1 (13%)
Fat, sarcoma		1 (14%)		
Oral mucosa	(2)		(1)	
Pharyngeal, squamous cell carcinoma			1 (100%)	
Pancreas	(50)	(50)	(50)	(49)
Leiomyosarcoma, metastatic, intestine large, colon				1 (2%)
Acinus, adenocarcinoma		2 (4%)		
Acinus, adenoma			1 (2%)	
Acinus, carcinoma		1 (2%)		
Stomach, forestomach	(50)	(50)	(50)	(50)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Squamous cell papilloma	1 (2%)		1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Carcinoid tumor benign			1 (2%)	
Leiomyosarcoma	1 (2%)			
Sarcoma, metastatic, uncertain primary site				1 (2%)
Schwannoma malignant, metastatic, heart	1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Heart	(50)	(50)	(50)	(50)
Schwannoma malignant	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma			1 (2%)	
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant	1 (2%)	1 (2%)		1 (2%)
Pheochromocytoma benign	5 (10%)	10 (20%)	6 (12%)	9 (18%)
Bilateral, pheochromocytoma benign	1 (2%)			1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Adenoma	4 (8%)			1 (2%)
Carcinoma	1 (2%)			2 (4%)
Parathyroid gland	(45)	(48)	(49)	(48)
Adenoma			1 (2%)	
Pituitary gland	(50)	(49)	(50)	(50)
Sarcoma NOS				1 (2%)
Pars distalis, adenoma	13 (26%)	13 (27%)	15 (30%)	10 (20%)
Pars intermedia, adenoma				1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, adenoma	12 (24%)	8 (16%)	7 (14%)	4 (8%)
C-cell, adenoma, multiple				1 (2%)
C-cell, carcinoma	2 (4%)		2 (4%)	1 (2%)
Follicular cell, adenoma	1 (2%)		1 (2%)	1 (2%)
Follicular cell, carcinoma	1 (2%)			
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)	(50)
Adenoma		3 (6%)	1 (2%)	2 (4%)
Carcinoma	5 (10%)	1 (2%)	7 (14%)	5 (10%)
Prostate	(50)	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)	(49)
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	37 (74%)	44 (88%)	38 (76%)	40 (80%)
Interstitial cell, adenoma	10 (20%)	2 (4%)	9 (18%)	6 (12%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Hematopoietic System (continued)				
Lymph node	(5)	(4)	(4)	(2)
Carcinoma, metastatic, thyroid gland	1 (20%)			
Deep cervical, histiocytic sarcoma		1 (25%)		
Pancreatic, sarcoma, metastatic, uncertain primary site				1 (50%)
Lymph node, mandibular	(48)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Spleen	(50)	(50)	(50)	(50)
Fibroma				1 (2%)
Fibrosarcoma		1 (2%)		
Histiocytic sarcoma				1 (2%)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Thymus	(50)	(49)	(49)	(48)
Histiocytic sarcoma		1 (2%)		
Integumentary System				
Mammary gland	(45)	(47)	(47)	(47)
Carcinoma			1 (2%)	
Fibroadenoma	3 (7%)	5 (11%)	2 (4%)	
Fibroadenoma, multiple			1 (2%)	
Skin	(49)	(50)	(50)	(50)
Basal cell adenoma		1 (2%)		
Basal cell carcinoma	1 (2%)			
Fibroma		1 (2%)	5 (10%)	3 (6%)
Fibroma, multiple			1 (2%)	
Fibrosarcoma	1 (2%)			2 (4%)
Keratoacanthoma	2 (4%)	3 (6%)	4 (8%)	3 (6%)
Keratoacanthoma, multiple				1 (2%)
Lipoma	1 (2%)			
Sarcoma			1 (2%)	
Squamous cell carcinoma		1 (2%)		
Trichoepithelioma		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma				1 (2%)
Maxilla, osteosarcoma	1 (2%)			
Skeletal muscle	(1)			(1)
Sarcoma, metastatic, uncertain primary site				1 (100%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma			1 (2%)	
Carcinoma, metastatic, thyroid gland	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Leiomyosarcoma, metastatic, intestine large, colon				1 (2%)
Schwannoma malignant, metastatic, heart	1 (2%)			
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
Harderian gland		(2)		
Histiocytic sarcoma		1 (50%)		
Zymbal's gland	(1)			(2)
Carcinoma	1 (100%)			2 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Renal tubule, adenoma			1 (2%)	
Urinary bladder	(49)	(50)	(50)	(50)
Transitional epithelium, papilloma	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		1 (2%)
Leukemia mononuclear	17 (34%)	12 (24%)	7 (14%)	3 (6%)
Lymphoma malignant		1 (2%)		
Mesothelioma malignant	3 (6%)	3 (6%)	4 (8%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	49	49	50	50
Total primary neoplasms	129	120	123	107
Total animals with benign neoplasms	47	48	49	49
Total benign neoplasms	93	94	99	86
Total animals with malignant neoplasms	30	22	21	20
Total malignant neoplasms	36	26	24	21
Total animals with metastatic neoplasms	2			2
Total metastatic neoplasms	6			11
Total animals with malignant neoplasms of uncertain primary site				1

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	2 5 2	4 0 0	4 8 6	4 8 9	5 2 3	5 2 9	5 5 8	5 7 3	5 8 9	5 8 9	6 0 5	6 1 0	6 2 0	6 2 4	6 3 1	6 3 6	6 4 8	6 6 6	6 8 0	6 8 3	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 3 4	0 1 5	0 0 8	0 3 2	0 1 8	0 1 0	0 4 1	0 4 0	0 0 4	0 2 0	0 0 5	0 2 1	0 4 4	0 4 5	0 3 5	0 1 3	0 0 6	0 2 6	0 1 6	0 4 3	0 1 4	0 1 3	0 1 2	0 1 7	0 1 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestinal arge, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, heart				X																					
Intestinal arge, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestinos malli, leum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastic, heart				X																					
Mesentery			+				+									+	+	+							
Oral mucosa															+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary, lands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma											X														
Schwannoma malignant, metastatic, heart				X																					
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant				X																					
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign													X												
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Carcinoma																									
Parathyroid gland	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X						X			X						X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X				X							X	
C-cell, carcinoma																						X			
Follicular cell, adenoma																			X						
Follicular cell, carcinoma																				X					
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma		X			X																				

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	00330	00338	00442	00447	00501	00507	00509	00511	00522	00523	00524	00527	00529	00539	00546	00548	00549	00550	00502	00528	00531	00533	00536	00537	00545	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestinal large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, heart																										1
Intestinal large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastic, heart																										1
Mesentery	+	+				+												+					+	+		11
Oral mucosa						+																				2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma								X																		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										
Schwannoma malignant, metastatic, heart																										
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																						X				1
Pheochromocytoma benign		X								X					X					X						5
Bilateral, pheochromocytoma benign												X														1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X						X				X					4
Carcinoma																						X				1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma					X		X	X					X	X	X	X		X				X				13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X	X							X	X	X							X	X			X			X	12
C-cell, carcinoma													X													2
Follicular cell, adenoma																										1
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma						X						X						X								5

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	2 5 2	4 0 0	4 8 6	4 8 9	5 2 3	5 2 9	5 5 8	5 7 3	5 8 9	5 8 9	6 0 5	6 1 0	6 2 0	6 2 4	6 3 1	6 3 6	6 4 8	6 6 6	6 8 0	6 8 3	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 3 4	0 1 5	0 0 8	0 3 2	0 1 8	0 1 0	0 1 4	0 4 0	0 4 0	0 2 0	0 0 5	0 2 1	0 4 4	0 2 5	0 3 5	0 1 3	0 0 6	0 2 6	0 1 6	0 4 3	0 1 4	0 1 0	0 1 2	0 1 7	0 1 9
Genital System (continued)																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			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						+					+			+				+		+					
Carcinoma, metastatic, thyroid gland																				X					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Fibroadenoma									X				X												
Skin	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																				X					
Fibrosarcoma																									
Keratoacanthoma			X																						
Lipoma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Maxilla, osteosarcoma																									
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Carcinoma, metastatic, thyroid gland																				X					
Schwannoma malignant, metastatic, heart				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland												+													
Carcinoma												X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma															X										
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			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 Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	00330	00338	00442	00447	00501	00507	00509	00511	00522	00523	00524	00527	00529	00539	00546	00548	00549	00550	00602	00628	00631	00633	00636	00637	00645	Total Tissues/ Tumors
Genital System (continued)																										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	37
Interstitial cell, adenoma				X														X		X						10
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										5
Carcinoma, metastatic, thyroid gland																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Fibroadenoma															X											3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell carcinoma																										1
Fibrosarcoma					X																					1
Keratoacanthoma											X															2
Lipoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Maxilla, osteosarcoma						X																				1
Skeletal muscle																	+									1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																		X								2
Carcinoma, metastatic, thyroid gland																										1
Schwannoma malignant, metastatic, heart																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X				X			X			X	X	X				X							17
Mesothelioma malignant			X														X									3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

Number of Days on Study	4 1 5	4 8 0	4 8 1	5 5 2	5 8 2	6 0 1	6 4 1	6 4 6	6 6 9	6 8 0	6 9 1	6 9 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 5 9	0 6 2	0 5 5	0 7 1	0 6 6	0 8 5	0 6 0	0 6 9	0 6 9	0 8 7	0 5 1	0 6 5	0 5 3	0 5 4	0 5 6	0 5 8	0 6 7	0 6 8	0 7 0	0 7 2	0 7 3	0 7 4	0 7 7	0 7 8	0 8 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestinal argec olon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																				X					
Intestinal argec ectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestinos malli leum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Mesentery							+					+				+		+						+	
Fat, sarcoma																								X	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenocarcinoma									X																
Acinus, carcinoma																									
Salivarg lands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomachf orestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant			X																						
Pheochromocytoma benign			X							X	X		X		X						X	X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pars distalis, adenoma			X					X			X		X			X	X								X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma														X							X				
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																					X				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma						X																			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

Number of Days on Study	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	08 83	08 84	08 88	09 91	09 97	10 00	05 57	06 03	06 64	07 76	07 79	08 81	08 82	08 86	09 02	09 04	09 06	09 08	05 52	06 11	07 15	08 89	09 00	09 03	09 05	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestinal arge, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestinal arge, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestinal malli leum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Mesentery															+								+			7
Fat, sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenocarcinoma																									X	2
Acinus, carcinoma																									X	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign		X							X	X																10
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X			X				X									X				X			13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X	X			X							X	X			X						8
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X					X													X							3
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	44
Interstitial cell, adenoma			X																							2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

Number of Days on Study	4 1 5	4 8 0	4 8 1	5 5 2	5 8 2	6 0 1	6 4 1	6 4 6	6 6 9	6 8 0	6 9 1	6 9 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 5 9	0 6 2	0 5 5	0 7 1	0 6 6	0 8 5	0 6 0	0 6 9	0 9 9	0 8 7	0 5 1	0 6 5	0 5 3	0 5 4	0 5 6	0 5 8	0 6 7	0 6 8	0 7 0	0 7 2	0 7 3	0 7 4	0 7 7	0 7 8	0 8 0
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+		+		+											+		
Deep cervical, histiocytic sarcoma										X															
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Integumentary System																									
Mammary gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Fibroma																				X					
Keratoacanthoma										X															X
Squamous cell carcinoma		X																							
Trichoepithelioma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Histiocytic sarcoma										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+																								
Harderian gland										+															
Histiocytic sarcoma										X															
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Leukemia mononuclear				X		X		X	X			X							X				X		
Lymphoma malignant																	X								
Mesothelioma malignant							X														X				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

Number of Days on Study	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	08833	08844	08881	08991	09907	10100	10575	10633	10644	10766	10799	10811	10822	10866	10922	10944	10966	10982	11052	11061	11075	11089	11090	11093	11095	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										4
Deep cervical, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma		X																								1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibroadenoma		X					X		X		X								X							5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma													X													1
Fibroma																										1
Keratoacanthoma										X																3
Squamous cell carcinoma																										1
Trichoepithelioma																X										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X											X		X						3
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland									+																	2
Histiocytic sarcoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear						X			X		X		X					X								12
Lymphoma malignant																										1
Mesothelioma malignant											X															3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	4 0 0	5 0 5	5 5 1	5 8 2	5 9 3	6 2 0	6 8 0	6 9 4	6 9 5	6 9 7	7 0 8	7 1 6	7 1 4	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 3 7	1 2 6	1 2 4	1 0 8	1 2 3	1 4 4	1 5 0	1 4 3	1 1 7	1 0 2	1 0 5	1 4 0	1 1 4	1 3 6	1 0 7	1 0 9	1 1 1	1 1 2	1 1 3	1 1 5	1 1 8	1 1 9	1 2 2	1 2 9	1 3 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma															X										
Mesentery												+								+					
Oral mucosa					+																				
Pharyngeal, squamous cell carcinoma					X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																X									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoid tumor benign																								X	
Tongue																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign													X	X							X		X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X													X	X		X			X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X		X							X					
C-cell, carcinoma				X																					
Follicular cell, adenoma																X									
General Body System																									
Peritoneum																								+	
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Carcinoma													X	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
Interstitial cell, adenoma		X		X								X		X	X			X	X						

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	13303	14407	10401	10404	11010	12020	12505	12808	13030	13232	13434	13505	14101	14505	14606	14808	14909	10303	10606	11616	12121	12727	13838	13939	14042	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery								+		+											+					5
Oral mucosa																										1
Pharyngeal, squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma						X																				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoid tumor benign																										1
Tongue												+														1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign		X																					X			6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X		X	X											X	X	X		X				15
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X					X									X						X	7
C-cell, carcinoma																					X					2
Follicular cell, adenoma																										1
General Body System																										
Peritoneum																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma			X							X		X								X						7
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		38
Interstitial cell, adenoma		X																							X	9

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	4 0 0	5 0 5	5 5 1	5 8 2	5 9 3	6 2 0	6 8 0	6 9 4	6 9 5	6 9 7	7 0 8	7 1 6	7 2 4	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 3 7	1 2 6	1 2 4	1 0 8	1 2 3	1 4 4	1 5 0	1 4 3	1 1 7	1 0 2	1 0 5	1 4 0	1 1 4	1 3 6	1 0 7	1 0 9	1 1 1	1 1 2	1 1 3	1 1 5	1 1 8	1 1 9	1 2 2	1 2 9	1 3 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+	+		+																
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma											X				X										
Fibroadenoma, multiple																X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma								X				X													
Fibroma, multiple										X															
Keratoacanthoma																			X					X	
Sarcoma	X																								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X													
Alveolar/bronchiolar carcinoma																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Mesothelioma malignant					X					X															

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	
Carcass ID Number	13 33	14 47	10 01	00 04	11 00	12 00	12 25	12 28	13 00	13 32	13 34	13 35	14 01	14 45	14 46	14 48	14 49	14 03	00 06	11 16	12 11	12 17	13 18	13 39	14 02	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																				+						4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma		X																								1
Fibroadenoma																										2
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma															X	X								X		5
Fibroma, multiple																										1
Keratoacanthoma																	X								X	4
Sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X											2
Alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										7
Mesothelioma malignant								X					X													4

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	520	523	551	589	605	622	636	638	655	697	698	705	710	715	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	193	151	178	159	181	180	177	167	166	161	175	197	164	179	154	155	157	162	165	174	176	182	183	185	195
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma														X											
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Leiomyosarcoma, metastatic, intestine large, colon														X											
Sarcoma, metastatic, uncertain primary site										X															
Mesentery					+						+	+		+						+					
Fat, leiomyosarcoma, metastatic, intestine large, colon														X											
Pancreas	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, intestine large, colon														X											
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site										X															
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site										X															
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign					X							X			X		X		X			X			
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Carcinoma							X																		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma NOS								X																	
Pars distalis, adenoma						X									X										X
Pars intermedia, adenoma																								X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X																	X	
C-cell, adenoma, multiple																									
C-cell, carcinoma												X													
Follicular cell, adenoma						X																			
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	
Carcass ID Number	19 96	19 98	19 99	20 00	15 02	15 56	15 58	16 00	16 03	16 68	16 69	17 00	17 01	17 02	17 03	18 84	18 87	19 01	19 04	15 53	18 86	18 88	18 89	19 00	19 02	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leiomyosarcoma, metastatic, intestine large, colon																										1
Sarcoma, metastatic, uncertain primary site																										1
Mesentery							+							+										+		8
Fat, leiomyosarcoma, metastatic, intestine large, colon																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma, metastatic, intestine large, colon																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, uncertain primary site																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, uncertain primary site																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant							X																			1
Pheochromocytoma benign	X													X											X	9
Bilateral, pheochromocytoma benign																								X		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Carcinoma					X																					2
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma NOS																										1
Pars distalis, adenoma		X			X							X	X	X					X					X		10
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma											X								X							4
C-cell, adenoma, multiple															X											1
C-cell, carcinoma																										1
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	520	523	551	589	605	622	636	638	655	697	698	705	710	715	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	193	151	178	189	181	180	777	676	666	661	775	797	764	779	754	755	757	762	765	774	776	782	783	785	795
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Carcinoma		X		X	X										X				X						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Lymph node										+				+											
Pancreatic, sarcoma, metastatic, uncertain primary site										X															
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site										X															
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma	X																								
Histiocytic sarcoma			X																						
Sarcoma, metastatic, uncertain primary site										X															
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma										X											X				
Fibrosarcoma	X															X									
Keratoacanthoma															X										
Keratoacanthoma, multiple																								X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Skeletal muscle										+															
Sarcoma, metastatic, uncertain primary site										X															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X																			
Leiomyosarcoma, metastatic, intestine large, colon														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	
Carcass ID Number	19 96	19 98	19 99	20 00	15 02	15 56	15 58	16 00	16 03	16 68	16 69	17 00	17 01	17 02	17 03	18 84	18 87	19 01	19 04	15 53	18 86	18 88	18 89	19 00	19 02	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														2
Carcinoma																										5
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X		X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	40
Interstitial cell, adenoma					X											X	X									6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node																										2
Pancreatic, sarcoma, metastatic, uncertain primary site																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, uncertain primary site																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																										1
Histiocytic sarcoma																										1
Sarcoma, metastatic, uncertain primary site																										1
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma		X																								3
Fibrosarcoma																										2
Keratoacanthoma																X					X					3
Keratoacanthoma, multiple																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																X										1
Skeletal muscle																										1
Sarcoma, metastatic, uncertain primary site																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X										2
Leiomyosarcoma, metastatic, intestine large, colon																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	520	523	551	589	605	622	636	638	655	697	698	705	710	715	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	193	151	178	159	181	180	177	167	166	161	175	197	164	179	154	155	157	162	165	174	176	182	183	185	195
Special Senses System																									
Eye																				+					
Zymbal's gland									+																
Carcinoma									X																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Leukemia mononuclear											X		X												
Mesothelioma malignant												X													

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	
Carcass ID Number	19696	19698	19699	20200	15252	15256	15258	16060	16063	16068	16069	17070	17071	17072	17073	18484	18487	19191	19494	15353	18586	18888	18989	19090	19092	Total Tissues/ Tumors
Special Senses System																											
Eye															+											2
Zymbal's gland										+																2
Carcinoma										X																2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear													X													3
Mesothelioma malignant																										1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a] 6/50 (12%)	10/50 (20%)	6/50 (12%)	10/50 (20%)	
Adjusted rate[b]	14.7%	21.7%	13.1%	21.7%
Terminal rate[c]	5/29 (21%)	7/38 (18%)	4/36 (11%)	8/36 (22%)
First incidence (days)	620	481	724	605
Poly-3 test[d]	P=0.336	P=0.287	P=0.535N	P=0.287
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	7/50 (14%)	10/50 (20%)	6/50 (12%)	11/50 (22%)
Adjusted rate	17.2%	21.7%	13.1%	23.9%
Terminal rate	6/29 (21%)	7/38 (18%)	4/36 (11%)	9/36 (25%)
First incidence (days)	620	481	724	605
Poly-3 test	P=0.314	P=0.397	P=0.408N	P=0.307
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted rate	5.0%	6.7%	4.4%	4.4%
Terminal rate	2/29 (7%)	3/38 (8%)	1/36 (3%)	1/36 (3%)
First incidence (days)	729 (T)	729 (T)	716	622
Poly-3 test	P=0.474N	P=0.549	P=0.647N	P=0.647N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	2/50 (4%)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted rate	5.0%	6.7%	6.5%	4.4%
Terminal rate	2/29 (7%)	3/38 (8%)	2/36 (6%)	1/36 (3%)
First incidence (days)	729 (T)	729 (T)	716	622
Poly-3 test	P=0.487N	P=0.549	P=0.559	P=0.647N
Mammary Gland: Fibroadenoma				
Overall rate	3/50 (6%)	5/50 (10%)	3/50 (6%)	0/50 (0%)
Adjusted rate	7.3%	11.1%	6.5%	0.0%
Terminal rate	1/29 (3%)	5/38 (13%)	2/36 (6%)	0/36 (0%)
First incidence (days)	589	729 (T)	708	—[e]
Poly-3 test	P=0.047N	P=0.405	P=0.611N	P=0.102N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	4/50 (8%)	0/50 (0%)
Adjusted rate	7.3%	11.1%	8.7%	0.0%
Terminal rate	1/29 (3%)	5/38 (13%)	3/36 (8%)	0/36 (0%)
First incidence (days)	589	729 (T)	708	—
Poly-3 test	P=0.058N	P=0.405	P=0.559	P=0.102N
Pancreatic Islets: Adenoma				
Overall rate	4/50 (8%)	0/50 (0%)	0/50 (0%)	1/49 (2%)
Adjusted rate	9.9%	0.0%	0.0%	2.2%
Terminal rate	4/29 (14%)	0/38 (0%)	0/36 (0%)	0/36 (0%)
First incidence (days)	729 (T)	—	—	638
Poly-3 test	P=0.135N	P=0.047N	P=0.045N	P=0.147N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	0/50 (0%)	0/50 (0%)	3/49 (6%)
Adjusted rate	12.4%	0.0%	0.0%	6.6%
Terminal rate	5/29 (17%)	0/38 (0%)	0/36 (0%)	1/36 (3%)
First incidence (days)	729 (T)	—	—	636
Poly-3 test	P=0.426N	P=0.022N	P=0.021N	P=0.295N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	13/50 (26%)	13/49 (27%)	15/50 (30%)	10/50 (20%)
Adjusted rate	31.5%	28.8%	31.5%	21.8%
Terminal rate	10/29 (35%)	10/37 (27%)	12/36 (33%)	9/36 (25%)
First incidence (days)	589	481	505	622
Poly-3 test	P=0.191N	P=0.488N	P=0.587	P=0.218N
Preputial Gland: Adenoma				
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rate	0.0%	6.7%	2.2%	4.4%
Terminal rate	0/29 (0%)	3/38 (8%)	0/36 (0%)	1/36 (3%)
First incidence (days)	—	729 (T)	697	698
Poly-3 test	P=0.397	P=0.139	P=0.526	P=0.265
Preputial Gland: Carcinoma				
Overall rate	5/50 (10%)	1/50 (2%)	7/50 (14%)	5/50 (10%)
Adjusted rate	12.0%	2.2%	15.3%	10.6%
Terminal rate	3/29 (10%)	1/38 (3%)	5/36 (14%)	2/36 (6%)
First incidence (days)	400	729 (T)	724	523
Poly-3 test	P=0.397	P=0.085N	P=0.446	P=0.555N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	4/50 (8%)	8/50 (16%)	7/50 (14%)
Adjusted rate	12.0%	8.9%	17.4%	14.9%
Terminal rate	3/29 (10%)	4/38 (11%)	5/36 (14%)	3/36 (8%)
First incidence (days)	400	729 (T)	697	523
Poly-3 test	P=0.301	P=0.455N	P=0.340	P=0.465
Skin: Keratoacanthoma				
Overall rate	2/50 (4%)	3/50 (6%)	4/50 (8%)	4/50 (8%)
Adjusted rate	4.9%	6.6%	8.7%	8.8%
Terminal rate	1/29 (3%)	2/38 (5%)	4/36 (11%)	4/36 (11%)
First incidence (days)	486	680	729 (T)	729 (T)
Poly-3 test	P=0.310	P=0.543	P=0.389	P=0.385
Skin: Keratoacanthoma or Squamous Cell Carcinoma				
Overall rate	2/50 (4%)	4/50 (8%)	4/50 (8%)	4/50 (8%)
Adjusted rate	4.9%	8.7%	8.7%	8.8%
Terminal rate	1/29 (3%)	2/38 (5%)	4/36 (11%)	4/36 (11%)
First incidence (days)	486	480	729 (T)	729 (T)
Poly-3 test	P=0.372	P=0.389	P=0.389	P=0.385

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Skin: Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma				
Overall rate	3/50 (6%)	6/50 (12%)	4/50 (8%)	4/50 (8%)
Adjusted rate	7.3%	13.1%	8.7%	8.8%
Terminal	1/29 (3%)	4/38 (11%)	4/36 (11%)	4/36 (11%)
First incidence (days)	486	480	729 (T)	729 (T)
Poly-3 test	P=0.525N	P=0.299	P=0.560	P=0.555
Skin: Fibroma				
Overall rate	0/50 (0%)	1/50 (2%)	6/50 (12%)	3/50 (6%)
Adjusted rate	0.0%	2.2%	13.0%	6.6%
Terminal	0/29 (0%)	1/38 (3%)	3/36 (8%)	2/36 (6%)
First incidence (days)	—	729 (T)	694	697
Poly-3 test	P=0.103	P=0.521	P=0.024	P=0.142
Skin: Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	1/50 (2%)	1/50 (2%)	7/50 (14%)	5/50 (10%)
Adjusted rate	2.5%	2.2%	14.9%	10.8%
Terminal	1/29 (3%)	1/38 (3%)	3/36 (8%)	3/36 (8%)
First incidence (days)	729 (T)	729 (T)	400	520
Poly-3 test	P=0.054	P=0.736N	P=0.050	P=0.136
Testes: Adenoma				
Overall rate	47/50 (94%)	46/50 (92%)	47/50 (94%)	46/50 (92%)
Adjusted rate	98.9%	96.3%	96.7%	95.1%
Terminal rate	29/29 (100%)	37/38 (97%)	35/36 (97%)	36/36 (100%)
First incidence (days)	486	552	505	520
Poly-3 test	P=0.200N	P=0.416N	P=0.478N	P=0.248N
Thyroid Gland (C-cell): Adenoma				
Overall rate	12/50 (24%)	8/50 (16%)	7/50 (14%)	5/50 (10%)
Adjusted rate	29.3%	17.8%	15.2%	10.9%
Terminal rate	10/29 (35%)	8/38 (21%)	5/36 (14%)	4/36 (11%)
First incidence (days)	620	729 (T)	708	636
Poly-3 test	P=0.028N	P=0.157N	P=0.092N	P=0.028N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	14/50 (28%)	8/50 (16%)	9/50 (18%)	6/50 (12%)
Adjusted rate	34.1%	17.8%	19.4%	13.1%
Terminal rate	12/29 (41%)	8/38 (21%)	6/36 (17%)	4/36 (11%)
First incidence (days)	620	729 (T)	582	636
Poly-3 test	P=0.027N	P=0.066N	P=0.091N	P=0.017N
All Organs: Mononuclear Cell Leukemia				
Overall rate	17/50 (34%)	12/50 (24%)	7/50 (14%)	3/50 (6%)
Adjusted rate	37.9%	25.7%	15.0%	6.6%
Terminal	7/29 (24%)	7/38 (18%)	1/36 (3%)	1/36 (3%)
First incidence (days)	486	552	620	698
Poly-3 test	P<0.001N	P=0.151N	P=0.010N	P<0.001N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
All Organs: Malignant Mesothelioma				
Overall rate	3/50 (6%)	3/50 (6%)	4/50 (8%)	1/50 (2%)
Adjusted rate	7.3%	6.6%	8.6%	2.2%
Terminal rate	2/29 (7%)	2/38 (5%)	2/36 (6%)	0/36 (0%)
First incidence (days)	558	641	593	705
Poly-3 test	P=0.211N	P=0.615N	P=0.569	P=0.267N
All Organs: Benign Neoplasms				
Overall rate	47/50 (94%)	48/50 (96%)	49/50 (98%)	49/50 (98%)
Adjusted rate	98.9%	99.0%	99.7%	99.1%
Terminal rate	29/29 (100%)	38/38 (100%)	36/36 (100%)	36/36 (100%)
First incidence (days)	486	481	505	520
Poly-3 test	P=0.775	P=0.973	P=0.951	P=0.946
All Organs: Malignant Neoplasms				
Overall rate	30/50 (60%)	22/50 (44%)	21/50 (42%)	20/50 (40%)
Adjusted rate	63.1%	45.3%	43.1%	40.6%
Terminal rate	14/29 (48%)	13/38 (34%)	10/36 (28%)	8/36 (22%)
First incidence (days)	400	480	400	520
Poly-3 test	P=0.029N	P=0.058N	P=0.036N	P=0.020N
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	49/50 (98%)	50/50 (100%)	50/50 (100%)
Adjusted rate	99.9%	99.6%	100.0%	100.0%
Terminal rate	29/29 (100%)	38/38 (100%)	36/36 (100%)	36/36 (100%)
First incidence (days)	400	480	400	520
Poly-3 test	P=0.998	P=1.000N	P=1.000	P=1.000

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

TABLE A4a
Historical Incidence of Skin Fibroma or Fibrosarcoma in Control Male F344/N Rats

Study	Incidence in Controls		
	Fibroma	Fibrosarcoma	Fibroma or Fibrosarcoma
Historical Incidence in Controls Given NTP-2000 Diet[a]			
p,p′-Dichlorodiphenyl sulfone (feed)	2/50	0/50	2/50
Indium phosphide (inhalation)	1/50	1/50	2/50
Methacrylonitrile (gavage)	3/50	0/50	3/50
Naphthalene (inhalation)	5/49	2/49	7/49
p-Nitrotoluene (feed)	1/50	0/50	1/50
Sodium nitrite (drinking water)	0/50	1/50	1/50
Overall Historical Incidence in Controls Given NTP-2000 Diet			
Total (%)	12/299 (4.0%)	4/299 (1.3%)	16/299 (5.4%)
Mean ± standard deviation	4.0% ± 3.7%	1.4% ± 1.7%	5.3% ± 4.5%
Range	0%-10%	0%-4%	2%-14%
Historical Incidence in Drinking Water Controls Given NIH-07 Diet at Battelle Columbus Laboratories[b]			
Sodium fluoride	0/80	1/80	1/80
Overall Historical Incidence in Drinking Water Controls Given NIH-07 Diet			
Total (%)	8/331 (2.4%)	5/331 (1.5%)	13/331 (3.9%)
Mean ± standard deviation	2.7% ± 3.5%	1.5% ± 1.5%	4.2% ± 2.9%
Range	0%-8%	0%-4%	1%-8%

[a] Data as of 15 March 2000
[b] Data as of 21 December 1999

TABLE A4b
Historical Incidence of Mononuclear Cell Leukemia in Control Male F344/N Rats

Study	Incidence in Controls
Historical Incidence in Controls Given NTP-2000 Diet[a]	
p,p′-Dichlorodiphenyl sulfone (feed)	27/50
Indium phosphide (inhalation)	16/50
Methacrylonitrile (gavage)	20/50
Naphthalene (inhalation)	26/49
p-Nitrotoluene (feed)	24/50
Sodium nitrite (drinking water)	17/50
Overall Historical Incidence in Controls Given NTP-2000 Diet	
Total (%)	130/299 (43.5%)
Mean ± standard deviation	43.5% ± 9.6%
Range	32%-54%
Historical Incidence in Drinking Water Controls Given NIH-07 Diet at Battelle Columbus Laboratories[b]	
Sodium fluoride	54/80
Overall Historical Incidence in Drinking Water Controls Given NIH-07 Diet	
Total (%)	205/331 (61.9%)
Mean ± standard deviation	61.4% ± 7.6%
Range	49%-70%

[a] Data as of 15 March 2000; includes data for lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemia
[b] Data as of 21 December 1999; includes data for lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemia

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite[a]

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	16	4	12	8
Natural deaths	5	8	2	6
Survivors				
Died last week of study		1		
Terminal sacrifice	29	37	36	36
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, rectum	(50)	(50)	(50)	(50)
Parasite metazoan	5 (10%)	4 (8%)	3 (6%)	2 (4%)
Intestine large, cecum	(50)	(50)	(50)	(49)
Congestion	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Angiectasis		2 (4%)	3 (6%)	1 (2%)
Basophilic focus	31 (62%)	34 (68%)	37 (74%)	42 (84%)
Clear cell focus	19 (38%)	25 (50%)	26 (52%)	23 (46%)
Cyst				1 (2%)
Degeneration	1 (2%)			
Degeneration, cystic	5 (10%)	15 (30%)	12 (24%)	4 (8%)
Eosinophilic focus	4 (8%)	10 (20%)	11 (22%)	6 (12%)
Fibrosis	2 (4%)			
Hemorrhage	1 (2%)	1 (2%)		
Hepatodiaphragmatic nodule	11 (22%)	6 (12%)	4 (8%)	8 (16%)
Inflammation, chronic active	13 (26%)	19 (38%)	25 (50%)	24 (48%)
Mixed cell focus	7 (14%)	7 (14%)	4 (8%)	2 (4%)
Necrosis	5 (10%)	2 (4%)	1 (2%)	4 (8%)
Regeneration	1 (2%)	1 (2%)		1 (2%)
Vacuolization cytoplasmic	8 (16%)	5 (10%)	4 (8%)	1 (2%)
Bile duct, hyperplasia	41 (82%)	38 (76%)	43 (86%)	38 (76%)
Mesentery	(11)	(7)	(5)	(8)
Fat, inflammation, chronic active	8 (73%)	5 (71%)	5 (100%)	6 (75%)
Fat, mineralization	1 (9%)			
Fat, necrosis			1 (20%)	
Oral mucosa	(2)		(1)	
Pharyngeal, cyst	1 (50%)			
Pancreas	(50)	(50)	(50)	(49)
Atrophy		1 (2%)		
Inflammation, chronic active		1 (2%)		
Acinus, atrophy	16 (32%)	27 (54%)	22 (44%)	28 (57%)
Acinus, hyperplasia	4 (8%)	3 (6%)	6 (12%)	8 (16%)
Salivary glands	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		
Cyst		1 (2%)		
Inflammation, chronic active	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema	1 (2%)		1 (2%)	1 (2%)
Erosion	2 (4%)			
Hyperkeratosis		1 (2%)	4 (8%)	4 (8%)
Inflammation, chronic active	1 (2%)	1 (2%)		1 (2%)
Mineralization			1 (2%)	1 (2%)

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

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Alimentary System (continued)				
Ulcer	4 (8%)	1 (2%)	2 (4%)	1 (2%)
Epithelium, hyperplasia	12 (24%)	9 (18%)	10 (20%)	44 (88%)
Stomach, glandular	(50)	(50)	(50)	(50)
Erosion	1 (2%)		3 (6%)	1 (2%)
Thrombosis	1 (2%)			
Ulcer	2 (4%)	1 (2%)	1 (2%)	
Epithelium, hyperplasia				1 (2%)
Tongue			(1)	
Epithelium, hyperplasia			1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Inflammation, chronic active	9 (18%)	15 (30%)	16 (32%)	12 (24%)
Thrombosis	1 (2%)	1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule		1 (2%)		
Angiectasis	16 (32%)	21 (42%)	15 (30%)	22 (44%)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia	11 (22%)	15 (30%)	15 (30%)	10 (20%)
Hypertrophy	7 (14%)	7 (14%)	2 (4%)	9 (18%)
Necrosis		1 (2%)		
Vacuolization cytoplasmic	3 (6%)	3 (6%)	8 (16%)	3 (6%)
Bilateral, hyperplasia	1 (2%)			
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	11 (22%)	18 (36%)	16 (32%)	13 (26%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Hyperplasia		1 (2%)		1 (2%)
Pituitary gland	(50)	(49)	(50)	(50)
Angiectasis		1 (2%)		
Cyst		2 (4%)	1 (2%)	
Hemorrhage		1 (2%)		
Pigmentation, hemosiderin			1 (2%)	
Pars distalis, angiectasis		1 (2%)	1 (2%)	1 (2%)
Pars distalis, cyst	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Pars distalis, hyperplasia	9 (18%)	9 (18%)	18 (36%)	10 (20%)
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	11 (22%)	17 (34%)	16 (32%)	13 (26%)
Follicle, cyst		3 (6%)	1 (2%)	
General Body System				
Peritoneum			(1)	
Inflammation, chronic active			1 (100%)	
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Degeneration	1 (2%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Genital System (continued)				
Preputial gland	(50)	(50)	(50)	(50)
Cyst	3 (6%)	1 (2%)	1 (2%)	3 (6%)
Hyperplasia	1 (2%)	1 (2%)		1 (2%)
Inflammation, chronic active	8 (16%)	10 (20%)	6 (12%)	1 (2%)
Inflammation, suppurative				1 (2%)
Prostate	(50)	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)	
Seminal vesicle	(50)	(50)	(50)	(49)
Atrophy	34 (68%)	34 (68%)	36 (72%)	33 (67%)
Cyst			1 (2%)	
Testes	(50)	(50)	(50)	(50)
Degeneration	8 (16%)	12 (24%)	11 (22%)	11 (22%)
Mineralization	7 (14%)	1 (2%)	2 (4%)	2 (4%)
Interstitial cell, hyperplasia	9 (18%)	6 (12%)	9 (18%)	7 (14%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Atrophy				1 (2%)
Myelofibrosis	1 (2%)		3 (6%)	
Lymph node	(5)	(4)	(4)	(2)
Ectasia			1 (25%)	
Pancreatic, ectasia	1 (20%)			
Lymph node, mandibular	(48)	(50)	(50)	(50)
Congestion	1 (2%)			1 (2%)
Hyperplasia	1 (2%)		1 (2%)	2 (4%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Amyloid deposition				1 (2%)
Congestion		1 (2%)	1 (2%)	
Ectasia			1 (2%)	
Hyperplasia	1 (2%)			
Pigmentation, lipofuscin	1 (2%)	1 (2%)		
Spleen	(50)	(50)	(50)	(50)
Accessory spleen	1 (2%)		1 (2%)	
Congestion	2 (4%)	3 (6%)		
Fibrosis	2 (4%)	2 (4%)	3 (6%)	4 (8%)
Hematopoietic cell proliferation	5 (10%)		2 (4%)	1 (2%)
Hyperplasia	1 (2%)			
Hyperplasia, histiocytic		1 (2%)		
Inflammation, granulomatous		1 (2%)		
Necrosis	1 (2%)	1 (2%)		
Pigmentation, hemosiderin	1 (2%)		1 (2%)	1 (2%)
Capsule, fibrosis		1 (2%)		
Lymphoid follicle, depletion cellular		1 (2%)		
Thymus	(50)	(49)	(49)	(48)
Atrophy		1 (2%)	2 (4%)	
Integumentary System				
Mammary gland	(45)	(47)	(47)	(47)
Cyst		1 (2%)		
Galactocele		2 (4%)		1 (2%)
Hyperplasia	4 (9%)	6 (13%)	4 (9%)	3 (6%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Integumentary System (continued)				
Skin	(49)	(50)	(50)	(50)
Acanthosis			1 (2%)	
Hyperkeratosis		1 (2%)	1 (2%)	
Hyperplasia, basal cell	1 (2%)			
Inflammation, chronic active				1 (2%)
Mineralization				1 (2%)
Epidermis, cyst	1 (2%)			
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)	1 (2%)	
Hydrocephalus		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion			1 (2%)	2 (4%)
Hemorrhage				1 (2%)
Inflammation, chronic active	18 (36%)	7 (14%)	11 (22%)	11 (22%)
Metaplasia, osseous		1 (2%)		
Necrosis			1 (2%)	
Parasite metazoan		1 (2%)		
Alveolar epithelium, hyperplasia	11 (22%)	11 (22%)	20 (40%)	14 (28%)
Bronchiole, epithelium, hyperplasia				1 (2%)
Bronchus, inflammation, suppurative	1 (2%)			
Interstitium, fibrosis			1 (2%)	1 (2%)
Nose	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)	1 (2%)		
Inflammation, granulomatous		1 (2%)		
Inflammation, suppurative		1 (2%)		1 (2%)
Special Senses System				
Eye		(1)	(1)	(2)
Hemorrhage			1 (100%)	
Lens capsule, mineralization				1 (50%)
Retina, degeneration				2 (100%)
Retrobulbar, inflammation, chronic active			1 (100%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Congestion				1 (2%)
Crystals				1 (2%)
Cyst			2 (4%)	4 (8%)
Infarct	1 (2%)			
Mineralization	1 (2%)		1 (2%)	
Nephropathy	42 (84%)	45 (90%)	47 (94%)	47 (94%)
Pigmentation	1 (2%)	1 (2%)		
Renal tubule, degeneration				1 (2%)
Renal tubule, necrosis	1 (2%)			
Urinary bladder	(49)	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)	6 (12%)	1 (2%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF SODIUM NITRITE

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TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite[a]

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	6	10	15
Natural deaths	6	13	4	2
Survivors				
Terminal sacrifice	33	31	36	33
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, rectum	(50)	(50)	(50)	(50)
Fibroma			1 (2%)	
Intestine small, jejunum	(50)	(44)	(49)	(50)
Leiomyoma			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Oral mucosa	(1)	(1)		
Squamous cell carcinoma	1 (100%)	1 (100%)		
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma				1 (2%)
Tongue		(2)	(1)	
Squamous cell carcinoma		1 (50%)	1 (100%)	
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Heart	(50)	(49)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Carcinoma		1 (2%)		1 (2%)
Adrenal medulla	(50)	(50)	(45)	(49)
Pheochromocytoma benign	4 (8%)	2 (4%)		2 (4%)
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	24 (48%)	25 (50%)	17 (34%)	21 (42%)
Thyroid gland	(50)	(49)	(48)	(50)
Bilateral, C-cell, adenoma				1 (2%)
C-cell, adenoma	7 (14%)	4 (8%)	10 (21%)	6 (12%)
C-cell, carcinoma	2 (4%)			1 (2%)
Follicular cell, adenoma	1 (2%)			
Follicular cell, carcinoma	1 (2%)		1 (2%)	1 (2%)
General Body System				
None				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Genital System				
Clitoral gland	(46)	(48)	(49)	(49)
Adenoma	8 (17%)	8 (17%)	5 (10%)	3 (6%)
Carcinoma	2 (4%)	1 (2%)		1 (2%)
Bilateral, adenoma		2 (4%)	1 (2%)	
Ovary	(50)	(49)	(50)	(50)
Granulosa cell tumor benign		1 (2%)		
Schwannoma malignant			1 (2%)	
Sertoli cell tumor malignant			1 (2%)	
Uterus	(50)	(50)	(50)	(50)
Adenocarcinoma	2 (4%)			
Adenoma		1 (2%)		
Polyp stromal	7 (14%)	3 (6%)	8 (16%)	7 (14%)
Sarcoma stromal			1 (2%)	
Cervix, carcinoma		1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(2)	(1)	(2)	(1)
Carcinoma, metastatic, lung			1 (50%)	
Mediastinal, carcinoma, metastatic, adrenal cortex		1 (100%)		
Lymph node, mandibular	(49)	(49)	(50)	(50)
Carcinoma, metastatic, Zymbal's gland				1 (2%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Spleen	(50)	(50)	(50)	(50)
Thymus	(49)	(47)	(49)	(48)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)		3 (6%)
Adenoma, multiple	1 (2%)			
Carcinoma	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Fibroadenoma	14 (28%)	14 (28%)	18 (36%)	20 (40%)
Fibroadenoma, multiple	7 (14%)	13 (26%)	13 (26%)	5 (10%)
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma				1 (2%)
Basal cell carcinoma	1 (2%)			1 (2%)
Fibroma	1 (2%)		1 (2%)	1 (2%)
Fibrosarcoma				1 (2%)
Hemangiopericytoma	1 (2%)			
Lipoma			2 (4%)	
Squamous cell carcinoma	1 (2%)			1 (2%)
Trichoepithelioma	1 (2%)			
Pinna, melanoma malignant		1 (2%)		1 (2%)
Subcutaneous tissue, fibroma			1 (2%)	
Musculoskeletal System				
None				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)	
Spinal cord			(1)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	2 (4%)	3 (6%)	2 (4%)
Alveolar/bronchiolar carcinoma			1 (2%)	
Carcinoma, metastatic, adrenal cortex		1 (2%)		
Sarcoma			1 (2%)	
Nose	(50)	(49)	(50)	(50)
Squamous cell carcinoma, metastatic, skin				1 (2%)
Special Senses System				
Zymbal's gland			(2)	(2)
Carcinoma			1 (50%)	1 (50%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Nephroblastoma			1 (2%)	
Renal tubule, adenoma				1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	15 (30%)	10 (20%)	1 (2%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	45	45	49	45
Total primary neoplasms	107	94	95	87
Total animals with benign neoplasms	42	42	46	42
Total benign neoplasms	81	77	82	75
Total animals with malignant neoplasms	23	16	12	12
Total malignant neoplasms	26	17	13	12
Total animals with metastatic neoplasms		1	1	2
Total metastatic neoplasms		2	1	2

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	5 1 1	5 1 3	5 4 7	5 4 8	5 6 7	5 9 6	6 0 1	6 4 4	6 4 8	6 6 1	6 6 2	6 6 9	6 6 9	6 9 3	6 9 4	7 1 4	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1
Carcass ID Number	2 1 1	2 1 2	2 1 7	2 1 1	2 1 0	2 2 6	2 1 3	2 3 1	2 0 5	2 3 2	2 2 0	2 0 8	2 3 9	2 3 5	2 0 6	2 1 2	2 4 4	2 0 1	2 0 4	2 0 9	2 2 8	2 3 0	2 3 8	2 0 2	2 1 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestinal arge, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestinal arge, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestinal malli, leum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																	+			+		+			+
Oral mucosa											+														
Squamous cell carcinoma											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign													X												
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X						X	X	X		X	X			X	X		X		X	X	X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																			X						
C-cell, carcinoma																						X			
Follicular cell, adenoma																									
Follicular cell, carcinoma			X																						
General Body System																									
None																									
Genital System																									
Clitoral gland	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma					X																				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma				X																					
Polyp stromal																							X		

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	22 2	22 3	23 3	23 4	23 7	24 0	24 1	24 6	24 8	24 9	25 0	26 3	26 7	27 6	27 8	27 9	28 1	28 4	28 5	28 9	29 6	30 2	30 3	30 4	30 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestinal arge, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestinal arge, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestines malli, leum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery									+					+							+					7
Oral mucosa																										1
Squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary gl lands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular system																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign						X			X															X		4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X					X	X	X		X	X	X	X				X		X						24
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X							X	X				X	X									X	7
C-cell, carcinoma																			X							2
Follicular cell, adenoma																								X		1
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma	X		X		X			X										X	X		X		X			8
Carcinoma										X																2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma						X																				2
Polyp stromal										X		X		X				X						X	X	7

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	5 1 1	5 1 3	5 4 7	5 4 8	5 6 7	5 9 6	6 0 1	6 4 4	6 4 8	6 6 1	6 6 2	6 6 9	6 6 9	6 9 3	6 9 4	7 1 4	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1
Carcass ID Number	2 1 1	2 1 2	2 1 7	2 1 1	2 1 0	2 2 6	2 1 3	2 3 1	2 0 5	2 3 2	2 2 0	2 0 8	2 3 9	2 3 5	2 0 6	2 1 2	2 4 4	2 0 1	2 0 4	2 0 9	2 2 8	2 3 0	2 3 8	2 0 2	2 1 4
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+							+																
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adenoma, multiple																							X		
Carcinoma																									
Fibroadenoma			X					X			X	X			X									X	X
Fibroadenoma, multiple													X					X	X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma		X																							
Fibroma																	X								
Hemangiopericytoma	X																								
Squamous cell carcinoma													X												
Trichoepithelioma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X									X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X	X			X	X			X			X			X						X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	22 2	22 3	23 3	23 4	23 7	24 0	24 1	24 6	24 8	24 9	25 0	26 3	26 7	26 6	26 8	26 9	27 1	27 4	27 5	27 9	28 6	28 2	28 3	28 5	28 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Adenoma, multiple																										1
Carcinoma															X											1
Fibroadenoma											X					X		X	X	X		X			X	14
Fibroadenoma, multiple					X									X			X							X		7
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										1
Fibroma																										1
Hemangiopericytoma																										1
Squamous cell carcinoma																										1
Trichoepithelioma																		X								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																									X	3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X							X			X	X				X								X		15

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	25 6	26 7	27 0	27 7	28 0	28 1	28 6	28 8	29 8	30 0	25 1	25 8	26 0	26 2	26 3	26 8	27 1	27 3	27 4	27 6	28 2	28 4	29 1	29 4	29 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestinal arge, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestinal arge, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestinal malli, leum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+																		+				5
Oral mucosa																										1
Squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										2
Squamous cell carcinoma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																								X		2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X				X	X			X	X		X		X	X	X	X	X				X		25
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma							X		X																	4
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma	X			X	X											X			X				X			8
Carcinoma									X																	1
Bilateral, adenoma												X														2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Polyp stromal																										3
Cervix, carcinoma																				X						1
Vagina																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

Number of Days on Study	3 3 2	4 8 0	5 3 6	5 4 1	6 0 9	6 1 6	6 4 8	6 5 1	6 6 2	6 6 5	6 7 6	6 8 0	6 8 5	6 9 0	6 9 6	7 0 6	7 1 8	7 2 3	7 2 8	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1
Carcass ID Number	2 6 4	2 7 2	2 8 3	2 9 5	2 6 9	2 7 8	2 9 3	2 5 5	2 9 2	2 6 6	2 5 9	2 9 0	2 8 5	2 5 7	2 9 6	2 8 9	2 5 4	2 7 9	2 6 5	2 5 2	2 6 1	2 7 5	2 8 7	2 9 7	2 5 3
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+																						
Mediastinal, carcinoma, metastatic, adrenal cortex		X																						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X			
Carcinoma																								
Fibroadenoma				X			X	X		X				X	X		X						X	X
Fibroadenoma, multiple																X		X	X		X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pinna, melanoma malignant																						X		
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X												
Carcinoma, metastatic, adrenal cortex		X																						
Nose	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Special Senses System																								
Eye										+														
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X				X		X	X	X									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	25 6	26 7	27 0	27 7	28 0	28 1	28 6	28 8	29 8	30 0	25 1	25 8	26 0	26 2	26 3	26 8	27 1	27 3	27 4	27 6	28 2	28 4	29 1	29 4	29 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Mediastinal, carcinoma, metastatic, adrenal cortex																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																					X					1
Fibroadenoma					X		X			X														X	X	14
Fibroadenoma, multiple	X		X						X		X	X				X	X		X		X					13
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pinna, melanoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																			X							2
Carcinoma, metastatic, adrenal cortex																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X													X			X				X	10

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	337	341	411	554	596	624	626	638	658	668	687	696	723	727	730	730	730	730	730	731	731	731	731	731	731
Carcass ID Number	322	318	400	402	311	488	420	407	332	319	310	306	311	316	308	012	139	242	249	001	004	009	015	017	021
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery					+																	+		+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue									+																
Squamous cell carcinoma									X																
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X			X				X		X		X		X	X		X						X
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma									X	X				X	X					X					
Follicular cell, carcinoma													X												
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant											X														
Sertoli cell tumor malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal							X				X									X					X
Sarcoma stromal																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 2 4	3 2 5	3 2 9	3 3 0	3 3 5	3 3 7	3 3 8	3 4 3	3 4 4	3 4 6	3 0 3	3 0 5	3 1 3	3 1 4	3 1 6	3 2 3	3 2 6	3 2 7	3 2 8	3 3 3	3 3 4	4 1	4 4 5	4 4 7	3 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma											X															1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyoma															X											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery										+	+						+								+	7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell carcinoma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	M	45
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X					X									X	X						17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma												X	X	X	X										X	10
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Adenoma			X				X		X														X			5
Bilateral, adenoma				X																						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Sertoli cell tumor malignant								X																		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal		X												X		X		X								8
Sarcoma stromal												X														1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	337	341	411	545	596	624	626	638	658	668	687	696	723	727	730	730	730	730	730	731	731	731	731	731	731
Carcass ID Number	322	318	400	402	431	488	420	407	432	519	510	506	511	536	508	512	539	542	549	601	604	609	615	617	621
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+																	
Carcinoma, metastatic, lung																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma		X					X						X			X		X				X		X	
Fibroadenoma, multiple						X					X						X		X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Lipoma				X																					
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant	X																								
Peripheral nerve								+																	
Spinal cord								+																	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Alveolar/bronchiolar carcinoma																									
Sarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																					+				
Zymbal's gland			+		+																				
Carcinoma					X																				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nephroblastoma		X																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	32 4	32 5	32 9	33 0	33 5	33 7	33 8	34 3	34 4	34 6	00 3	00 5	01 3	01 4	01 6	02 3	02 6	02 7	02 8	03 3	03 4	04 1	04 5	04 7	05 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node													+													2
Carcinoma, metastatic, lung													X													1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma					X														X							2
Fibroadenoma		X									X			X	X		X	X		X	X		X	X	X	18
Fibroadenoma, multiple	X			X		X		X	X	X		X				X						X				13
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma					X																					1
Lipoma													X													2
Subcutaneous tissue, fibroma														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X												X								3
Alveolar/bronchiolar carcinoma													X													1
Sarcoma													X													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Zymbal's gland																										2
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nephroblastoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	361	465	474	513	624	626	627	629	658	680	680	694	704	715	718	723	723	730	730	730	730	730	730	730	730
Carcass ID Number	364	394	398	381	511	569	577	593	572	777	780	895	986	588	587	676	796	535	554	662	668	744	778	844	889
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																			+				+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma						X																			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Carcinoma										X															
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pheochromocytoma benign														X											
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X	X				X	X	X	X						X					X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma										X									X			X			X
C-cell, carcinoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X				X				X						
Carcinoma						X																			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal										X															

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	730	730	700	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	391	392	400	056	061	063	065	067	073	079	082	085	090	099	052	055	059	060	066	070	071	075	083	088	097	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery			+																						+	4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																				X						2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X				X	X	X				X		X		X		X		X	X	X		21
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma												X														1
C-cell, adenoma																X								X		6
C-cell, carcinoma																								X		1
Follicular cell, carcinoma															X											1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										3
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal						X								X			X	X				X			X	7

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	361	465	474	513	624	622	627	629	658	680	680	694	704	715	718	723	723	730	730	730	730	730	730	730	730
Carcass ID Number	364	394	398	381	511	569	577	593	572	777	780	895	866	558	587	676	796	553	554	662	668	674	678	784	889
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node										+															
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland			X																						
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma	X										X														
Fibroadenoma						X		X	X	X			X		X	X	X			X	X		X		X
Fibroadenoma, multiple														X										X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma					X																				
Basal cell carcinoma									X																
Fibroma														X											
Fibrosarcoma																									
Squamous cell carcinoma															X										
Pinna, melanoma malignant																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, skin															X										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye															+	+									
Harderian gland								+																	
Zymbal's gland			+					+																	
Carcinoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									X
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	730	730	730	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	391	392	400	456	461	463	465	467	473	479	482	485	490	499	525	555	559	600	666	700	711	775	783	788	897	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+		48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X					X						3
Carcinoma																										2
Fibroadenoma								X					X					X	X	X		X		X	X	20
Fibroadenoma, multiple			X								X	X														5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Basal cell carcinoma																										1
Fibroma																										1
Fibrosarcoma							X																			1
Squamous cell carcinoma																										1
Pinna, melanoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X																		2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastic, skin																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																			+							3
Harderian gland																										1
Zymbal's gland																										2
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X																	1

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a] 4/50 (8%)	2/50 (4%)	0/45 (0%)	2/49 (4%)	
Adjusted rate[b]	9.0%	4.5%	0.0%	4.6%
Terminal rate[c]	3/33 (9%)	2/31 (7%)	0/31 (0%)	1/32 (3%)
First incidence (days)	669	730 (T)	—[e]	715
Poly-3 test[d]	P=0.243N	P=0.339N	P=0.074N	P=0.346N
Clitoral Gland: Adenoma				
Overall rate	8/46 (17%)	10/48 (21%)	6/49 (12%)	3/49 (6%)
Adjusted rate	19.2%	23.5%	13.6%	6.7%
Terminal rate	8/32 (25%)	9/30 (30%)	6/35 (17%)	1/33 (3%)
First incidence (days)	730 (T)	680	730 (T)	680
Poly-3 test	P=0.029N	P=0.417	P=0.343N	P=0.077N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	10/46 (22%)	11/48 (23%)	6/49 (12%)	4/49 (8%)
Adjusted rate	23.7%	25.8%	13.6%	8.9%
Terminal rate	9/32 (28%)	10/30 (33%)	6/35 (17%)	1/33 (3%)
First incidence (days)	567	680	730 (T)	626
Poly-3 test	P=0.019N	P=0.511	P=0.177N	P=0.054N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	6.8%	4.5%	6.7%	4.5%
Terminal rate	2/33 (6%)	1/31 (3%)	3/36 (8%)	2/33 (6%)
First incidence (days)	693	680	730 (T)	730 (T)
Poly-3 test	P=0.455N	P=0.499N	P=0.656N	P=0.498N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	4/50 (8%)	2/50 (4%)
Adjusted rate	6.8%	4.5%	8.9%	4.5%
Terminal rate	2/33 (6%)	1/31 (3%)	4/36 (11%)	2/33 (6%)
First incidence (days)	693	680	730 (T)	730 (T)
Poly-3 test	P=0.477N	P=0.499N	P=0.508	0.498N
Mammary Gland: Fibroadenoma				
Overall rate	21/50 (42%)	27/50 (54%)	31/50 (62%)	25/50 (50%)
Adjusted rate	45.7%	58.5%	66.7%	54.4%
Terminal rate	15/33 (46%)	17/31 (55%)	26/36 (72%)	16/33 (49%)
First incidence (days)	547	541	541	626
Poly-3 test	P=0.268	P=0.149	P=0.029	P=0.263
Mammary Gland: Adenoma				
Overall rate	2/50 (4%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rate	4.5%	2.3%	0.0%	6.7%
Terminal rate	2/33 (6%)	1/31 (3%)	0/36 (0%)	3/33 (9%)
First incidence (days)	730 (T)	730 (T)	—	730 (T)
Poly-3 test	P=0.339	P=0.499N	P=0.233N	P=0.503

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	23/50 (46%)	27/50 (54%)	31/50 (62%)	28/50 (56%)
Adjusted rate	50.1%	58.5%	66.7%	61.0%
Terminal rate	17/33 (52%)	17/31 (55%)	26/36 (72%)	19/33 (58%)
First incidence (days)	547	541	541	626
Poly-3 test	P=0.169	P=0.270	P=0.073	P=0.196
Mammary Gland: Adenoma or Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	2/50 (4%)	5/50 (10%)
Adjusted rate	4.5%	4.5%	4.4%	11.0%
Terminal rate	2/33 (6%)	2/31 (7%)	2/36 (6%)	3/33 (9%)
First incidence (days)	730 (T)	730 (T)	730 (T)	361
Poly-3 test	P=0.121	P=0.694N	P=0.687N	P=0.228
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	23/50 (46%)	27/50 (54%)	33/50 (66%)	30/50 (60%)
Adjusted rate	50.1%	58.5%	71.0%	63.8%
Terminal rate	17/33 (52%)	17/31 (55%)	28/36 (78%)	19/33 (58%)
First incidence (days)	547	541	541	361
Poly-3 test	P=0.092	P=0.270	P=0.027	P=0.124
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	24/50 (48%)	25/50 (50%)	17/50 (34%)	21/50 (42%)
Adjusted rate	51.9%	53.9%	36.7%	45.6%
Terminal rate	16/33 (49%)	16/31 (52%)	12/36 (33%)	14/33 (42%)
First incidence (days)	513	536	541	624
Poly-3 test	P=0.207N	P=0.507	P=0.099N	P=0.342N
Skin: Trichoepithelioma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	6.7%	0.0%	0.0%	6.6%
Terminal rate	1/33 (3%)	0/31 (0%)	0/36 (0%)	0/33 (0%)
First incidence (days)	513	—	—	624
Poly-3 test	P=0.449	P=0.122N	P=0.119N	P=0.661N
Thyroid Gland (C-cell): Adenoma				
Overall rate	7/50 (14%)	4/49 (8%)	10/48 (21%)	7/50 (14%)
Adjusted rate	15.8%	9.1%	22.7%	15.7%
Terminal rate	7/33 (21%)	2/31 (7%)	7/36 (19%)	6/33 (18%)
First incidence (days)	730 (T)	616	658	680
Poly-3 test	P=0.399	P=0.263N	P=0.293	P=0.605N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	9/50 (18%)	4/49 (8%)	10/48 (21%)	7/50 (14%)
Adjusted rate	20.4%	9.1%	22.7%	15.7%
Terminal rate	9/33 (27%)	2/31 (7%)	7/36 (19%)	6/33 (18%)
First incidence (days)	730 (T)	616	658	680
Poly-3 test	P=0.518N	P=0.115N	P=0.498	P=0.382N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Uterus: Stromal Polyp				
Overall rate	7/50 (14%)	3/50 (6%)	8/50 (16%)	7/50 (14%)
Adjusted rate	15.8%	6.5%	17.6%	15.7%
Terminal rate	7/33 (21%)	0/31 (0%)	6/36 (17%)	6/33 (18%)
First incidence (days)	730 (T)	332	626	680
Poly-3 test	P=0.364	P=0.138N	P=0.525	P=0.605N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	7/50 (14%)	3/50 (6%)	9/50 (18%)	7/50 (14%)
Adjusted rate	15.8%	6.5%	19.8%	15.7%
Terminal rate	7/33 (21%)	0/31 (0%)	7/36 (19%)	6/33 (18%)
First incidence (days)	730 (T)	332	626	680
Poly-3 test	P=0.352	P=0.138N	P=0.417	P=0.605N
All Organs: Mononuclear Cell Leukemia				
Overall rate	15/50 (30%)	10/50 (20%)	1/50 (2%)	1/50 (2%)
Adjusted rate	32.1%	21.9%	2.2%	2.2%
Terminal rate	8/33 (24%)	4/31 (13%)	0/36 (0%)	1/33 (3%)
First incidence (days)	513	616	638	730 (T)
Poly-3 test	P<0.001N	P=0.191N	P<0.001N	P<0.001N
All Organs: Benign Neoplasms				
Overall rate	42/50 (84%)	42/50 (84%)	46/50 (92%)	42/50 (84%)
Adjusted rate	87.5%	84.6%	95.2%	89.4%
Terminal rate	29/33 (88%)	25/31 (81%)	35/36 (97%)	29/33 (88%)
First incidence (days)	511	332	541	624
Poly-3 test	P=0.303	P=0.452N	P=0.140	P=0.517
All Organs: Malignant Neoplasms				
Overall rate	23/50 (46%)	16/50 (32%)	12/50 (24%)	12/50 (24%)
Adjusted rate	47.8%	34.0%	25.1%	25.5%
Terminal rate	13/33 (39%)	7/31 (23%)	5/36 (14%)	5/33 (15%)
First incidence (days)	513	480	337	361
Poly-3 test	P=0.013N	P=0.121N	P=0.016N	P=0.018N
All Organs: Benign or Malignant Neoplasms				
Overall rate	45/50 (90%)	45/50 (90%)	49/50 (98%)	45/50 (90%)
Adjusted rate	90.8%	90.0%	98.0%	92.6%
Terminal rate	29/33 (88%)	26/31 (84%)	35/36 (97%)	30/33 (91%)
First incidence (days)	511	332	337	361
Poly-3 test	P=0.333	P=0.581N	P=0.124	P=0.519

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

TABLE B4a
Historical Incidence of Mammary Gland Fibroadenoma in Control Female F344/N Rats

Study	Incidence in Controls
Historical Incidence in Controls Given NTP-2000 Diet[a]	
p,p′-Dichlorodiphenyl sulfone (feed)	15/50
Indium phosphide (inhalation)	20/50
Methacrylonitrile (gavage)	21/50
Naphthalene (inhalation)	17/49
p-Nitrotoluene (feed)	14/50
Sodium nitrite (drinking water)	21/50
Overall Historical Incidence in Controls Given NTP-2000 Diet	
Total (%)	108/299 (36.1%)
Mean ± standard deviation	36.1% ± 6.2%
Range	28%-42%
Historical Incidence in Drinking Water Controls Given NIH-07 Diet at Battelle Columbus Laboratories[b]	
Sodium fluoride	22/80
Overall Historical Incidence in Drinking Water Controls Given NIH-07 Diet	
Total (%)	121/330 (36.7%)
Mean ± standard deviation	37.6% ± 14.6%
Range	24%-58%

[a] Data as of 15 March 2000
[b] Data as of 21 December 1999

TABLE B4b
Historical Incidence of Mononuclear Cell Leukemia in Control Female F344/N Rats

Study	Incidence in Controls
Historical Incidence in Controls Given NTP-2000 Diet[a]	
p,p′-Dichlorodiphenyl sulfone (feed)	8/50
Indium phosphide (inhalation)	14/50
Methacrylonitrile (gavage)	21/50
Naphthalene (inhalation)	16/49
p-Nitrotoluene (feed)	13/50
Sodium nitrite (drinking water)	15/50
Overall Historical Incidence in Controls Given NTP-2000 Diet	
Total (%)	87/299 (29.1%)
Mean ± standard deviation	29.1% ± 8.5%
Range	16%-42%
Historical Incidence in Drinking Water Controls Given NIH-07 Diet at Battelle Columbus Laboratories[b]	
Sodium fluoride	26/80
Overall Historical Incidence in Drinking Water Controls Given NIH-07 Diet	
Total (%)	102/330 (30.9%)
Mean ± standard deviation	30.8% ± 10.0%
Range	16%-44%

[a] Data as of 15 March 2000; includes data for lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemia
[b] Data as of 21 December 1999; includes data for lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemia

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite[a]

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	6	10	15
Natural deaths	6	13	4	2
Survivors				
Terminal sacrifice	33	31	36	33
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(49)	(50)	(50)
Inflammation			1 (2%)	
Intestine large, colon	(50)	(48)	(50)	(50)
Parasite metazoan		1 (2%)	1 (2%)	1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(50)
Inflammation, granulomatous				1 (2%)
Parasite metazoan	4 (8%)	1 (2%)	2 (4%)	7 (14%)
Liver	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)	3 (6%)	5 (10%)
Basophilic focus	45 (90%)	42 (84%)	48 (96%)	45 (90%)
Clear cell focus	9 (18%)	6 (12%)	8 (16%)	7 (14%)
Cyst				1 (2%)
Eosinophilic focus	9 (18%)	10 (20%)	8 (16%)	10 (20%)
Hemorrhage	1 (2%)			1 (2%)
Hepatodiaphragmatic nodule	4 (8%)	11 (22%)	7 (14%)	8 (16%)
Inflammation, chronic active	23 (46%)	23 (46%)	28 (56%)	28 (56%)
Inflammation, granulomatous			1 (2%)	1 (2%)
Mixed cell focus	11 (22%)	3 (6%)	7 (14%)	9 (18%)
Necrosis	5 (10%)	2 (4%)		4 (8%)
Pigmentation, lipofuscin			1 (2%)	
Regeneration	1 (2%)			
Vacuolization cytoplasmic	1 (2%)	5 (10%)	4 (8%)	4 (8%)
Bile duct, hyperplasia	8 (16%)	4 (8%)	4 (8%)	4 (8%)
Mesentery	(7)	(5)	(7)	(4)
Fat, inflammation, chronic active	6 (86%)	5 (100%)	7 (100%)	4 (100%)
Fat, necrosis	1 (14%)			
Pancreas	(50)	(50)	(49)	(50)
Atrophy				1 (2%)
Inflammation, chronic active			1 (2%)	
Acinus, atrophy	6 (12%)	6 (12%)	8 (16%)	8 (16%)
Acinus, hyperplasia	1 (2%)		1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema		1 (2%)	2 (4%)	2 (4%)
Erosion	1 (2%)	1 (2%)	1 (2%)	
Hyperkeratosis	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Inflammation, chronic active	1 (2%)			
Ulcer	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Epithelium, hyperplasia	8 (16%)	6 (12%)	8 (16%)	40 (80%)
Stomach, glandular	(50)	(50)	(50)	(50)
Erosion		2 (4%)	1 (2%)	
Inflammation, chronic active	1 (2%)			
Mineralization	1 (2%)	3 (6%)	1 (2%)	

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

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Cardiovascular System				
Bood vessel	(50)	(50)	(50)	(50)
Mineralization		2 (4%)		
Heart	(50)	(49)	(50)	(50)
Inflammation, chronic active	3 (6%)	4 (8%)	3 (6%)	3 (6%)
Mineralization		2 (4%)		
Necrosis	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Angiectasis	40 (80%)	39 (78%)	45 (90%)	45 (90%)
Degeneration	1 (2%)			
Hemorrhage	1 (2%)			
Hyperplasia	15 (30%)	11 (22%)	11 (22%)	10 (20%)
Hypertrophy	8 (16%)	7 (14%)	7 (14%)	4 (8%)
Necrosis	2 (4%)	1 (2%)		
Vacuolization cytoplasmic	4 (8%)	5 (10%)	1 (2%)	3 (6%)
Adrenal medulla	(50)	(50)	(45)	(49)
Hyperplasia	6 (12%)	7 (14%)	4 (9%)	5 (10%)
Bilateral, hyperplasia			1 (2%)	
Pituitary gland	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			
Cyst	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Hemorrhage	3 (6%)			
Pigmentation, hemosiderin		1 (2%)		
Pars distalis, angiectasis	2 (4%)			
Pars distalis, cyst	4 (8%)	10 (20%)	5 (10%)	9 (18%)
Pars distalis, hemorrhage		1 (2%)		
Pars distalis, hyperplasia	10 (20%)	10 (20%)	19 (38%)	12 (24%)
Pars intermedia, cyst				1 (2%)
Thyroid gland	(50)	(49)	(48)	(50)
Inflammation, chronic active			1 (2%)	
Ultimobranchial cyst	1 (2%)		1 (2%)	4 (8%)
Vacuolization cytoplasmic	1 (2%)			
Bilateral, C-cell, hyperplasia		1 (2%)		
C-cell, hyperplasia	24 (48%)	26 (53%)	34 (71%)	26 (52%)
Follicle, cyst			1 (2%)	
General Body System				
None				
Genital System				
Clitoral gland	(46)	(48)	(49)	(49)
Atrophy	1 (2%)			
Cyst	9 (20%)	1 (2%)	12 (24%)	3 (6%)
Hyperplasia	8 (17%)	4 (8%)	7 (14%)	7 (14%)
Inflammation, chronic active		1 (2%)	2 (4%)	1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Genital System (continued)				
Ovary	(50)	(49)	(50)	(50)
Cyst	4 (8%)	4 (8%)	3 (6%)	5 (10%)
Inflammation, chronic active				1 (2%)
Follicle, cyst	1 (2%)		2 (4%)	2 (4%)
Periovarian tissue, cyst	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Uterus	(50)	(50)	(50)	(50)
Cyst		2 (4%)		
Dysplasia				1 (2%)
Fibrosis	1 (2%)			
Hemorrhage		1 (2%)	2 (4%)	1 (2%)
Hydrometra	3 (6%)	4 (8%)	4 (8%)	5 (10%)
Inflammation, chronic active			1 (2%)	
Thrombosis			2 (4%)	1 (2%)
Cervix, hydrometra			1 (2%)	
Cervix, hyperplasia				1 (2%)
Cervix, hypertrophy	1 (2%)			
Cervix, epithelium, cyst				1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia			1 (2%)	
Myelofibrosis			1 (2%)	
Lymph node	(2)	(1)	(2)	(1)
Ectasia				1 (100%)
Lymph node, mandibular	(49)	(49)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)		2 (4%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Pigmentation, lipofuscin		1 (2%)	1 (2%)	
Spleen	(50)	(50)	(50)	(50)
Fibrosis	1 (2%)			
Hematopoietic cell proliferation	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Necrosis			1 (2%)	
Pigmentation, hemosiderin	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Vacuolization cytoplasmic	1 (2%)			
Lymphoid follicle, depletion cellular				1 (2%)
Thymus	(49)	(47)	(49)	(48)
Atrophy	1 (2%)		1 (2%)	
Cyst	1 (2%)			
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Galactocele	14 (28%)	10 (20%)	12 (24%)	10 (20%)
Hyperplasia	10 (20%)	5 (10%)	3 (6%)	9 (18%)
Skin	(50)	(50)	(50)	(50)
Ulcer				2 (4%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosclerosis	1 (2%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Hydrocephalus			1 (2%)	1 (2%)
Mineralization				1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion		1 (2%)	2 (4%)	
Inflammation, chronic active	16 (32%)	13 (26%)	14 (28%)	17 (34%)
Pigmentation	1 (2%)			
Alveolar epithelium, hyperplasia	10 (20%)	10 (20%)	8 (16%)	3 (6%)
Bronchiole, epithelium, hyperplasia	1 (2%)		1 (2%)	
Nose	(50)	(49)	(50)	(50)
Inflammation, chronic active				3 (6%)
Olfactory epithelium, metaplasia	1 (2%)			
Special Senses System				
Eye		(1)	(1)	(3)
Inflammation, chronic active		1 (100%)		
Cornea, inflammation, chronic active				1 (33%)
Lens, mineralization				1 (33%)
Retina, degeneration			1 (100%)	3 (100%)
Harderian gland				(1)
Inflammation, chronic active				1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet		1 (2%)		
Casts protein				1 (2%)
Cyst			2 (4%)	4 (8%)
Infarct	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)	5 (10%)	4 (8%)	5 (10%)
Mineralization	1 (2%)	1 (2%)	2 (4%)	
Necrosis	1 (2%)			
Nephropathy	14 (28%)	16 (32%)	20 (40%)	23 (46%)
Pigmentation	2 (4%)	3 (6%)	1 (2%)	
Renal tubule, regeneration		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Inflammation, chronic active	3 (6%)	2 (4%)	2 (4%)	5 (10%)

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF SODIUM NITRITE

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TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite[a]

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	3	2	3	1
Natural deaths	8	3	5	10
Survivors				
Terminal sacrifice	39	45	42	39
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, duodenum	(49)	(50)	(48)	(49)
Carcinoma		1 (2%)		
Carcinoma, metastatic, intestine small, jejunum			1 (2%)	
Polyp adenomatous	2 (4%)	3 6%)	1 (2%)	
Intestine small, jejunum	(50)	(50)	(50)	(50)
Carcinoma	5 (10%)	1 (2%)	1 (2%)	
Leiomyosarcoma			1 (2%)	
Polyp adenomatous				1 (2%)
Liver	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Cholangiocarcinoma				1 (2%)
Hemangiosarcoma	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Hemangiosarcoma, metastatic, spleen	2 (4%)			
Hepatoblastoma	5 (10%)	1 (2%)	2 (4%)	
Hepatocellular carcinoma	9 (18%)	10 (20%)	6 (12%)	6 (12%)
Hepatocellular carcinoma, multiple				3 (6%)
Hepatocellular adenoma	10 (20%)	15 (30%)	8 (16%)	13 (26%)
Hepatocellular adenoma, multiple	9 (18%)	2 (4%)	5 (10%)	5 (10%)
Sarcoma			1 (2%)	
Mesentery	(7)	(6)	(7)	(5)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (20%)
Cholangiocarcinoma, metastatic, liver				1 (20%)
Hepatoblastoma, metastatic, liver			1 (14%)	
Sarcoma, metastatic, liver			1 (14%)	
Pancreas	(49)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Cholangiocarcinoma, metastatic, liver				1 (2%)
Hepatoblastoma, metastatic, liver	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)		1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Sarcoma, metastatic, liver			1 (2%)	
Tooth	(5)	(5)	(4)	(1)
Odontoma		2 (40%)	1 (25%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Fibrosarcoma, metastatic, uncertain primary site		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Cholangiocarcinoma, metastatic, liver				1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	3 (6%)	2 (4%)	2 (4%)	
Carcinoma		1 (2%)		
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Prostate	(50)	(50)	(49)	(50)
Cholangiocarcinoma, metastatic, liver				1 (2%)
Seminal vesicle	(50)	(50)	(50)	(50)
Cholangiocarcinoma, metastatic, liver				1 (2%)
Testes	(50)	(50)	(50)	(50)
Hemangiosarcoma, metastatic, liver				1 (2%)
Interstitial cell, adenoma		2 (4%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Hemangiosarcoma	2 (4%)			
Lymph node	(1)	(1)	(3)	(5)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung				1 (20%)
Pancreatic, cholangiocarcinoma, metastatic, liver				1 (20%)
Renal, cholangiocarcinoma, metastatic, liver				1 (20%)
Lymph node, mandibular	(47)	(50)	(47)	(48)
Carcinoma, metastatic, harderian gland			1 (2%)	
Lymph node, mesenteric	(49)	(49)	(48)	(49)
Hemangiosarcoma, metastatic, liver				1 (2%)
Spleen	(50)	(50)	(50)	(50)
Hemangiosarcoma	3 (6%)		2 (4%)	
Hemangiosarcoma, metastatic, bone marrow	1 (2%)			
Hemangiosarcoma, metastatic, liver			1 (2%)	1 (2%)
Hemangiosarcoma, metastatic, skin	1 (2%)			
Thymus	(37)	(39)	(38)	(42)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, sarcoma, metastatic, brain	1 (2%)			
Subcutaneous tissue, pinna, melanoma malignant				1 (2%)
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Sarcoma	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	10 (20%)	5 (10%)	8 (16%)	10 (20%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)	
Alveolar/bronchiolar carcinoma	4 (8%)	1 (2%)	3 (6%)	7 (14%)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	1 (2%)
Carcinoma, metastatic, harderian gland			1 (2%)	
Carcinoma, metastatic, intestine small, jejunum	1 (2%)			
Cholangiocarcinoma, metastatic, liver				1 (2%)
Fibrosarcoma, metastatic, uncertain primary site		1 (2%)		
Hemangiosarcoma, metastatic, liver	1 (2%)			
Hepatoblastoma, metastatic, liver	2 (4%)			
Hepatocellular carcinoma, metastatic, liver	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Sarcoma, metastatic, brain	1 (2%)			
Sarcoma, metastatic, liver			1 (2%)	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			2 (4%)
Mediastinum, fibrosarcoma, metastatic, uncertain primary site		1 (2%)		
Mediastinum, hemangiosarcoma, metastatic, bone marrow	1 (2%)			
Mediastinum, sarcoma, metastatic, brain	1 (2%)			
Special Senses System				
Harderian gland	(5)	(4)	(6)	(1)
Adenoma	4 (80%)	3 (75%)	4 (67%)	1 (100%)
Carcinoma			2 (33%)	
Sarcoma, metastatic, brain	1 (20%)			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				2 (4%)
Renal tubule, adenoma		1 (2%)		
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Lymphoma malignant	1 (2%)	1 (2%)	4 (8%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	40	35	36	38
Total primary neoplasms	72	54	53	52
Total animals with benign neoplasms	28	28	26	29
Total benign neoplasms	39	36	30	31
Total animals with malignant neoplasms	27	15	20	20
Total malignant neoplasms	33	18	23	21
Total animals with metastatic neoplasms	13	4	7	7
Total metastatic neoplasms	18	7	11	24
Total animals with malignant neoplasms of uncertain primary site		1		

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	501	502	616	617	643	647	652	661	687	701	705	713	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727
Carcass ID Number	00222	00213	00234	00249	00203	00216	00201	00202	00248	00236	00208	00205	00207	00209	00211	00212	00215	00221	00224	00226	00230	00235	00237	00244	00245
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																					X			X			
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X																							
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X		X															
Hemangiosarcoma, metastatic, spleen							X																				X
Hepatoblastoma			X						X																		
Hepatocellular carcinoma			X															X					X				
Hepatocellular adenoma							X				X	X													X		
Hepatocellular adenoma, multiple				X												X				X			X				
Mesentery			+																+			+					+
Oral mucosa					+							+			+	+			+			+	+		+	+	
Pancreas	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma, metastatic, liver																											
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																											
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth						+			+																		
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X		X													X						
Parathyroid gland	M	+	+	+	M	+	M	M	+	+	+	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	0 4 6	0 0 4	0 1 0	0 1 4	0 1 8	0 2 0	0 2 3	0 2 5	0 3 1	0 3 2	0 3 3	0 3 8	0 4 0	0 4 2	0 5 0	0 0 6	0 1 7	0 1 9	0 2 7	0 2 8	0 3 9	0 4 1	0 4 3	0 4 7	0 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp adenomatous																										2
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma	X					X						X					X									5
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Hemangiosarcoma, metastatic, spleen																										2
Hepatoblastoma				X															X						X	5
Hepatocellular carcinoma							X			X	X				X		X								X	9
Hepatocellular adenoma				X	X	X								X				X					X			10
Hepatocellular adenoma, multiple			X					X		X							X								X	9
Mesentery	+										+													+		7
Oral mucosa	+	+		+	+		+			+	+	+	+	+			+	+	+	+	+	+		+		26
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatoblastoma, metastatic, liver																			X							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma												X														1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																		+	+				+			5
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										3
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	M	M	+	36
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	5 0 1	5 2 6	6 1 7	6 4 3	6 4 7	6 5 2	6 6 1	6 8 7	7 0 1	7 0 5	7 1 3	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7
Carcass ID Number	0 2 2	0 1 3	0 3 4	0 2 9	0 0 3	0 1 6	0 0 1	0 0 2	0 0 4 8	0 3 6	0 0 8	0 0 5	0 0 7	0 0 9	0 1 1	0 1 2	0 1 5	0 2 1	0 2 4	0 2 6	0 3 0	0 3 5	0 3 7	0 4 4	0 4 5
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																		
Lymph node																				+					
Lymph node, mandibular	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X															X			X
Hemangiosarcoma, metastatic, bone marrow																									
Hemangiosarcoma, metastatic, skin																									
Thymus	+	+	+	+	M	+	M	M	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, sarcoma, metastatic, brain	X																								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma	X																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X												X				X	X		X	X		
Alveolar/bronchiolar carcinoma		X											X												
Carcinoma, metastatic, intestine small, jejunum																									
Hemangiosarcoma, metastatic, liver										X															
Hepatoblastoma, metastatic, liver									X																
Hepatocellular carcinoma, metastatic, liver																						X			
Sarcoma, metastatic, brain	X																								
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung		X																							
Mediastinum, hemangiosarcoma, metastatic, bone marrow																									
Mediastinum, sarcoma, metastatic, brain	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye							+																		
Harderian gland	+						+				+		+												
Adenoma							X				X		X												
Sarcoma, metastatic, brain	X																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	727	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	00466	00404	00110	00114	00118	00120	00223	00225	00231	00232	00233	00238	00240	00242	00250	00206	00217	00219	00227	00228	00239	00241	00243	00247	00249	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X																							2
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										3
Hemangiosarcoma, metastatic, bone marrow			X																							1
Hemangiosarcoma, metastatic, skin																				X						1
Thymus	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	M	+	37
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																				X						1
Subcutaneous tissue, sarcoma, metastatic, brain																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X												X		X						X	10
Alveolar/bronchiolar carcinoma			X														X									4
Carcinoma, metastatic, intestine small, jejunum	X																									1
Hemangiosarcoma, metastatic, liver																										1
Hepatoblastoma, metastatic, liver																				X						2
Hepatocellular carcinoma, metastatic, liver							X											X								3
Sarcoma, metastatic, brain																										1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinum, hemangiosarcoma, metastatic, bone marrow			X																							1
Mediastinum, sarcoma, metastatic, brain																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland										+																5
Adenoma										X																4
Sarcoma, metastatic, brain																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	727	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	04 6	04 4	10 0	11 4	11 8	12 0	22 3	22 5	23 1	33 2	33 3	33 8	40 0	42 2	45 0	50 6	01 7	11 9	12 7	22 8	23 9	34 1	44 3	44 7	44 9	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	06 7	07 3	07 4	07 5	07 6	07 7	07 8	07 9	08 0	08 1	08 6	09 2	09 4	05 1	05 2	05 3	05 7	05 8	06 0	06 2	06 4	07 1	08 3	08 4	09 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestinal arge, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestinal arge, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																				X						1
Polyp adenomatous				X								X											X			3
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic																										1
Hemangiosarcoma																					X		X			2
Hepatoblastoma				X																						1
Hepatocellular carcinoma					X										X		X						X			10
Hepatocellular adenoma								X		X	X			X	X			X	X	X	X		X			15
Hepatocellular adenoma, multiple							X																			2
Mesentery											+															6
Oral mucosa		+		+	+	+			+	+	+	+	+	+		+	+				+	+	+			27
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth			+	+																						5
Odontoma			X																							2
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, uncertain primary site																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		2
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

Number of Days on Study	4 4 4	6 0 1	6 1 2	6 3 7	6 4 4	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8
Carcass ID Number	0 0 8 7	0 0 9 9	0 0 8 5	0 0 9 7	0 0 7 2	0 0 5 4	0 0 5 5	0 0 5 6	0 0 6 3	0 0 6 5	0 0 6 6	0 0 6 8	0 0 6 9	0 0 7 0	0 0 8 2	0 0 8 8	0 0 8 9	0 0 9 1	0 0 9 3	0 0 9 5	0 0 9 6	0 0 9 8	0 1 0 0	0 0 5 9	0 0 6 1
Genital System																									
Coagulating gland				+																					
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma										X							X								
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	M	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X																				
Alveolar/bronchiolar carcinoma																							X		
Fibrosarcoma, metastatic, uncertain primary site					X																				
Hepatocellular carcinoma, metastatic, liver		X			X																				
Hepatocholangiocarcinoma, metastatic, liver																X									
Mediastinum, fibrosarcoma, metastatic, uncertain primary site						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland			+										+												
Adenoma			X										X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant									X																

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	06 7	07 3	07 4	07 5	07 6	07 7	07 8	07 9	08 0	08 1	08 6	08 2	09 4	09 1	05 2	05 3	05 7	05 8	06 0	06 2	06 4	07 1	08 3	08 4	09 0	Total Tissues/ Tumors
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node															+											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	39
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X	X						X	X						5
Alveolar/bronchiolar carcinoma																										1
Fibrosarcoma, metastatic, uncertain primary site																										1
Hepatocellular carcinoma, metastatic, liver																										2
Hepatocholangiocarcinoma, metastatic, liver																										1
Mediastinum, fibrosarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland				+																	+					4
Adenoma																					X					3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma															X											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	577	596	641	643	643	664	667	707	727	727	727	727	727	727	727	727	727	727	727	727	727	727	728	728
Carcass ID Number	10303	10444	10447	10401	10335	10232	10319	10108	10202	10206	10515	10717	10828	10930	10931	10933	10934	10938	11040	11043	11046	11048	11050	11004	11005
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small, jejunum																									
Polyp adenomatous															X										
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Leiomyosarcoma			X																						
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Hepatoblastoma																									
Hepatocellular carcinoma		X												X				X							X
Hepatocellular adenoma											X								X			X	X		
Hepatocellular adenoma, multiple																		X		X					
Sarcoma				X																					
Mesentery				+																	+			+	
Hepatoblastoma, metastatic, liver																									
Sarcoma, metastatic, liver				X																					
Oral mucosa					+			+	+	+				+	+		+		+	+				+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, liver				X																					
Tooth											+											+			+
Odontoma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+
Pituitary gland	+	+	+	+	I	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	
Carcass ID Number	10107	11010	11101	11313	11414	11616	11818	12121	12424	12525	12626	12727	13636	13939	14041	14242	14545	14949	10901	11202	12020	12222	12323	12929	13037	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, intestine small, jejunum			X																							1
Polyp adenomatous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma			X																							1
Leiomyosarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatoblastoma		X			X																					2
Hepatocellular carcinoma					X													X								6
Hepatocellular adenoma				X	X							X				X										8
Hepatocellular adenoma, multiple																	X	X							X	5
Sarcoma																										1
Mesentery			+		+																+	+				7
Hepatoblastoma, metastatic, liver					X																					1
Sarcoma, metastatic, liver																										1
Oral mucosa	+	+													+		+	+							+	17
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, liver																										1
Tooth														+												4
Odontoma														X												1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X								X												2
Parathyroid gland	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	
Carcass ID Number	10707	11010	11101	11313	11414	11616	11818	12101	12404	12505	12606	12707	13606	13909	14101	14202	14505	14909	15009	15112	15320	15522	15623	15729	15837	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node					+																					3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, metastatic, harderian gland																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X																	2
Hemangiosarcoma, metastatic, liver																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	38
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																											
Bone	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X	X		X										X	X				8
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma				X						X						X										3
Alveolar/bronchiolar carcinoma, metastatic, lung																X										1
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver					X													X								2
Sarcoma, metastatic, liver																										1
Nose	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Harderian gland			+					+		+	+									+						6
Adenoma			X					X			X									X						4
Carcinoma								X																		2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant					X						X								X							4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	1 9 8	1 9 9	2 0 0	1 5 2	1 5 6	1 5 8	1 6 0	1 6 3	1 6 5	1 6 6	1 6 9	1 7 0	1 7 3	1 7 4	1 7 6	1 8 3	1 8 7	1 9 2	1 9 5	1 5 4	1 6 8	1 7 9	1 8 2	1 9 0	1 9 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Intestinal arge, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestinal arge, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous							X																			1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Cholangiocarcinoma																										1
Hemangiosarcoma																										2
Hepatocellular carcinoma																										6
Hepatocellular carcinoma, multiple							X			X																3
Hepatocellular adenoma			X						X		X								X					X		13
Hepatocellular adenoma, multiple														X				X		X			X			5
Mesentery																				+						5
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Cholangiocarcinoma, metastatic, liver																										1
Oral mucosa				+		+	+		+			+	+		+	+			+			+			+	19
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Cholangiocarcinoma, metastatic, liver																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma						X																				1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, metastatic, liver																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	M	+	+	+	M	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	4 7 2	5 0 2	5 4 9	5 5 6	5 8 3	5 9 4	6 2 9	6 5 4	6 6 5	6 8 5	6 9 8	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7
Carcass ID Number	1 9 7	1 7 7	1 8 8	1 8 5	1 8 1	1 5 9	1 5 5	1 6 2	1 7 5	1 8 0	1 9 1	1 1 1	1 5 3	1 5 7	1 6 1	1 6 4	1 6 7	1 7 1	1 7 2	1 7 8	1 8 4	1 8 6	1 8 9	1 9 3	1 9 4
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver								X																	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver								X																	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver			X																						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+				+		+			+												+		
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung		X																							
Pancreatic, cholangiocarcinoma, metastatic, liver								X																	
Renal, cholangiocarcinoma, metastatic, liver								X																	
Lymph node, mandibular	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver											X														
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver			X																						
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	M	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung		X																							
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, pinna, melanoma, malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X		X				X	X					
Alveolar/bronchiolar carcinoma		X					X																	X	
Alveolar/bronchiolar carcinoma, metastatic, lung							X																		
Cholangiocarcinoma, metastatic, liver								X																	
Hepatocellular carcinoma, metastatic, liver					X																				
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung		X					X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																						+			
Adenoma																						X			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	727	727	727	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	
Carcass ID Number	19 8	19 9	20 0	15 2	15 6	15 8	16 0	16 3	16 5	16 6	16 9	17 0	17 3	17 4	17 6	18 3	18 7	19 2	19 5	15 4	16 8	17 9	18 2	19 0	19 6	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, metastatic, liver																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, metastatic, liver																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, liver																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										5
Mediastinal, alveolar/bronchiolar, carcinoma, metastatic, lung																										1
Pancreatic, cholangiocarcinoma, metastatic, liver																										1
Renal, cholangiocarcinoma, metastatic, liver																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Hemangiosarcoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, liver																										1
Thymus	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	42
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, pinna, melanoma, malignant																				X						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X			X							X									X	X	X			10
Alveolar/bronchiolar carcinoma	X								X						X									X		7
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Cholangiocarcinoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver							X																			2
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										1
Adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	472	502	549	556	583	594	629	654	665	685	698	727	727	727	727	727	727	727	727	727	727	727	727	727	727
Carcass ID Number	197	177	188	185	181	159	155	162	175	180	191	151	153	157	161	164	167	171	172	178	184	186	189	193	194
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung		X					X																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant						X																			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	727	727	727	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	
Carcass ID Number	19 8	19 9	20 0	15 2	15 6	15 8	16 0	16 3	16 5	16 6	16 9	17 0	17 3	17 4	17 6	18 3	18 7	19 2	19 5	15 4	16 8	17 9	18 2	19 0	19 6	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Harderian Gland: Adenoma				
Overall rate[a]	4/50 (8%)	3/50 (6%)	4/50 (8%)	1/50 (2%)
Adjusted rate[b]	8.5%	6.2%	8.4%	2.2%
Terminal rate[c]	2/39 (5%)	2/45 (4%)	4/42 (10%)	1/39 (3%)
First incidence (days)	661	612	727 (T)	727 (T)
Poly-3 test[d]	P=0.173N	P=0.488N	P=0.637N	P=0.190N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	3/50 (6%)	5/50 (10%)	1/50 (2%)
Adjusted rate	8.5%	6.2%	10.5%	2.2%
Terminal rate	2/39 (5%)	2/45 (4%)	5/42 (12%)	1/39 (3%)
First incidence (days)	661	612	727 (T)	727 (T)
Poly-3 test	P=0.198N	P=0.488N	P=0.506	P=0.190N
Small Intestine (Duodenum): Adenomatous Polyp				
Overall rate	2/50 (4%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	4.3%	6.3%	2.1%	0.0%
Terminal rate	2/39 (5%)	3/45 (7%)	1/42 (2%)	0/39 (0%)
First incidence (days)	727 (T)	727 (T)	727 (T)	—[e]
Poly-3 test	P=0.108N	P=0.509	P=0.494N	P=0.244N
Small Intestine (Duodenum and Jejunum): Adenomatous Polyp				
Overall rate	2/50 (4%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	4.3%	6.3%	2.1%	2.2%
Terminal rate	2/39 (5%)	3/45 (9%)	1/42 (2%)	1/39 (3%)
First incidence (days)	727 (T)	727 (T)	727 (T)	727 (T)
Poly-3 test	P=0288N	P=0.509	P=0.494N	P=0.510N
Small Intestine (Jejunum): Carcinoma				
Overall rate	5/50 (10%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	10.6%	2.1%	2.1%	0.0%
Terminal rate	4/39 (10%)	1/45 (2%)	1/42 (2%)	0/39 (0%)
First incidence (days)	643	727 (T)	727 (T)	—
Poly-3 test	P=0.016N	P=0.098N	P=0.099N	P=0.034N
Small Intestine (Duodenum and Jejunum): Carcinoma				
Overall rate	5/50 (10%)	2/50 (4%)	1/50 (2%)	0/50 (0%)
Adjusted rate	10.6%	4.2%	2.1%	0.0%
Terminal rate	4/39 (10%)	2/45 (4%)	1/42 (2%)	0/39 (0%)
First incidence (days)	643	727 (T)	727 (T)	—
Poly-3 test	P=0.014N	P=0.211N	P=0.099N	P=0.034N
Liver: Hepatocellular Adenoma				
Overall rate	19/50 (38%)	17/50 (34%)	13/50 (26%)	18/50 (36%)
Adjusted rate	40.1%	35.4%	27.3%	38.5%
Terminal rate	16/39 (41%)	16/45 (36%)	13/42 (31%)	14/39 (36%)
First incidence (days)	643	637	727 (T)	472
Poly-3 test	P=0.473N	P=0.395N	P=0.134N	P=0.521N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Liver: Hepatocellular Carcinoma				
Overall rate	9/50 (18%)	10/50 (20%)	6/50 (12%)	9/50 (18%)
Adjusted rate	19.1%	20.6%	12.5%	19.3%
Terminal rate	8/39 (21%)	8/45 (18%)	5/42 (12%)	5/39 (13%)
First incidence (days)	617	601	596	583
Poly-3 test	P=0.490N	P=0.527	P=0.275N	P=0.591
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	24/50 (48%)	24/50 (48%)	16/50 (32%)	25/50 (50%)
Adjusted rate	50.2%	49.2%	33.3%	52.4%
Terminal rate	20/39 (51%)	21/45 (47%)	15/42 (36%)	18/39 (46%)
First incidence (days)	617	601	596	472
Poly-3 test	P=0.516	P=0.539N	P=0.068N	P=0.499
Liver: Hepatoblastoma				
Overall rate	5/50 (10%)	1/50 (2%)	2/50 (4%)	0/50 (0%)
Adjusted rate	10.6%	2.1%	4.2%	0.0%
Terminal rate	3/39 (8%)	1/45 (2%)	2/42 (5%)	0/39 (0%)
First incidence (days)	617	727 (T)	727 (T)	—
Poly-3 test	P=0.027N	P=0.099N	P=0.214N	P=0.034N
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	12/50 (24%)	11/50 (22%)	7/50 (14%)	9/50 (18%)
Adjusted rate	25.4%	22.7%	14.6%	19.3%
Terminal rate	10/39 (26%)	9/45 (20%)	6/42 (14%)	5/39 (13%)
First incidence (days)	617	601	596	583
Poly-3 test	P=0.239N	P=0.472N	P=0.143N	P=0.325N
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	26/50 (52%)	25/50 (50%)	17/50 (34%)	25/50 (50%)
Adjusted rate	54.3%	51.2%	35.4%	52.4%
Terminal rate	21/39 (54%)	22/45 (49%)	16/42 (38%)	18/39 (46%)
First incidence (days)	617	601	596	472
Poly-3 test	P=0.410N	P=0.460N	P=0.046N	P=0.506N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	10/50 (20%)	5/50 (10%)	9/50 (18%)	10/50 (20%)
Adjusted rate	21.2%	10.4%	18.9%	22.0%
Terminal rate	9/39 (23%)	4/45 (9%)	8/42 (19%)	10/39 (26%)
First incidence (days)	617	644	707	727 (T)
Poly-3 test	P=0.335	P=0.121N	P=0.490N	P=0.562
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	4/50 (8%)	1/50 (2%)	3/50 (6%)	7/50 (14%)
Adjusted rate	8.4%	2.1%	6.3%	15.1%
Terminal rate	3/39 (8%)	1/45 (2%)	3/42 (7%)	5/39 (13%)
First incidence (days)	526	727 (T)	727 (T)	502
Poly-3 test	P=0.074	P=0.177N	P=0.498N	P=0.249

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	13/50 (26%)	6/50 (12%)	12/50 (24%)	17/50 (34%)
Adjusted rate	27.2%	12.5%	25.2%	36.6%
Terminal rate	11/39 (28%)	5/45 (11%)	11/42 (26%)	15/39 (39%)
First incidence (days)	526	644	707	502
Poly-3 test	P=0.057	P=0.059N	P=0.503N	P=0.223
Pancreatic Islets: Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)	0/50 (0%)
Adjusted rate	6.4%	4.2%	4.2%	0.0%
Terminal rate	1/39 (3%)	2/45 (4%)	2/42 (5%)	0/39 (0%)
First incidence (days)	652	727 (T)	727 (T)	—
Poly-3 test	P=0.093N	P=0.495N	P=0.497N	P=0.126N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	6.4%	6.3%	4.2%	0.0%
Terminal rate	1/39 (3%)	3/45 (7%)	2/42 (5%)	0/39 (0%)
First incidence (days)	652	727 (T)	727 (T)	—
Poly-3 test	P=0.078N	P=0.657N	P=0.497N	P=0.126N
Spleen: Hemangiosarcoma				
Overall rate	3/50 (6%)	0/50 (0%)	2/50 (4%)	0/50 (0%)
Adjusted rate	6.4%	0.0%	4.2%	0.0%
Terminal rate	2/39 (5%)	0/45 (0%)	1/42 (2%)	0/39 (0%)
First incidence (days)	661	—	707	—
Poly-3 test	P=0.131N	P=0.116N	P=0.494N	P=0.125N
All Organs: Hemangiosarcoma				
Overall rate	7/50 (14%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	14.9%	4.2%	6.3%	4.3%
Terminal rate	5/39 (13%)	2/45 (4%)	1/42 (2%)	0/39 (0%)
First incidence (days)	661	727 (T)	664	549
Poly-3 test	P=0.083N	P=0.076N	P=0.151N	P=0.084N
All Organs: Malignant Lymphoma				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted rate	2.1%	2.1%	8.4%	2.2%
Terminal rate	1/39 (3%)	1/45 (2%)	3/42 (7%)	0/39 (0%)
First incidence (days)	727 (T)	727 (T)	664	594
Poly-3 test	P=0.508	P=0.756N	P=0.186	P=0.756
All Organs: Benign Neoplasms				
Overall rate	28/50 (56%)	28/50 (56%)	26/50 (52%)	29/50 (58%)
Adjusted rate	58.1%	57.4%	54.6%	62.0%
Terminal rate	22/39 (56%)	25/45 (56%)	25/42 (60%)	25/39 (64%)
First incidence (days)	617	612	707	472
Poly-3 test	P=0.385	P=0.555N	P=0.444N	P=0.427

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
All Organs: Malignant Neoplasms				
Overall rate	27/50 (54%)	15/50 (30%)	20/50 (40%)	20/50 (40%)
Adjusted rate	54.9%	30.9%	40.8%	41.1%
Terminal rate	20/39 (51%)	13/45 (29%)	15/42 (36%)	11/39 (28%)
First incidence (days)	501	601	596	502
Poly-3 test	P=0.234N	P=0.013N	P=0.116N	P=0.121N
All Organs: Benign or Malignant Neoplasms				
Overall rate	40/50 (80%)	35/50 (70%)	36/50 (72%)	38/50 (76%)
Adjusted rate	80.5%	71.1%	73.5%	76.8%
Terminal rate	30/39 (77%)	31/45 (69%)	31/42 (74%)	28/39 (72%)
First incidence (days)	501	601	596	472
Poly-3 test	P=0.479N	P=0.196N	P=0.279N	P=0.423N

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

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite[a]

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	3	2	3	1
Natural deaths	8	3	5	10
Survivors				
Terminal sacrifice	39	45	42	39
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(50)	(50)	(49)	(49)
Cyst	1 (2%)			
Intestine small, duodenum	(49)	(50)	(48)	(49)
Ectasia		2 (4%)		2 (4%)
Hyperplasia		1 (2%)	2 (4%)	
Intestine small, jejunum	(50)	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)	
Intussusception			1 (2%)	
Peyer's patch, hyperplasia, lymphoid		2 (4%)		
Peyer's patch, inflammation, granulomatous				1 (2%)
Intestine small, ileum	(50)	(49)	(50)	(50)
Parasite metazoan			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Basophilic focus	3 (6%)	3 (6%)		1 (2%)
Clear cell focus	4 (8%)	6 (12%)	10 (20%)	7 (14%)
Eosinophilic focus	12 (24%)	14 (28%)	14 (28%)	7 (14%)
Fibrosis	1 (2%)			
Hematopoietic cell proliferation			1 (2%)	1 (2%)
Infarct	2 (4%)			
Infiltration cellular, mononuclear cell	2 (4%)		3 (6%)	1 (2%)
Inflammation, chronic active	25 (50%)	25 (50%)	31 (62%)	19 (38%)
Mineralization	1 (2%)	1 (2%)		2 (4%)
Mixed cell focus	6 (12%)	2 (4%)	7 (14%)	9 (18%)
Necrosis	12 (24%)	4 (8%)	6 (12%)	2 (4%)
Pigmentation	2 (4%)		2 (4%)	1 (2%)
Vacuolization cytoplasmic	3 (6%)		3 (6%)	1 (2%)
Bile duct, cyst				1 (2%)
Bile duct, hyperplasia	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Hepatocyte, karyomegaly			1 (2%)	
Mesentery	(7)	(6)	(7)	(5)
Infiltration cellular, mononuclear cell	2 (29%)			
Inflammation, granulomatous	2 (29%)		2 (29%)	
Mineralization	1 (14%)	1 (17%)		
Pigmentation		1 (17%)	1 (14%)	
Artery, inflammation, chronic active		1 (17%)		
Fat, necrosis	4 (57%)	4 (67%)	3 (43%)	2 (40%)
Oral mucosa	(26)	(27)	(17)	(19)
Gingival, foreign body	26 (100%)	27 (100%)	17 (100%)	19 (100%)
Gingival, inflammation, chronic active	21 (81%)	22 (81%)	14 (82%)	11 (58%)
Pancreas	(49)	(50)	(50)	(50)
Fibrosis	1 (2%)			
Infiltration cellular, mononuclear cell	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Inflammation, chronic active	1 (2%)			
Acinus, atrophy	1 (2%)	1 (2%)		

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

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Alimentary System (continued)				
Pancreas (continued)	(49)	(50)	(50)	(50)
Acinus, hypertrophy			1 (2%)	
Artery, inflammation, chronic active		1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	1 (2%)			
Infiltration cellular, mononuclear cell	27 (54%)	28 (56%)	33 (66%)	32 (64%)
Mineralization	1 (2%)			1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Ulcer	3 (6%)		1 (2%)	1 (2%)
Epithelium, hyperplasia	6 (12%)	1 (2%)	2 (4%)	3 (6%)
Epithelium, inflammation, chronic active	2 (4%)		2 (4%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Mineralization			1 (2%)	
Epithelium, erosion			1 (2%)	
Epithelium, hyperplasia			2 (4%)	10 (20%)
Epithelium, necrosis				1 (2%)
Glands, ectasia	12 (24%)	18 (36%)	16 (32%)	14 (28%)
Tooth	(5)	(5)	(4)	(1)
Malformation	5 (100%)	4 (80%)	3 (75%)	1 (100%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Aorta, inflammation, chronic active		1 (2%)		
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy				1 (2%)
Inflammation, chronic active		1 (2%)		
Mineralization	3 (6%)		1 (2%)	
Artery, inflammation, chronic active		2 (4%)		
Atrium, thrombosis	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	2 (4%)		6 (12%)	4 (8%)
Degeneration, fatty	1 (2%)		1 (2%)	
Pigmentation		1 (2%)		
Capsule, hyperplasia	46 (92%)	42 (84%)	40 (80%)	40 (80%)
Zona fasciculata, hyperplasia		1 (2%)		1 (2%)
Zona fasciculata, hypertrophy	18 (36%)	24 (48%)	14 (28%)	21 (42%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia		1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	46 (92%)	47 (94%)	49 (98%)	44 (88%)
Parathyroid gland	(36)	(48)	(38)	(41)
Cyst			1 (3%)	
Pituitary gland	(49)	(49)	(47)	(47)
Pars distalis, cyst	3 (6%)	2 (4%)	2 (4%)	4 (9%)
Pars distalis, hyperplasia		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)		
Follicle, cyst	4 (8%)	1 (2%)	1 (2%)	2 (4%)
Follicular cell, hyperplasia		1 (2%)		

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
General Body System				
None				
Genital System				
Coagulating gland		(1)		
Inflammation, chronic active		1 (100%)		
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	1 (2%)	1 (2%)		1 (2%)
Infiltration cellular, mononuclear cell	21 (42%)	22 (44%)	25 (50%)	25 (50%)
Infiltration cellular, mixed cell				1 (2%)
Inflammation, chronic active			1 (2%)	
Preputial gland	(50)	(50)	(49)	(50)
Atrophy	1 (2%)		1 (2%)	
Infiltration cellular, mononuclear cell	27 (54%)	28 (56%)	29 (59%)	25 (50%)
Inflammation, chronic active	7 (14%)	8 (16%)	4 (8%)	4 (8%)
Inflammation, suppurative			2 (4%)	
Duct, cyst	33 (66%)	32 (64%)	33 (67%)	39 (78%)
Prostate	(50)	(50)	(49)	(50)
Infiltration cellular, mononuclear cell	15 (30%)	22 (44%)	29 (59%)	28 (56%)
Inflammation, chronic active	1 (2%)	2 (4%)	3 (6%)	
Inflammation, suppurative	1 (2%)		1 (2%)	
Artery, inflammation, chronic active		2 (4%)		
Seminal vesicle	(50)	(50)	(50)	(50)
Congestion				1 (2%)
Dilatation	2 (4%)	2 (4%)		
Infiltration cellular, mononuclear cell		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic active	2 (4%)			
Inflammation, suppurative			1 (2%)	
Bilateral, dilatation	1 (2%)	1 (2%)	1 (2%)	
Testes	(50)	(50)	(50)	(50)
Mineralization				2 (4%)
Germinal epithelium, atrophy		1 (2%)		1 (2%)
Germinal epithelium, necrosis			1 (2%)	
Interstitial cell, hyperplasia			2 (4%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Hemorrhage			1 (2%)	
Thrombosis			1 (2%)	
Myeloid cell, hyperplasia			1 (2%)	2 (4%)
Lymph node	(1)	(1)	(3)	(5)
Lumbar, hyperplasia, plasma cell			1 (33%)	
Mediastinal, hemorrhage				1 (20%)
Mediastinal, inflammation, granulomatous				1 (20%)
Renal, hyperplasia, lymphoid		1 (100%)		
Renal, hyperplasia, plasma cell			1 (33%)	
Lymph node, mandibular	(47)	(50)	(47)	(48)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	1 (2%)	

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Hematopoietic System (continued)				
Lymph node, mesenteric	(49)	(49)	(48)	(49)
Ectasia		1 (2%)		
Hematopoietic cell proliferation				1 (2%)
Hyperplasia, plasma cell		2 (4%)	1 (2%)	
Hyperplasia, lymphocyte	1 (2%)		1 (2%)	
Infiltration cellular, eosinophil		1 (2%)		
Inflammation, chronic active				1 (2%)
Inflammation, granulomatous			1 (2%)	2 (4%)
Spleen	(50)	(50)	(50)	(50)
Hematopoietic cell proliferation	22 (44%)	11 (22%)	14 (28%)	20 (40%)
Hyperplasia, lymphoid	1 (2%)		1 (2%)	
Thymus	(37)	(39)	(38)	(42)
Cyst	9 (24%)	14 (36%)	16 (42%)	9 (21%)
Hemorrhage	1 (3%)			
Inflammation, granulomatous	1 (3%)			
Necrosis	1 (3%)			
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Inflammation, chronic active	4 (8%)	1 (2%)	1 (2%)	2 (4%)
Ulcer	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Epidermis, hyperplasia	2 (4%)	1 (2%)	1 (2%)	
Subcutaneous tissue, infiltration cellular, mononuclear cell			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(49)	(50)
Cranium, hyperostosis	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Neuron, necrosis	2 (4%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Inflammation, chronic	1 (2%)			
Inflammation, chronic active	1 (2%)	1 (2%)	1 (2%)	
Mineralization	4 (8%)		3 (6%)	
Necrosis				2 (4%)
Alveolar epithelium, hyperplasia	3 (6%)	2 (4%)	6 (12%)	9 (18%)
Alveolus, infiltration cellular, histiocyte	3 (6%)	1 (2%)	2 (4%)	3 (6%)
Interstitium, inflammation, chronic active			1 (2%)	
Mediastinum, inflammation, chronic active		1 (2%)		
Mediastinum, inflammation, suppurative			1 (2%)	
Mediastinum, pigmentation		1 (2%)		

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Respiratory System (continued)				
Nose	(50)	(50)	(49)	(50)
Foreign body	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, suppurative	1 (2%)		1 (2%)	
Nasolacrimal duct, inflammation, suppurative		1 (2%)		
Special Senses System				
Eye	(1)			
Atrophy	1 (100%)			
Harderian gland	(5)	(4)	(6)	(1)
Hyperplasia		1 (25%)		
Inflammation, chronic		1 (25%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Hydronephrosis			1 (2%)	1 (2%)
Infarct	11 (22%)	10 (20%)	9 (18%)	13 (26%)
Infiltration cellular, mononuclear cell	42 (84%)	41 (82%)	41 (82%)	45 (90%)
Infiltration cellular, plasma cell			1 (2%)	
Inflammation, chronic active	2 (4%)	1 (2%)		1 (2%)
Inflammation, suppurative	1 (2%)		1 (2%)	
Metaplasia, osseous	2 (4%)	3 (6%)		
Mineralization	48 (96%)	50 (100%)	48 (96%)	46 (92%)
Necrosis	1 (2%)	1 (2%)		
Nephropathy	44 (88%)	49 (98%)	45 (90%)	42 (84%)
Pigmentation	1 (2%)			
Artery, inflammation, chronic active		2 (4%)	1 (2%)	
Cortex, cyst	5 (10%)	9 (18%)	6 (12%)	4 (8%)
Renal tubule, hypertrophy, focal				1 (2%)
Urinary bladder	(50)	(50)	(50)	(49)
Infiltration cellular, mononuclear cell	6 (12%)	7 (14%)	16 (32%)	10 (20%)
Inflammation, suppurative		1 (2%)		

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF SODIUM NITRITE

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TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite[a]

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	1	7	2	4
Natural deaths	9	9	11	5
Survivors				
Terminal sacrifice	40	34	37	41
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(48)	(50)	(50)	(49)
Intestine large, rectum	(49)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin			1 (2%)	
Intestine small, jejunum	(50)	(50)	(50)	(50)
Intestine small, ileum	(49)	(49)	(50)	(50)
Leiomyosarcoma, metastatic, uterus			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Fibrosarcoma, metastatic, skin			1 (2%)	
Hemangiosarcoma			1 (2%)	
Hepatocellular carcinoma	2 (4%)	2 (4%)	4 (8%)	1 (2%)
Hepatocellular adenoma	9 (18%)	6 (12%)	2 (4%)	5 (10%)
Hepatocellular adenoma, multiple		1 (2%)	1 (2%)	1 (2%)
Hepatocholangiocarcinoma	1 (2%)	1 (2%)		
Mesentery	(14)	(19)	(17)	(13)
Carcinoma, metastatic, islets, pancreatic		1 (5%)		
Fibrosarcoma, metastatic, skin		1 (5%)	1 (6%)	
Hepatocholangiocarcinoma, metastatic, liver	1 (7%)	1 (5%)		
Osteosarcoma, metastatic, bone			1 (6%)	
Sarcoma			1 (6%)	
Pancreas	(50)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)		
Salivary glands	(49)	(49)	(48)	(50)
Schwannoma malignant, metastatic, skin				1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell carcinoma				2 (4%)
Squamous cell papilloma	1 (2%)		1 (2%)	3 (6%)
Stomach, glandular	(50)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Fibrosarcoma, metastatic, skin			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Osteosarcoma, metastatic, bone			1 (2%)	
Adrenal medulla	(50)	(50)	(48)	(49)
Pheochromocytoma benign		1 (2%)	1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Endocrine System (continued)				
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma			3 (6%)	
Carcinoma		1 (2%)		
Pituitary gland	(48)	(47)	(43)	(48)
Pars distalis, adenoma	1 (2%)	3 (6%)		1 (2%)
Thyroid gland	(49)	(49)	(48)	(49)
Bilateral, follicular cell, adenoma		1 (2%)		
Follicular cell, carcinoma				1 (2%)
General Body System				
Peritoneum		(1)		(1)
Hepatocholangiocarcinoma, metastatic, liver		1 (100%)		
Genital System				
Clitoral gland	(50)	(49)	(50)	(48)
Ovary	(47)	(49)	(50)	(49)
Cystadenoma		2 (4%)	1 (2%)	3 (6%)
Granulosa cell tumor benign			1 (2%)	
Hemangioma		2 (4%)	1 (2%)	1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Luteoma				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Teratoma benign		1 (2%)		
Uterus	(50)	(50)	(50)	(50)
Leiomyosarcoma			1 (2%)	
Polyp stromal		3 (6%)		1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Lymph node	(7)	(7)	(8)	(4)
Mediastinal, hepatocholangiocarcinoma, metastatic, liver	1 (14%)	1 (14%)		
Mediastinal, sarcoma, metastatic, skin	1 (14%)			
Lymph node, mandibular	(47)	(46)	(48)	(48)
Lymph node, mesenteric	(50)	(49)	(47)	(49)
Spleen	(49)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	2 (4%)	
Thymus	(46)	(47)	(44)	(46)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Thymoma benign	1 (2%)			
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibrosarcoma		5 (10%)	1 (2%)	2 (4%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, sarcoma	1 (2%)			
Subcutaneous tissue, schwannoma malignant				2 (4%)
Subcutaneous tissue, pinna, fibroma				1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Femur, osteosarcoma			1 (2%)	
Vertebra, osteosarcoma				1 (2%)
Skeletal muscle	(3)	(2)	(1)	(3)
Carcinoma, metastatic, islets, pancreatic		1 (50%)		
Hepatocholangiocarcinoma, metastatic, liver	1 (33%)			
Osteosarcoma, metastatic, bone			1 (100%)	
Nervous System				
Brain	(50)	(50)	(49)	(50)
Spinal cord				(2)
Meninges, meningioma malignant				1 (50%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	4 (8%)	2 (4%)	5 (10%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)	
Alveolar/bronchiolar carcinoma		3 (6%)	2 (4%)	1 (2%)
Carcinoma, metastatic, uncertain primary site		1 (2%)		
Fibrosarcoma, metastatic, skin		2 (4%)	1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)		1 (2%)	1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)		
Osteosarcoma, metastatic, bone			1 (2%)	1 (2%)
Sarcoma, metastatic, skin	1 (2%)			
Schwannoma malignant, metastatic, skin				1 (2%)
Special Senses System				
Harderian gland		(1)	(1)	(2)
Adenoma		1 (100%)		2 (100%)
Carcinoma			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Lymphoma malignant	7 (14%)	10 (20%)	8 (16%)	6 (12%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	21	32	31	32
Total primary neoplasms	25	49	36	41
Total animals with benign neoplasms	13	22	14	20
Total benign neoplasms	13	25	14	24
Total animals with malignant neoplasms	12	20	19	17
Total malignant neoplasms	12	24	22	17
Total animals with metastatic neoplasms	3	6	4	3
Total metastatic neoplasms	11	15	13	4
Total animals with malignant neoplasms of uncertain primary site		1		

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	4 5 6	5 4 7	5 6 5	5 8 0	5 8 6	6 1 5	6 2 2	6 3 1	6 6 3	7 1 6	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 3 2	2 1 3	2 1 0	2 0 2	2 0 1 8	2 1 3 6	2 2 1	2 1 1 7	2 0 0 9	2 0 0 1	2 0 0 3	2 2 4	2 4 9	2 0 4	2 0 0 5	2 0 0 7	2 0 0 8	2 1 1 1	2 1 1 6	2 1 1 9	2 2 2 2	2 2 2 5	2 2 2 8	2 2 2 9	2 3 3 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma					X						X						X				X				
Hepatocholangiocarcinoma									X																
Mesentery		+					+	+	+			+		+					+			+		+	
Hepatocholangiocarcinoma, metastatic, liver									X																
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X																
Salivary glands	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue									M																
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X																
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	M	M	+	M	+	M	+	+	+	M	+	+	+	+	M	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																							X		
Thyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X																
Oviduct																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	23 3	23 4	23 9	24 0	24 4	24 6	24 7	24 8	25 6	26 2	26 4	26 5	27 0	27 3	27 6	27 7	28 0	28 5	28 7	28 8	29 1	29 2	29 3	29 5	29 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Intestinal arge, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestinal arge, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestinal malli, leum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																				X	X					2
Hepatocellular adenoma		X									X										X		X		X	9
Hepatocholangiocarcinoma																										1
Mesentery						+		+			+										+				+	14
Hepatocholangiocarcinoma, metastatic, liver																										1
Oral mucosa														+												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Salivary gl lands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, f orestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																	X									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	M	+	+	M	+	+	M	+	M	M	M	+	M	+	M	+	M	+	+	+	33
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Hepatocholangiocarcinoma, metastatic, liver																										1
Oviduct												+														1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	4 5 6	5 4 7	5 6 5	5 8 0	5 8 6	6 1 5	6 2 2	6 3 1	6 6 3	7 1 6	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 3 2	2 1 3	2 1 0	2 0 2	2 1 8	2 3 6	2 2 1	2 1 7	2 0 9	2 0 1	2 0 3	2 2 4	2 4 9	2 0 4	2 0 5	2 0 7	2 0 8	2 1 1	2 1 6	2 1 9	2 2 2	2 2 5	2 2 8	2 2 9	2 3 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+	+			+	+					+											
Mediastinal, hepatocholangiocarcinoma, metastatic, liver									X																
Mediastinal, sarcoma, metastatic, skin					X																				
Lymph node, mandibular	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X																
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, sarcoma					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+					+		+														
Hepatocholangiocarcinoma, metastatic, liver									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Hepatocellular carcinoma, metastatic, liver																									
Hepatocholangiocarcinoma, metastatic, liver									X																
Sarcoma, metastatic, skin					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant				X			X	X			X			X										X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 0 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	23 3	23 4	23 9	24 0	24 4	24 6	24 7	24 8	25 0	25 6	26 2	26 4	26 5	27 0	27 3	27 6	27 7	28 0	28 5	28 7	28 8	29 1	29 2	29 3	29 5	29 0	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																	+			+							7
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																											1
Mediastinal, sarcoma, metastatic, skin																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hepatocholangiocarcinoma, metastatic, liver																											1
Thymoma benign																X											1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma							X																				1
Subcutaneous tissue, sarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																											3
Hepatocholangiocarcinoma, metastatic, liver																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																											1
Hepatocellular carcinoma, metastatic, liver																					X						1
Hepatocholangiocarcinoma, metastatic, liver																											1
Sarcoma, metastatic, skin																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																											
None																											
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																				X							7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

Number of Days on Study	4 8 4	6 0 5	6 4 3	6 5 0	6 5 1	6 5 1	6 5 2	6 5 9	6 5 9	6 6 4	6 6 7	6 7 3	6 7 3	6 8 3	7 0 6	7 0 9	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9
Carcass ID Number	2 5 7	2 6 9	2 7 7	2 7 4	2 5 4	2 8 8	2 6 4	2 7 2	2 8 9	2 6 7	2 7 5	2 6 8	2 9 3	2 7 1	2 9 4	2 8 0	2 5 5	2 5 8	2 5 9	2 7 9	2 8 2	2 9 1	2 9 6	2 5 2	2 5 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic										X															
Hepatocellular carcinoma													X				X								
Hepatocellular adenoma											X		X												
Hepatocellular adenoma, multiple																									
Hepatocholangiocarcinoma									X																
Mesentery			+	+	+				+	+	+			+	+			+			+				
Carcinoma, metastatic, islets, pancreatic										X															
Fibrosarcoma, metastatic, skin														X											
Hepatocholangiocarcinoma, metastatic, liver									X																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X																
Salivary glands	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X																
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																						X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X															
Parathyroid gland	+	+	+	M	M	M	M	M	+	+	M	+	+	M	+	+	+	M	+	M	+	M	+	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X																						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, follicular cell, adenoma																									
General Body System																									
Peritoneum									+																
Hepatocholangiocarcinoma, metastatic, liver									X																
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Hemangioma																									
Teratoma benign			X																						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal										X					X										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	26 1	26 2	26 3	26 5	26 6	27 0	28 4	29 0	29 2	29 8	29 9	30 0	25 1	25 3	26 0	27 3	27 6	27 8	28 1	28 3	28 5	28 6	28 7	29 5	29 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic																										1
Hepatocellular carcinoma																										2
Hepatocellular adenoma	X				X										X							X			6
Hepatocellular adenoma, multiple				X																						1
Hepatocholangiocarcinoma																										1
Mesentery							+			+	+	+	+					+			+		+	+		19
Carcinoma, metastatic, islets, pancreatic																										1
Fibrosarcoma, metastatic, skin																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Parathyroid gland	+	M	+	M	M	+	+	M	M	+	+	+	+	+	+	+	M	M	+	+	+	M	+	M	+	31
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	M	+	+	+	+	+	47
Pars distalis, adenoma														X			X									3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Bilateral, follicular cell, adenoma														X												1
General Body System																										
Peritoneum																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma									X												X					2
Hemangioma				X			X																			2
Teratoma benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X																							3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

Number of Days on Study	4 8 4	6 0 5	6 4 3	6 5 0	6 5 1	6 5 1	6 5 2	6 5 9	6 5 9	6 6 4	6 6 7	6 7 3	6 7 3	6 8 3	7 0 6	7 0 9	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9
Carcass ID Number	2 5 7	2 6 9	2 7 7	2 7 4	2 5 4	2 8 8	2 6 4	2 7 2	2 8 9	2 6 7	2 7 5	2 6 8	2 9 3	2 7 1	2 9 4	2 8 0	2 5 5	2 5 8	2 5 9	2 7 9	2 8 2	2 9 1	2 9 6	2 5 2	2 5 6
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																						
Lymph node			+	+	+				+	+														
Mediastinal, hepatocholangiocarcinoma, metastatic, liver									X															
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																						
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma						X					X	X		X										
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+				+														
Carcinoma, metastatic, islets, pancreatic										X														
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X				X												
Alveolar/bronchiolar carcinoma																								
Carcinoma, metastatic, uncertain primary site																								
Fibrosarcoma, metastatic, skin						X						X												
Hepatocholangiocarcinoma, metastatic, liver									X															
Nose	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Harderian gland																								
Adenoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X															
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant				X	X					X							X			X				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 750 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	26 61	26 62	26 63	26 65	26 66	27 00	28 04	29 00	29 02	29 98	29 99	30 00	25 01	25 53	26 00	27 30	27 60	27 61	28 10	28 13	28 30	28 36	28 37	29 05	29 07	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node																					+		+			7
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																										1
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma											X															5
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Carcinoma, metastatic, islets, pancreatic																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X		X													4
Alveolar/bronchiolar carcinoma								X					X											X		3
Carcinoma, metastatic, uncertain primary site																			X							1
Fibrosarcoma, metastatic, skin																										2
Hepatocholangiocarcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																+										1
Adenoma																X										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant				X			X														X	X	X			10

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	4 7 7	5 2 4	6 1 0	6 1 7	6 2 1	6 7 7	6 8 7	6 9 1	7 0 6	7 1 6	7 1 6	7 2 3	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 1 0	3 1 3	3 0 7	3 3 8	3 4 7	3 0 2	3 0 5	3 1 5	3 4 5	3 1 2	3 1 4	3 4 1	3 0 4	3 0 1	3 0 3	3 0 9	3 1 1	3 2 0	3 2 4	3 3 3	3 4 6	3 5 0	3 0 6	3 1 6	3 1 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin	X																								
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, uterus				X																					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin	X																								
Hemangiosarcoma																	X								
Hepatocellular carcinoma								X								X			X						
Hepatocellular adenoma															X								X		
Hepatocellular adenoma, multiple																									
Mesentery	+	+	+	+					+	+		+	+			+		+			+				
Fibrosarcoma, metastatic, skin	X																								
Osteosarcoma, metastatic, bone									X																
Sarcoma													X												
Oral mucosa												+													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																		X							
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue									M																
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin	X																								
Osteosarcoma, metastatic, bone									X																
Adrenal medulla	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Parathyroid gland	M	+	+	+	M	+	+	+	M	+	+	+	M	M	M	+	+	M	M	M	+	+	+	+	+
Pituitary gland	I	+	+	+	+	+	+	+	M	+	+	+	M	+	M	I	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	321	323	337	340	444	449	008	018	119	122	223	225	226	227	228	229	230	231	234	235	236	239	242	243	248	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, uterus																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Hemangiosarcoma																										1
Hepatocellular carcinoma									X																	4
Hepatocellular adenoma																										2
Hepatocellular adenoma, multiple					X																					1
Mesentery	+														+			+		+	+	+				17
Fibrosarcoma, metastatic, skin																										1
Osteosarcoma, metastatic, bone																										1
Sarcoma																										1
Oral mucosa																		+								2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, skin																										1
Osteosarcoma, metastatic, bone																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign																X										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X				X	3
Parathyroid gland	+	M	M	M	+	+	+	M	+	+	+	M	+	+	M	M	+	+	M	I	+	+	M	+	+	31
Pituitary gland	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	43
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	4 7 7	5 2 4	6 1 0	6 1 7	6 2 1	6 7 7	6 8 7	6 9 1	7 0 6	7 1 6	7 1 6	7 2 3	7 2 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 1 0	3 1 3	3 0 7	3 3 8	3 4 7	3 0 2	3 0 5	3 1 5	3 4 5	3 1 2	3 1 4	3 4 1	3 0 4	3 0 1	3 0 3	3 0 9	3 1 1	3 2 0	3 2 4	3 3 3	3 4 6	3 5 0	3 0 6	3 1 6	3 1 7
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																				X					
Granulosa cell tumor benign			X																						
Hemangioma																									
Osteosarcoma, metastatic, bone									X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma				X																					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+								+		+					+							
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	M	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma	X																								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma									X																
Skeletal muscle									+																
Osteosarcoma, metastatic, bone									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx									M																
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma														X											
Fibrosarcoma, metastatic, skin	X																								
Hepatocellular carcinoma, metastatic, liver								X																	
Osteosarcoma, metastatic, bone									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																	+								
Harderian gland																	+								
Carcinoma																	X								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	32 1	32 2	33 7	34 0	44 4	44 9	70 8	71 8	71 9	72 2	72 3	72 5	72 6	72 7	72 8	72 9	73 0	73 1	73 4	73 5	73 6	73 9	74 2	74 3	74 8	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										1
Granulosa cell tumor benign																										1
Hemangioma													X													1
Osteosarcoma, metastatic, bone																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+					+															+					8
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma												X														2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femur, osteosarcoma																										1
Skeletal muscle																										1
Osteosarcoma, metastatic, bone																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Larynx																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X			X																						2
Alveolar/bronchiolar adenoma, multiple																						X				1
Alveolar/bronchiolar carcinoma																								X		2
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver																										1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland																										1
Carcinoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 1,500 ppm

Number of Days on Study	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	32 1	33 2	33 7	34 0	44 4	44 9	40 8	11 8	11 9	12 2	22 3	22 5	22 6	22 7	22 8	22 9	23 0	23 1	23 4	23 5	23 6	23 9	24 2	44 3	44 8	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant															X						X					8

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	4 0 1	4 8 4	5 2 0	5 6 7	6 5 9	6 7 3	6 8 7	7 0 5	7 0 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 9 4	3 5 1	3 5 9	3 8 0	3 6 6	3 6 4	3 5 8	3 9 2	4 0 0	3 5 6	3 5 7	3 6 1	3 6 3	3 6 8	3 7 1	3 7 6	3 8 2	3 9 6	3 5 2	3 5 3	3 5 4	3 5 5	3 6 0	3 6 9	3 7 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																			X						
Hepatocellular adenoma											X					X									
Hepatocellular adenoma, multiple																									
Mesentery						+			+		+		+		+						+				
Oral mucosa																								+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin			X																						
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Squamous cell papilloma									X																
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	M	+	+	M	+	+	+	M	+	M	+	+	+	+	+	M	+	M	+	+	M
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, carcinoma																									
General Body System																									
Peritoneum																									
Genital System																									
Clitoral gland	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																					X				
Hemangioma																									
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal					X																				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	377	379	381	385	388	390	393	395	398	399	362	365	367	370	372	373	375	378	383	384	386	387	389	391	397	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma	X																		X			X				5
Hepatocellular adenoma, multiple					X																					1
Mesentery					+			+		+					+	+					+			+		13
Oral mucosa														+	+											3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, skin																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma					X							X														2
Squamous cell papilloma									X										X							3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma				X																						1
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, carcinoma													X													1
General Body System																										
Peritoneum																							+			1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma								X													X					3
Hemangioma	X																									1
Luteoma																	X									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	401	484	520	567	659	673	687	705	708	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729
Carcass ID Number	394	351	559	580	666	664	658	592	600	556	557	611	663	668	671	716	782	796	552	553	554	555	560	569	574
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+			+								+							
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma								X																	
Subcutaneous tissue, schwannoma malignant			X									X													
Subcutaneous tissue, pinna, fibroma																							X		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, osteosarcoma																									
Skeletal muscle	+			+																					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+			+																					
Spinal cord	+			+																					
Meninges, meningioma malignant	X																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																							X		
Hepatocellular carcinoma, metastatic, liver																		X							
Osteosarcoma, metastatic, bone																									
Schwannoma malignant, metastatic, skin			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant						X	X											X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite: 3,000 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	37 7	37 9	38 1	38 5	38 8	39 0	39 3	39 5	39 8	39 9	36 2	36 5	36 7	37 0	37 2	37 3	37 5	37 8	38 3	38 4	38 6	38 7	38 9	39 1	39 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node											+															4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma									X																	2
Subcutaneous tissue, schwannoma malignant																										2
Subcutaneous tissue, pinna, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, osteosarcoma		X																								1
Skeletal muscle																							+			3
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										2
Spinal cord																										2
Meninges, meningioma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X				X									X	X	X								5
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver																										1
Osteosarcoma, metastatic, bone		X																								1
Schwannoma malignant, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland						+													+							2
Adenoma						X													X							2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant								X			X										X					6

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Liver: Hepatocellular Adenoma				
Overall rate[a]	9/50 (18%)	7/50 (14%)	3/50 (6%)	6/50 (12%)
Adjusted rate[b]	19.5%	15.2%	6.4%	12.9%
Terminal rate[c]	8/40 (20%)	5/34 (15%)	3/37 (8%)	6/41 (15%)
First incidence (days)	586	667	728 (T)	728 (T)
Poly-3 test[d]	P=0.197N	P=0.394N	P=0.057N	P=0.283N
Liver: Hepatocellular Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	4/50 (8%)	1/50 (2%)
Adjusted rate	4.4%	4.4%	8.5%	2.2%
Terminal rate	2/40 (5%)	1/34 (3%)	3/37 (8%)	1/41 (2%)
First incidence (days)	728 (T)	673	691	728 (T)
Poly-3 test	P=0.422N	P=0.693N	P=0.349	P=0.494N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	10/50 (20%)	8/50 (16%)	7/50 (14%)	7/50 (14%)
Adjusted rate	21.6%	17.3%	14.9%	15.1%
Terminal rate	9/40 (23%)	6/34 (18%)	6/37 (16%)	7/41 (17%)
First incidence (days)	586	667	691	728 (T)
Poly-3 test	P=0.250N	P=0.399N	P=0.285N	P=0.292N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/50 (2%)	4/50 (8%)	3/50 (6%)	5/50 (10%)
Adjusted rate	2.2%	8.7%	6.4%	10.8%
Terminal rate	1/40 (3%)	2/34 (6%)	3/37 (8%)	5/41 (12%)
First incidence (days)	728 (T)	659	728 (T)	728 (T)
Poly-3 test	P=0.118	P=0.181	P=0.313	P=0.105
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	0/50 (0%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate	0.0%	6.6%	4.3%	2.2%
Terminal rate	0/40 (0%)	3/34 (9%)	2/37 (5%)	1/41 (2%)
First incidence (days)	—[e]	728 (T)	728 (T)	728 (T)
Poly-3 test	P=0.566	P=0.118	P=0.242	P=0.503
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	1/50 (2%)	6/50 (12%)	5/50 (10%)	6/50 (12%)
Adjusted rate	2.2%	13.0%	10.7%	12.9%
Terminal rate	1/40 (3%)	4/34 (12%)	5/37 (14%)	6/41 (15%)
First incidence (days)	728 (T)	659	728 (T)	728 (T)
Poly-3 test	P=0.110	P=0.057	P=0.106	P=0.059
Ovary: Cystadenoma				
Overall rate	0/47 (0%)	2/49 (4%)	1/50 (2%)	3/49 (6%)
Adjusted rate	0.0%	4.5%	2.1%	6.6%
Terminal rate	0/37 (0%)	2/33 (6%)	1/37 (3%)	3/40 (8%)
First incidence (days)	—	728 (T)	728 (T)	728 (T)
Poly-3 test	P=0.113	P=0.247	P=0.518	P=0.130

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Pancreatic Islets: Adenoma				
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	0.0%	6.4%	0.0%
Terminal rate	0/40 (0%)	0/34 (0%)	2/37 (5%)	0/41 (0%)
First incidence (days)	—	—[f]	716	—
Poly-3 test	P=0.550		P=0.123	—
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	2.2%	6.4%	0.0%
Terminal rate	0/40 (0%)	0/34 (0%)	2/37 (5%)	0/41 (0%)
First incidence (days)	—	664	716	—
Poly-3 test	P=0.627N	P=0.501	P=0.123	—
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	1/48 (2%)	3/47 (6%)	0/43 (0%)	1/48 (2%)
Adjusted rate	2.3%	6.9%	0.0%	2.2%
Terminal rate	1/38 (3%)	2/32 (6%)	0/33 (0%)	1/40 (3%)
First incidence (days)	728 (T)	643	—	728 (T)
Poly-3 test	P=0.401N	P=0.305	P=0.515N	P=0.754N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rate	0/50 (0%)	5/50 (10%)	1/50 (2%)	2/50 (4%)
Adjusted rate	0.0%	10.7%	2.1%	4.3%
Terminal rate	0/40 (0%)	1/34 (3%)	0/37 (0%)	1/41 (2%)
First incidence (days)	—	651	477	705
Poly-3 test	P=0.514	P=0.032	P=0.507	P=0.241
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	1/50 (2%)	5/50 (10%)	1/50 (2%)	2/50 (4%)
Adjusted rate	2.2%	10.7%	2.1%	4.3%
Terminal rate	0/40 (0%)	1/34 (3%)	0/37 (0%)	1/41 (2%)
First incidence (days)	586	651	477	705
Poly-3 test	P=0.517N	P=0.103	P=0.755N	P=0.503
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	1/50 (2%)	5/50 (10%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.2%	10.7%	2.1%	6.4%
Terminal rate	0/40 (0%)	1/34 (3%)	0/37 (0%)	2/41 (5%)
First incidence (days)	586	651	477	705
Poly-3 test	P=0.462	P=0.103	P=0.755N	P=0.308
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	1/50 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.2%	0.0%	2.1%	6.4%
Terminal rate	1/40 (3%)	0/34 (0%)	1/37 (3%)	2/41 (5%)
First incidence (days)	728 (T)	—	728 (T)	708
Poly-3 test	P=0.099	P=0.500N	P=0.756N	P=0.312

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Stomach (Forestomach): Squamous Cell Papilloma or Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	1/50 (2%)	5/50 (10%)
Adjusted rate	2.2%	0.0%	2.1%	10.7%
Terminal rate	1/40 (3%)	0/34 (0%)	1/37 (3%)	4/41 (10%)
First incidence (days)	728 (T)	—	728 (T)	708
Poly-3 test	P=0.011	P=0.500N	P=0.756N	P=0.106
Uterus: Stromal Polyp				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	0.0%	6.5%	0.0%	2.1%
Terminal rate	0/40 (0%)	1/34 (3%)	0/37 (0%)	0/41 (0%)
First incidence (days)	—	664	—	659
Poly-3 test	P=0.627N	P=0.120	—	P=0.504
All Organs: Hemangiosarcoma				
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	2.2%	2.2%	6.4%	0.0%
Terminal rate	1/40 (3%)	0/34 (0%)	3/37 (8%)	0/41 (0%)
First incidence (days)	728 (T)	605	728 (T)	—
Poly-3 test	P=0.402N	P=0.759N	P=0.313	P=0.497N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/50 (2%)	3/50 (6%)	4/50 (8%)	1/50 (2%)
Adjusted rate	2.2%	6.5%	8.6%	2.2%
Terminal rate	1/40 (3%)	2/34 (6%)	4/37 (11%)	1/41 (2%)
First incidence (days)	728 (T)	605	728 (T)	728 (T)
Poly-3 test	P=0.513N	P=0.308	P=0.185	P=0.757N
All Organs: Malignant Lymphoma				
Overall rate	7/50 (14%)	10/50 (20%)	8/50 (16%)	6/50 (12%)
Adjusted rate	14.9%	21.5%	16.7%	12.8%
Terminal rate	4/40 (10%)	7/34 (21%)	4/37 (11%)	4/41 (10%)
First incidence (days)	580	650	524	673
Poly-3 test	P=0.331N	P=0.288	P=0.515	P=0.502N
All Organs: Benign Neoplasms				
Overall rate	13/50 (26%)	22/50 (44%)	14/50 (28%)	20/50 (40%)
Adjusted rate	28.1%	46.6%	29.6%	42.7%
Terminal rate	12/40 (30%)	15/34 (44%)	12/37 (32%)	18/41 (44%)
First incidence (days)	586	643	610	659
Poly-3 test	P=0.208	P=0.048	P=0.526	P=0.103
All Organs: Malignant Neoplasms				
Overall rate	12/50 (24%)	21/50 (42%)	19/50 (38%)	17/50 (34%)
Adjusted rate	25.2%	43.5%	38.6%	35.1%
Terminal rate	7/40 (18%)	11/34 (32%)	11/37 (30%)	12/41 (29%)
First incidence (days)	580	605	477	401
Poly-3 test	P=0.320	P=0.045	P=0.113	P=0.201

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	21/50 (42%)	33/50 (66%)	31/50 (62%)	32/50 (64%)
Adjusted rate	44.0%	67.4%	63.0%	65.6%
Terminal rate	16/40 (40%)	20/34 (59%)	22/37 (60%)	25/41 (61%)
First incidence (days)	580	605	477	401
Poly-3 test	P=0.054	P=0.015	P=0.045	P=0.024

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

TABLE D4
Historical Incidence of Forestomach Neoplasms in Control Female B6C3F$_1$ Mice

Study	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Carcinoma
Historical Incidence in Controls Given NTP-2000 Diet[a]			
p,p′-Dichlorodiphenyl sulfone (feed)	0/50	0/50	0/50
Indium phosphide (inhalation)	0/50	1/50	1/50
Methacrylonitrile (gavage)	0/50	0/50	0/50
p-Nitrotoluene (feed)	0/50	0/50	0/50
Sodium nitrite (drinking water)	1/50	0/50	1/50
Overall Historical Incidence in Controls Given NTP-2000 Diet			
Total (%)	1/250 (0.4%)	1/250 (0.4%)	2/250 (0.8%)
Mean ± standard deviation	0.4% ± 0.9%	0.4% ± 0.9%	0.8% ± 1.1%
Range	0%-2%	0%-2%	0%-2%
Historical Incidence in Drinking Water Controls Given NIH-07 Diet at Battelle Columbus Laboratories[b]			
Sodium fluoride	3/80	0/80	3/80
Overall Historical Incidence in Drinking Water Controls Given NIH-07 Diet			
Total (%)	5/340 (1.5%)	0/340	5/340 (1.5%)
Mean ± standard deviation	1.3% ± 1.6%		1.3% ± 1.6%
Range	0%-4%		0%-4%
Overall Historical Incidence in Feed Controls Given NIH-07 Diet			
Total (%)	15/953 (1.6%)	1/953 (0.1%)	16/953 (1.7%)
Mean ± standard deviation	1.6% ± 2.0%	0.1% ± 0.5%	1.7% ± 2.0%
Range	0%-6%	0%-2%	0%-6%
Overall Historical Incidence in Gavage (Corn Oil) Controls Given NIH-07 Diet			
Total (%)	19/463 (4.1%)	0/463	19/463 (4.1%)
Mean ± standard deviation	4.1% ± 3.5%		4.1% ± 3.5%
Range	0%-10%		0%-10%
Overall Historical Incidence in Gavage (Water) Controls Given NIH-07 Diet			
Total	0/51	0/51	0/51
Overall Historical Incidence in Inhalation (Air) Controls Given NIH-07 Diet			
Total (%)	8/1,077 (0.7%)	2/1,077 (0.2%)	10/1,077 (0.9%)
Mean ± standard deviation	0.7% ± 1.0%	0.2% ± 0.6%	0.9% ± 1.1%
Range	0%-2%	0%-2%	0%-3%

[a] Data as of 14 March 2000
[b] Data as of 23 December 1999

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite[a]

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	1	7	2	4
Natural deaths	9	9	11	5
Survivors				
Terminal sacrifice	40	34	37	41
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(48)	(50)	(50)	(49)
Cyst	1 (2%)	1 (2%)		
Infiltration cellular, mononuclear cell		3 (6%)	1 (2%)	4 (8%)
Epithelium, cytoplasmic alteration		1 (2%)		
Epithelium, hyperplasia		1 (2%)		
Intestine small, duodenum	(50)	(48)	(50)	(49)
Epithelium, inflammation, chronic active	1 (2%)			
Epithelium, ulcer	1 (2%)			
Intestine small, jejunum	(50)	(50)	(50)	(50)
Necrosis	1 (2%)			
Peyer's patch, hyperplasia, lymphoid				1 (2%)
Intestine small, ileum	(49)	(49)	(50)	(50)
Inflammation, chronic active				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis				2 (4%)
Basophilic focus	3 (6%)	4 (8%)	3 (6%)	1 (2%)
Clear cell focus	2 (4%)	3 (6%)	3 (6%)	2 (4%)
Congestion				1 (2%)
Eosinophilic focus	7 (14%)	3 (6%)	4 (8%)	5 (10%)
Hematopoietic cell proliferation	2 (4%)	5 (10%)	3 (6%)	4 (8%)
Hemorrhage	1 (2%)			
Infiltration cellular, mononuclear cell	30 (60%)	32 (64%)	29 (58%)	35 (70%)
Inflammation, chronic active	36 (72%)	35 (70%)	30 (60%)	35 (70%)
Mineralization	1 (2%)	1 (2%)	1 (2%)	
Mixed cell focus	3 (6%)	1 (2%)		
Necrosis	5 (10%)	4 (8%)	3 (6%)	2 (4%)
Pigmentation	12 (24%)	17 (34%)	16 (32%)	18 (36%)
Thrombosis		1 (2%)		
Vacuolization cytoplasmic	10 (20%)	17 (34%)	12 (24%)	13 (26%)
Bile duct, cyst			1 (2%)	
Bile duct, hyperplasia	1 (2%)	1 (2%)		1 (2%)
Centrilobular, necrosis				2 (4%)
Centrilobular, vacuolization cytoplasmic				1 (2%)
Hepatocyte, centrilobular, hypertrophy	1 (2%)			

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

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Alimentary System (continued)				
Mesentery	(14)	(19)	(17)	(13)
Congestion		1 (5%)		
Hemorrhage			1 (6%)	
Infiltration cellular, mononuclear cell				1 (8%)
Inflammation, chronic active		1 (5%)		
Inflammation, granulomatous	1 (7%)			
Pigmentation, hemosiderin			1 (6%)	
Thrombosis		1 (5%)		
Artery, inflammation, chronic active				1 (8%)
Fat, necrosis	10 (71%)	7 (37%)	10 (59%)	11 (85%)
Oral mucosa	(1)		(2)	(3)
Gingival, foreign body	1 (100%)		2 (100%)	3 (100%)
Gingival, inflammation, chronic active	1 (100%)		2 (100%)	2 (67%)
Pancreas	(50)	(50)	(50)	(50)
Infiltration cellular, mononuclear cell	14 (28%)	10 (20%)	7 (14%)	13 (26%)
Inflammation, chronic active		1 (2%)		
Acinus, atrophy	1 (2%)			1 (2%)
Acinus, hyperplasia			1 (2%)	
Acinus, hypertrophy				1 (2%)
Artery, inflammation, chronic active			1 (2%)	1 (2%)
Duct, cyst	1 (2%)	1 (2%)		
Salivary glands	(49)	(49)	(48)	(50)
Atrophy				2 (4%)
Infiltration cellular, mononuclear cell	34 (69%)	36 (73%)	40 (83%)	35 (70%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Infiltration cellular, mononuclear cell		1 (2%)		
Ulcer	1 (2%)	2 (4%)	2 (4%)	
Epithelium, hyperkeratosis				1 (2%)
Epithelium, hyperplasia	2 (4%)	3 (6%)	3 (6%)	6 (12%)
Epithelium, inflammation, chronic active	2 (4%)	3 (6%)	3 (6%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Mineralization	1 (2%)			
Epithelium, hyperplasia			1 (2%)	1 (2%)
Epithelium, necrosis			1 (2%)	
Glands, ectasia	19 (38%)	16 (32%)	10 (20%)	21 (42%)
Glands, necrosis			1 (2%)	
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Infiltration cellular, mononuclear cell			1 (2%)	
Aorta, inflammation, chronic active				1 (2%)
Aorta, mineralization	2 (4%)			
Pulmonary artery, mineralization	1 (2%)			
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy		1 (2%)		
Inflammation, chronic active		1 (2%)	1 (2%)	
Infiltration cellular, mononuclear cell	1 (2%)			
Mineralization	1 (2%)	2 (4%)		1 (2%)
Artery, inflammation, chronic active				1 (2%)
Artery, mineralization		1 (2%)		
Valve, inflammation, chronic active	2 (4%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Accessory adrenal cortical nodule	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Degeneration, fatty			1 (2%)	2 (4%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)		2 (4%)
Inflammation, chronic active		1 (2%)		
Capsule, hyperplasia	49 (98%)	50 (100%)	49 (100%)	49 (98%)
Zona fasciculata, hyperplasia			1 (2%)	1 (2%)
Zona fasciculata, hypertrophy	1 (2%)	1 (2%)		
Zona glomerulosa, hyperplasia		1 (2%)		1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	45 (90%)	44 (88%)	40 (80%)	42 (84%)
Pigmentation			1 (2%)	
Parathyroid gland	(33)	(31)	(31)	(37)
Cyst			1 (3%)	
Pituitary gland	(48)	(47)	(43)	(48)
Pars distalis, angiectasis	1 (2%)	3 (6%)		3 (6%)
Pars distalis, cyst			2 (5%)	2 (4%)
Pars distalis, hyperplasia	2 (4%)	3 (6%)	4 (9%)	6 (13%)
Thyroid gland	(49)	(49)	(48)	(49)
Inflammation, chronic active	2 (4%)	1 (2%)		1 (2%)
Follicle, cyst		2 (4%)		1 (2%)
Follicular cell, hyperplasia			1 (2%)	
General Body System				
Peritoneum		(1)		(1)
Inflammation, granulomatous				1 (100%)
Genital System				
Clitoral gland	(50)	(49)	(50)	(48)
Infiltration cellular, mononuclear cell	7 (14%)	4 (8%)	13 (26%)	3 (6%)
Inflammation, chronic active	1 (2%)			1 (2%)
Inflammation, suppurative		2 (4%)	2 (4%)	
Duct, cyst	1 (2%)			
Ovary	(47)	(49)	(50)	(49)
Angiectasis				1 (2%)
Cyst	6 (13%)	9 (18%)	9 (18%)	7 (14%)
Hemorrhage	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, adenomatous		1 (2%)		
Mineralization	3 (6%)			1 (2%)
Pigmentation				1 (2%)
Thrombosis	2 (4%)		1 (2%)	1 (2%)
Uterus	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Hydrometra	32 (64%)	31 (62%)	33 (66%)	37 (74%)
Infiltration cellular, mononuclear cell	2 (4%)			
Inflammation, suppurative	1 (2%)		2 (4%)	
Endometrium, hyperplasia, cystic	13 (26%)	10 (20%)	16 (32%)	18 (36%)
Submucosa, hyperplasia, stromal			1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Atrophy				2 (4%)
Hyperplasia				1 (2%)
Myelofibrosis			2 (4%)	
Myeloid cell, hyperplasia	2 (4%)	3 (6%)	1 (2%)	3 (6%)
Lymph node	(7)	(7)	(8)	(4)
Inflammation, granulomatous				1 (25%)
Inguinal, hyperplasia, lymphoid			1 (13%)	
Lumbar, hyperplasia, lymphoid				1 (25%)
Mediastinal, hematopoietic cell proliferation				1 (25%)
Mediastinal, hyperplasia, lymphoid			3 (38%)	1 (25%)
Mediastinal, pigmentation, hemosiderin		1 (14%)		
Renal, ectasia	1 (14%)		1 (13%)	
Renal, hemorrhage	1 (14%)		1 (13%)	
Lymph node, mandibular	(47)	(46)	(48)	(48)
Hematopoietic cell proliferation				1 (2%)
Hyperplasia, lymphoid	1 (2%)		5 (10%)	5 (10%)
Hyperplasia, plasma cell		1 (2%)	1 (2%)	
Lymph node, mesenteric	(50)	(49)	(47)	(49)
Ectasia	1 (2%)	1 (2%)	2 (4%)	
Fibrosis			1 (2%)	
Hematopoietic cell proliferation				1 (2%)
Hyperplasia, lymphoid		1 (2%)	2 (4%)	
Inflammation, granulomatous				1 (2%)
Spleen	(49)	(50)	(50)	(50)
Hematopoietic cell proliferation	37 (76%)	39 (78%)	35 (70%)	39 (78%)
Hyperplasia, lymphoid	4 (8%)	3 (6%)	4 (8%)	1 (2%)
Metaplasia, osseous		1 (2%)		
Capsule, inflammation, chronic active				1 (2%)
Thymus	(46)	(47)	(44)	(46)
Cyst	10 (22%)	12 (26%)	17 (39%)	16 (35%)
Ectopic parathyroid gland	1 (2%)	5 (11%)	3 (7%)	2 (4%)
Hyperplasia, lymphoid			1 (2%)	
Integumentary System				
Mammary gland	(49)	(50)	(49)	(50)
Hyperplasia, cystic	1 (2%)	3 (6%)		1 (2%)
Skin	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)	3 (6%)	2 (4%)	
Ulcer	1 (2%)	1 (2%)	1 (2%)	
Epidermis, hyperplasia		1 (2%)	1 (2%)	
Subcutaneous tissue, fibrosis	2 (4%)			
Subcutaneous tissue, infiltration cellular, mononuclear cell				2 (4%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Periosteum, synovial tissue, inflammation, chronic active				1 (2%)
Skeletal muscle	(3)	(2)	(1)	(3)
Artery, inflammation, chronic active				1 (33%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
Nervous System				
Brain	(50)	(50)	(49)	(50)
Degeneration	1 (2%)			
Hemorrhage	1 (2%)	1 (2%)		
Peripheral nerve				(2)
Sciatic, inflammation, chronic active				1 (50%)
Spinal cord				(2)
Demyelination				2 (100%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
Infiltration cellular, mononuclear cell	1 (2%)	2 (4%)		1 (2%)
Inflammation, chronic active	2 (4%)	3 (6%)	2 (4%)	
Metaplasia, osseous				1 (2%)
Mineralization		1 (2%)	1 (2%)	
Alveolar epithelium, hyperplasia		1 (2%)	4 (8%)	3 (6%)
Alveolus, infiltration cellular, histiocyte		3 (6%)	2 (4%)	2 (4%)
Bronchus, mineralization	1 (2%)			
Interstitium, inflammation, chronic active				1 (2%)
Vein, mineralization	1 (2%)	1 (2%)	1 (2%)	
Nose	(50)	(49)	(50)	(50)
Foreign body			1 (2%)	
Inflammation, chronic active			1 (2%)	
Nasolacrimal duct, inflammation, suppurative		1 (2%)	1 (2%)	1 (2%)
Special Senses System				
Eye			(1)	
Cataract			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet		1 (2%)		
Infarct	2 (4%)	4 (8%)	3 (6%)	6 (12%)
Infiltration cellular, mononuclear cell	35 (70%)	37 (74%)	34 (68%)	40 (80%)
Infiltration cellular, plasma cell				1 (2%)
Inflammation, suppurative	1 (2%)			
Mineralization	5 (10%)	8 (16%)	6 (12%)	4 (8%)
Nephropathy	20 (40%)	17 (34%)	13 (26%)	20 (40%)
Cortex, cyst				1 (2%)
Vein, inflammation, chronic active				1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Infiltration cellular, mononuclear cell	25 (50%)	29 (58%)	24 (48%)	25 (50%)
Inflammation, chronic active	1 (2%)			1 (2%)
Mineralization	1 (2%)			

APPENDIX E
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1992). Sodium nitrite was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98 and TA100 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of sodium nitrite. The high dose was limited to 10,000 µg/plate. All positive trials were repeated under the conditions that elicited the positive response.

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

RAT AND MOUSE BONE MARROW MICRONUCLEUS TEST PROTOCOL

The standard three-exposure protocol is described in detail by Shelby *et al.* (1993). Male F344/N rats and B6C3F_1 mice were injected intraperitoneally (three times at 24-hour intervals) with sodium nitrite dissolved in phosphate-buffered saline. Solvent control animals were injected with phosphate-buffered saline only. The positive control animals received injections of cyclophosphamide. The animals were killed 24 hours after the third injection, and blood smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in up to five animals per dose group.

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

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). At the end of the 14-week toxicity study, peripheral blood samples were obtained from male and female mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with acridine orange and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 normochromatic erythrocytes (NCEs) in each of 10 animals per exposure group.

The results for NCEs in mouse peripheral blood were tabulated as described for PCEs in the rat and mouse bone marrow micronucleus test protocol.

EVALUATION PROTOCOL

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

RESULTS

Sodium nitrite (100-10,000 µg/plate) was mutagenic in *S. typhimurium* strain TA100, with and without Aroclor 1254-induced hamster and rat liver S9 enzymes; no mutagenicity was observed in strain TA98 (Table E1; Zeiger *et al.*, 1992). When sodium nitrite was administered by intraperitoneal injection at 6.25 to 200 mg/kg to male rats three times at 24-hour intervals, no significant increase in the frequency of micronucleated PCEs was observed in any of the dose groups (Table E2). The initial trial was judged to be positive, based on the trend test (P=0.001); however, results of a repeat trial, in which 50 mg/kg was the highest nonlethal dose tested, were negative, and the rat bone marrow micronucleus test with sodium nitrite was judged to be negative overall. A similar study in which male mice were administered 7.81 to 250 mg/kg also gave negative results (Table E3). A third *in vivo* study, a peripheral blood micronucleus test in mice administered sodium nitrite (375-5,000 ppm) for 14 weeks, showed no significant increase in the frequency of micronucleated NCEs in either males or females (Table E4). Thus, sodium nitrite demonstrated mutagenic activity in a strain of *S. typhimurium* that mutates via base-pair substitution, but no indication of chromosomal damage was observed in three micronucleus studies conducted in rats and mice *in vivo*.

TABLE E1
Mutagenicity of Sodium Nitrite in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/Plate[b]					
		-S9		+30% hamster S9		+30% rat S9	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	139 ± 19.4	171 ± 5.5	150 ± 0.7	158 ± 12.0	160 ± 0.6	173 ± 6.2
	100	143 ± 14.1		148 ± 8.5	187 ± 5.6	201 ± 13.3	199 ± 14.7
	333	126 ± 8.7		165 ± 4.4	182 ± 13.5	197 ± 9.2	233 ± 6.4
	1,000	142 ± 7.5	211 ± 19.9	223 ± 4.6	220 ± 4.7	237 ± 12.5	230 ± 11.8
	1,666		224 ± 10.6				
	3,333	195 ± 6.9	274 ± 21.4	341 ± 6.4	309 ± 11.7	259 ± 36.8	312 ± 10.4
	6,666		376 ± 7.5				
	10,000	280 ± 9.9	443 ± 12.0	508 ± 29.5	451 ± 20.1	390 ± 38.8	353 ± 5.4
Trial summary		Positive	Positive	Positive	Positive	Weakly Positive	Positive
Positive control[c]		1,036 ± 10.2	878 ± 22.7	832 ± 34.1	894 ± 24.1	568 ± 22.5	555 ± 18.3
TA98	0	31 ± 0.9		42 ± 1.7		40 ± 4.8	
	100	27 ± 0.6		40 ± 4.6		33 ± 3.6	
	333	26 ± 4.2		39 ± 3.1		41 ± 3.8	
	1,000	30 ± 3.5		47 ± 4.2		29 ± 1.0	
	3,333	25 ± 2.6		42 ± 2.1		33 ± 2.8	
	10,000	26 ± 2.8		30 ± 5.2		21 ± 5.0	
Trial summary		Negative		Negative		Negative	
Positive control		432 ± 19.0		539 ± 6.1		155 ± 14.3	

[a] Study was performed at SRI International. The detailed protocol and these data are presented by Zeiger *et al.* (1992). 0 µg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] The positive controls in the absence of metabolic activation were sodium azide (TA100) and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with both strains was 2-aminoanthracene.

TABLE E2
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Rats Treated with Sodium Nitrite by Intraperitoneal Injection[a]

Compound	Dose (mg/kg)	Number of Rats with Erythrocytes Scored	Micronucleated PCEs/ 1,000 PCEs[b]	P Value[c]
Trial 1				
Phosphate-buffered saline[d]	0	5	1.10 ± 0.24	
Cyclophosphamide[e]	25	5	26.20 ± 2.95	0.0000
Sodium nitrite	6.25	5	0.90 ± 0.33	0.6411
	12.5	5	0.80 ± 0.30	0.7109
	25	5	1.10 ± 0.48	0.5000
	50	5	1.30 ± 0.60	0.3707
	100	5	2.70 ± 0.60	0.0180
	200	Lethal		
			P=0.001[f]	
Trial 2				
Phosphate-buffered saline	0	5	1.10 ± 0.51	
Cyclophosphamide	25	3	24.83 ± 2.52	0.0000
Sodium nitrite	25	5	1.00 ± 0.45	0.5635
	50	5	1.10 ± 0.37	0.5000
			P=0.500	

[a] Study was performed at Integrated Laboratory Systems, Inc. The detailed protocol is presented by Shelby *et al.* (1993). PCE=polychromatic erythrocyte
[b] Mean ± standard error
[c] Pairwise comparison with the solvent control; significant at $P \leq 0.005$ for trial 1 and at $P \leq 0.012$ for trial 2 (ILS, 1990)
[d] Solvent control
[e] Positive control
[f] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at $P \leq 0.025$ (ILS, 1990)

TABLE E3
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Mice Treated with Sodium Nitrite by Intraperitoneal Injection[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/ 1,000 PCEs[b]	P Value[c]
Phosphate-buffered saline[d]	0	5	1.10 ± 0.51	
Cyclophosphamide[e]	50	5	28.60 ± 4.24	0.0000
Sodium nitrite	7.81	5	1.80 ± 0.34	0.1933
	15.63	5	1.80 ± 0.60	0.1933
	31.25	5	1.60 ± 0.78	0.2608
	62.5	5	1.60 ± 0.73	0.2608
	125	5	1.80 ± 0.49	0.1933
	250	Lethal		
			P=0.343[f]	

[a] Study was performed at Integrated Laboratory Systems, Inc. The detailed protocol is presented by Shelby *et al.* (1993). PCE=polychromatic erythrocyte
[b] Mean ± standard error
[c] Pairwise comparison with the solvent control; significant at P≤0.005 (ILS, 1990)
[d] Solvent control
[e] Positive control
[f] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)

TABLE E4
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Administration of Sodium Nitrite in Drinking Water for 14 Weeks[a]

	Concentration (ppm)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/ 1,000 NCEs[b]	P Value[c]
Male				
	0	10	0.65 ± 0.17	
	375	10	0.80 ± 0.15	0.2887
	750	10	0.50 ± 0.13	0.7343
	1,500	10	0.85 ± 0.22	0.2325
	3,000	10	0.90 ± 0.12	0.1845
	5,000	10	0.80 ± 0.08	0.2887
			P=0.204[d]	
Female				
	0	10	0.50 ± 0.17	
	375	10	0.70 ± 0.20	0.2070
	750	10	0.55 ± 0.16	0.4136
	1,500	10	0.55 ± 0.14	0.4136
	3,000	10	0.60 ± 0.16	0.3349
	5,000	10	0.45 ± 0.12	0.5907
			P=0.704	

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

APPENDIX F
CLINICAL PATHOLOGY RESULTS

TABLE F1 **Hematology and Clinical Chemistry Data for Rats in the 14-Week Drinking Water Study of Sodium Nitrite 222**
TABLE F2 **Hemoglobin, Methemoglobin, and Serum and Gastric Nitrosamine Data for Rats on Days 70 and 71 in the 14-Week Drinking Water Study of Sodium Nitrite 228**

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Drinking Water Study of Sodium Nitrite[a]

	0 ppm	375 ppm	750 ppm	1,500 ppm	3,000 ppm	5,000 ppm
Male						
Hematology						
n						
Day 5	9	6	10	7	8	9
Day 19	10	10	9	10	10	9
Week 14	10	10	10	9	10	10
Hematocrit (%)						
Day 5	41.6 ± 0.5[b]	41.1 ± 0.6[c]	39.2 ± 0.6*	40.0 ± 0.4[d]	41.0 ± 0.7[b]	39.5 ± 0.6[b]
Day 19	43.5 ± 0.2	43.9 ± 0.4	44.3 ± 0.4[b]	42.8 ± 1.0	46.3 ± 1.1	37.7 ± 1.3[b]
Week 14	43.8 ± 0.6	44.1 ± 0.5	42.0 ± 0.6	42.2 ± 0.6	45.5 ± 0.5	46.5 ± 0.7*
Hemoglobin (g/dL)						
Day 5	14.5 ± 0.2[b]	14.2 ± 0.2[c]	13.6 ± 0.2*	13.8 ± 0.1[d]	14.2 ± 0.2[b]	13.8 ± 0.2[b]
Day 19	14.9 ± 0.1	15.0 ± 0.1	15.1 ± 0.1[b]	14.7 ± 0.3	15.3 ± 0.3	12.5 ± 0.4**[b]
Week 14	15.0 ± 0.2	15.2 ± 0.1	14.7 ± 0.2	14.7 ± 0.2	15.7 ± 0.1*	16.0 ± 0.3**
Erythrocytes (10^6/μL)						
Day 5	7.08 ± 0.08[b]	6.95 ± 0.13[c]	6.90 ± 0.10	6.79 ± 0.08[d]	6.94 ± 0.13[b]	6.89 ± 0.12[b]
Day 19	7.61 ± 0.05	7.65 ± 0.10	7.90 ± 0.08*[b]	7.54 ± 0.17	8.44 ± 0.15**	8.10 ± 0.21**[b]
Week 14	8.30 ± 0.12	8.39 ± 0.08	7.97 ± 0.13	7.91 ± 0.10	8.29 ± 0.08	8.92 ± 0.25
Reticulocytes (10^6/μL)						
Day 5	0.45 ± 0.03	0.47 ± 0.05	0.72 ± 0.05**	0.51 ± 0.05	0.67 ± 0.06**	0.69 ± 0.03**[d]
Day 19	0.21 ± 0.02	0.19 ± 0.01	0.21 ± 0.02	0.23 ± 0.03	0.37 ± 0.02**	0.58 ± 0.05**
Week 14	0.22 ± 0.02	0.22 ± 0.03	0.26 ± 0.02	0.18 ± 0.02	0.30 ± 0.03*	0.37 ± 0.04**
Nucleated erythrocytes (10^3/μL)						
Day 5	1.00 ± 0.33	3.00 ± 0.45	2.80 ± 0.65	1.57 ± 0.69	2.75 ± 1.03	2.78 ± 0.49
Day 19	0.60 ± 0.22	0.90 ± 0.23	0.89 ± 0.35	1.20 ± 0.44	2.70 ± 0.52**	5.33 ± 1.12**
Week 14	0.70 ± 0.30	0.70 ± 0.21	0.60 ± 0.27	0.89 ± 0.20	1.10 ± 0.41	1.70 ± 0.50
Mean cell volume (fL)						
Day 5	58.8 ± 0.3[b]	59.2 ± 0.3[c]	56.9 ± 0.2**	59.0 ± 0.4[d]	59.1 ± 0.4[b]	57.4 ± 0.3[b]
Day 19	57.1 ± 0.4	57.4 ± 0.5	56.2 ± 0.5[b]	56.9 ± 0.5	54.9 ± 0.9	46.4 ± 0.5**[b]
Week 14	52.8 ± 0.2	52.5 ± 0.2	52.8 ± 0.1	53.3 ± 0.3	55.0 ± 0.2**	52.4 ± 1.2**
Mean cell hemoglobin (pg)						
Day 5	20.4 ± 0.1[b]	20.5 ± 0.1[c]	19.8 ± 0.1*	20.3 ± 0.1[d]	20.5 ± 0.2[b]	20.0 ± 0.1[b]
Day 19	19.6 ± 0.1	19.6 ± 0.2	19.1 ± 0.2*[b]	19.6 ± 0.2	18.1 ± 0.3**	15.4 ± 0.2**
Week 14	18.1 ± 0.1	18.1 ± 0.1	18.5 ± 0.1*	18.5 ± 0.1*	18.9 ± 0.1**	18.1 ± 0.5**
Mean cell hemoglobin concentration (g/dL)						
Day 5	34.7 ± 0.2[b]	34.6 ± 0.1[c]	34.7 ± 0.1	34.5 ± 0.2[d]	34.7 ± 0.2[b]	34.9 ± 0.2[b]
Day 19	34.3 ± 0.2	34.1 ± 0.2	34.0 ± 0.2[b]	34.4 ± 0.3	33.0 ± 0.2**	33.1 ± 0.3**[b]
Week 14	34.4 ± 0.2	34.4 ± 0.2	35.1 ± 0.2	34.8 ± 0.1	34.5 ± 0.1	34.4 ± 0.3
Platelets (10^3/μL)						
Day 5	999.9 ± 23.9[b]	1,028.6 ± 43.3[c]	1,140.8 ± 31.1*	966.3 ± 51.6[d]	1,008.7 ± 23.2[b]	1,166.4 ± 42.0*[b]
Day 19	763.6 ± 17.9	753.9 ± 24.5	827.4 ± 23.7[b]	777.3 ± 45.5	759.1 ± 30.6	1,815.2 ± 129.0**[b]
Week 14	577.7 ± 21.4	608.0 ± 13.0	597.9 ± 15.1	588.3 ± 18.3	606.1 ± 16.3	673.4 ± 56.4
Leukocytes (10^3/μL)						
Day 5	7.39 ± 0.79[b]	5.78 ± 0.55[c]	7.81 ± 0.75	6.34 ± 0.43[d]	7.79 ± 0.62[b]	8.33 ± 0.68[b]
Day 19	8.11 ± 0.26	7.22 ± 0.58	8.47 ± 0.41[b]	8.40 ± 0.60	7.66 ± 0.27	9.03 ± 0.49[b]
Week 14	9.68 ± 0.78	9.55 ± 0.54	9.67 ± 0.59	8.88 ± 0.73	8.91 ± 0.64	9.44 ± 0.57
Segmented neutrophils (10^3/μL)						
Day 5	0.93 ± 0.11	0.73 ± 0.15	0.90 ± 0.15	0.71 ± 0.09	1.14 ± 0.22	1.09 ± 0.10
Day 19	0.85 ± 0.11	0.80 ± 0.10	1.07 ± 0.19	1.09 ± 0.22	0.85 ± 0.08	1.20 ± 0.16
Week 14	1.62 ± 0.16	1.57 ± 0.22	1.45 ± 0.14	1.11 ± 0.20	1.38 ± 0.22	1.01 ± 0.13*

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Drinking Water Study of Sodium Nitrite

	0 ppm	375 ppm	750 ppm	1,500 ppm	3,000 ppm	5,000 ppm
Male (continued)						
Hematology (continued)						
n						
Day 5	9	6	10	7	8	9
Day 19	10	10	9	10	10	9
Week 14	10	10	10	9	10	10
Immature neutrophils (10^3/µL)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.014 ± 0.014	0.000 ± 0.000	0.000 ± 0.000
Day 19	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.011 ± 0.011
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Metamyelocytes (10^3/µL)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 19	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Myelocytes (10^3/µL)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 19	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Promyelocytes (10^3/µL)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 19	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Lymphocytes (10^3/µL)						
Day 5	6.80 ± 0.68	4.77 ± 0.57	6.88 ± 0.63	5.83 ± 0.37	6.89 ± 0.54	7.56 ± 0.54
Day 19	6.99 ± 0.22	6.24 ± 0.53	7.17 ± 0.40	7.14 ± 0.52	6.63 ± 0.23	7.76 ± 0.47
Week 14	8.02 ± 0.66	7.96 ± 0.47	8.16 ± 0.53	7.73 ± 0.61	7.43 ± 0.47	8.41 ± 0.50
Monocytes (10^3/µL)						
Day 5	0.08 ± 0.03	0.05 ± 0.02	0.04 ± 0.02	0.03 ± 0.02	0.08 ± 0.03	0.07 ± 0.02
Day 19	0.21 ± 0.03	0.15 ± 0.03	0.20 ± 0.03	0.13 ± 0.03	0.20 ± 0.05	0.18 ± 0.04
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Basophils (10^3/µL)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 19	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/µL)						
Day 5	0.01 ± 0.01	0.03 ± 0.03	0.01 ± 0.01	0.03 ± 0.02	0.05 ± 0.04	0.01 ± 0.01
Day 19	0.10 ± 0.04	0.06 ± 0.02	0.03 ± 0.02	0.03 ± 0.02	0.02 ± 0.01	0.01 ± 0.01*
Week 14	0.04 ± 0.02	0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.02	0.09 ± 0.04	0.02 ± 0.01
Methemoglobin (g/dL)						
Day 5	0.03 ± 0.02	0.04 ± 0.02	4.36 ± 0.78**[c]	0.08 ± 0.03**	1.37 ± 0.41**[e]	3.97 ± 0.75**
Day 19	0.09 ± 0.05	0.06 ± 0.02	0.28 ± 0.12*	0.38 ± 0.12**	1.25 ± 0.37**	3.26 ± 0.36**
Week 14	0.03 ± 0.01	0.08 ± 0.01**	0.12 ± 0.02**	0.25 ± 0.07**	0.71 ± 0.20**	3.38 ± 0.80**
Glutathione, erythrocyte (mg/dL erythrocytes)						
Day 5	89.6 ± 5.5	89.7 ± 3.7[e]	98.3 ± 5.0[c]	86.9 ± 6.6	98.3 ± 5.4	101.7 ± 9.6[b]
Day 19	90.3 ± 4.2[c]	95.1 ± 6.4[d]	98.1 ± 6.5[b]	94.1 ± 4.3	104.5 ± 4.9	116.0 ± 8.6*[c]
Week 14	63.7 ± 1.9[e]	67.5 ± 3.6[d]	72.5 ± 3.4[d]	70.7 ± 2.3	72.1 ± 2.5*[c]	73.8 ± 1.9**
Heinz bodies (10^6/µL)[f]						
Day 5	0.002 ± 0.001	0.005 ± 0.001	0.009 ± 0.002*	0.010 ± 0.004	0.007 ± 0.002	0.013 ± 0.004**[d]
Day 19	0.004 ± 0.002	0.004 ± 0.002	0.003 ± 0.001	0.004 ± 0.002	0.006 ± 0.002	0.006 ± 0.002
Week 14	0.170 ± 0.114	0.170 ± 0.114	0.470 ± 0.128	0.267 ± 0.133	0.240 ± 0.122	0.350 ± 0.144

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Drinking Water Study of Sodium Nitrite

	0 ppm	375 ppm	750 ppm	1,500 ppm	3,000 ppm	5,000 ppm
Male (continued)						
Clinical Chemistry						
n						
Day 5	10	10	10	9	10	10
Day 19	10	10	10	9	10	10
Week 14	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 5	20.4 ± 0.5	18.3 ± 0.7	21.7 ± 0.5	19.7 ± 1.0	19.9 ± 0.6	21.3 ± 0.6
Day 19	21.0 ± 0.7	21.4 ± 0.4	20.8 ± 0.5	22.3 ± 0.5	22.0 ± 0.3	24.9 ± 0.7**
Week 14	17.8 ± 0.5	20.5 ± 0.9*	21.2 ± 0.7**	20.4 ± 0.8*	22.3 ± 1.4**	22.0 ± 0.8**
Creatinine (mg/dL)						
Day 5	0.62 ± 0.01	0.66 ± 0.02	0.72 ± 0.03*	0.62 ± 0.03	0.71 ± 0.04	0.69 ± 0.02
Day 19	0.66 ± 0.03	0.63 ± 0.02	0.64 ± 0.03	0.70 ± 0.03	0.69 ± 0.03	0.76 ± 0.03
Week 14	0.68 ± 0.02	0.70 ± 0.02[c]	0.69 ± 0.02	0.71 ± 0.01	0.69 ± 0.01	0.69 ± 0.02
Total protein (g/dL)						
Day 5	6.5 ± 0.1	6.4 ± 0.1	6.0 ± 0.1**	6.3 ± 0.1**	6.2 ± 0.1*	6.1 ± 0.1**
Day 19	6.7 ± 0.2	7.0 ± 0.1	6.9 ± 0.1	6.7 ± 0.1	6.6 ± 0.1	6.4 ± 0.1
Week 14	6.7 ± 0.1	7.0 ± 0.1	7.0 ± 0.1	7.0 ± 0.1	7.0 ± 0.1	6.5 ± 0.1
Albumin (g/dL)						
Day 5	4.3 ± 0.1	4.3 ± 0.0	4.1 ± 0.0	4.2 ± 0.0	4.2 ± 0.0	4.2 ± 0.0
Day 19	4.4 ± 0.1	4.5 ± 0.0	4.5 ± 0.0	4.4 ± 0.1	4.4 ± 0.1	4.3 ± 0.0
Week 14	4.4 ± 0.0	4.5 ± 0.1	4.6 ± 0.1	4.5 ± 0.1	4.6 ± 0.1	4.4 ± 0.1
Alanine aminotransferase (IU/L)						
Day 5	45 ± 2	44 ± 2	40 ± 2	42 ± 2	45 ± 3	38 ± 2
Day 19	48 ± 3	42 ± 2	46 ± 3	55 ± 6	46 ± 1	45 ± 3
Week 14	52 ± 3	50 ± 3	57 ± 7	51 ± 3	56 ± 6	46 ± 2
Alkaline phosphatase (IU/L)						
Day 5	570 ± 12	586 ± 14	445 ± 8**	544 ± 11*	504 ± 8**	441 ± 5**
Day 19	448 ± 8	455 ± 8	450 ± 8	423 ± 13[b]	402 ± 6**	333 ± 11**
Week 14	216 ± 6	233 ± 9	231 ± 9	209 ± 6	213 ± 6	210 ± 7
Creatine kinase (IU/L)						
Day 5	302 ± 45[c]	397 ± 50	192 ± 32	245 ± 33	295 ± 34	199 ± 18
Day 19	295 ± 80[c]	274 ± 49	221 ± 38[c]	279 ± 79	234 ± 34	337 ± 60
Week 14	120 ± 32	132 ± 40	135 ± 28	184 ± 86	143 ± 27	131 ± 19
Sorbitol dehyrogenase (IU/L)						
Day 5	9 ± 1	13 ± 1	12 ± 2	11 ± 2	12 ± 3	12 ± 1
Day 19	12 ± 1	11 ± 1	11 ± 0	13 ± 2[b]	12 ± 1	14 ± 1
Week 14	14 ± 3	11 ± 4	17 ± 2	17 ± 4	19 ± 4	19 ± 4
Bile acids (μmol/L)						
Day 5	13.8 ± 2.9	24.6 ± 5.0*	12.9 ± 1.7	16.3 ± 3.9	14.0 ± 2.7	8.8 ± 1.3
Day 19	15.3 ± 4.6	14.2 ± 4.7	13.6 ± 2.1[c]	13.4 ± 2.3	7.9 ± 0.6	12.5 ± 1.9
Week 14	5.7 ± 0.7[c]	6.3 ± 0.5[g]	13.6 ± 4.7[d]	13.9 ± 1.8**	9.7 ± 2.6[e]	5.8 ± 0.5[g]

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Drinking Water Study of Sodium Nitrite

	0 ppm	375 ppm	750 ppm	1,500 ppm	3,000 ppm	5,000 ppm
Female						
Hematology						
n						
Day 5	9	8	9	9	8	9
Day 19	10	10	10	10	10	10
Week 14	10	10	10	10	9	10
Hematocrit (%)						
Day 5	45.6 ± 1.4	44.3 ± 1.2	46.0 ± 0.9[b]	46.0 ± 0.7	45.1 ± 1.0[c]	44.8 ± 0.6
Day 19	46.8 ± 0.5	46.0 ± 0.6	45.2 ± 0.5	46.6 ± 0.8	48.5 ± 1.3	42.7 ± 1.8
Week 14	43.8 ± 0.4	43.5 ± 0.4	42.1 ± 0.4	43.0 ± 0.4	47.1 ± 0.4**	51.3 ± 0.6**
Hemoglobin (g/dL)						
Day 5	15.3 ± 0.4	14.8 ± 0.3	15.4 ± 0.2[b]	15.4 ± 0.2	15.3 ± 0.2[c]	15.2 ± 0.1
Day 19	15.7 ± 0.1	15.3 ± 0.1	15.2 ± 0.2	15.6 ± 0.2	15.9 ± 0.4	13.9 ± 0.6*
Week 14	15.2 ± 0.1	15.0 ± 0.1	14.7 ± 0.1	15.0 ± 0.1	16.2 ± 0.1**	17.5 ± 0.1**
Erythrocytes (10^6/µL)						
Day 5	7.62 ± 0.26	7.27 ± 0.21	7.64 ± 0.13[b]	7.56 ± 0.13	7.44 ± 0.20[c]	7.49 ± 0.09
Day 19	7.87 ± 0.12	7.72 ± 0.13	7.54 ± 0.08	7.83 ± 0.17	8.36 ± 0.11*	8.71 ± 0.20**
Week 14	7.64 ± 0.07	7.61 ± 0.05	7.31 ± 0.06	7.35 ± 0.07	7.74 ± 0.05	8.49 ± 0.15**
Reticulocytes (10^6/µL)						
Day 5	0.29 ± 0.03	0.34 ± 0.02	0.36 ± 0.03	0.44 ± 0.05*	0.63 ± 0.03**	0.73 ± 0.07**
Day 19	0.14 ± 0.01	0.17 ± 0.01*	0.14 ± 0.01	0.20 ± 0.02**	0.41 ± 0.05**	0.65 ± 0.07**
Week 14	0.21 ± 0.02	0.15 ± 0.02	0.18 ± 0.02	0.23 ± 0.03	0.28 ± 0.03	0.40 ± 0.03**
Nucleated erythrocytes (10^3/µL)						
Day 5	1.80 ± 0.44[b]	1.13 ± 0.35	1.44 ± 0.48	1.56 ± 0.53	2.40 ± 0.43[b]	2.22 ± 0.36
Day 19	0.60 ± 0.22	0.40 ± 0.16	0.90 ± 0.48	1.10 ± 0.38	0.60 ± 0.27	3.00 ± 0.78*
Week 14	1.00 ± 0.30	0.60 ± 0.22	0.80 ± 0.25	1.60 ± 0.34	1.00 ± 0.37	1.70 ± 0.42
Mean cell volume (fL)						
Day 5	59.9 ± 0.4	60.9 ± 0.3	60.3 ± 0.4[b]	60.8 ± 0.3	60.7 ± 0.5[c]	59.8 ± 0.3
Day 19	59.5 ± 0.5	59.6 ± 0.6	60.0 ± 0.4	59.5 ± 0.5	58.0 ± 1.0	48.9 ± 1.0**
Week 14	57.2 ± 0.1	57.2 ± 0.3	57.6 ± 0.2	58.6 ± 0.2**	60.8 ± 0.2**	60.5 ± 0.7**
Mean cell hemoglobin (pg)						
Day 5	20.1 ± 0.2	20.3 ± 0.2	20.1 ± 0.2[b]	20.3 ± 0.1	20.7 ± 0.3[c]	20.3 ± 0.1
Day 19	19.9 ± 0.2	19.9 ± 0.2	20.1 ± 0.1	19.9 ± 0.3	19.0 ± 0.4	15.8 ± 0.3**
Week 14	19.9 ± 0.1	19.7 ± 0.1	20.1 ± 0.1	20.5 ± 0.1**	20.9 ± 0.1**	20.7 ± 0.3**
Mean cell hemoglobin concentration (g/dL)						
Day 5	33.6 ± 0.3	33.3 ± 0.2	33.4 ± 0.3[b]	33.4 ± 0.2	34.0 ± 0.3[c]	33.9 ± 0.3
Day 19	33.5 ± 0.2	33.4 ± 0.2	33.6 ± 0.1	33.4 ± 0.3	32.9 ± 0.2*	32.4 ± 0.2**
Week 14	34.7 ± 0.2	34.4 ± 0.1	34.9 ± 0.2	34.9 ± 0.2	34.3 ± 0.2	34.2 ± 0.2
Platelets (10^3/µL)						
Day 5	794.6 ± 41.0	891.1 ± 27.6	847.3 ± 35.4[b]	866.9 ± 16.3	995.3 ± 34.5**[c]	931.8 ± 43.9**
Day 19	701.8 ± 24.7	703.4 ± 22.4	698.4 ± 30.7	709.4 ± 16.3	726.7 ± 61.2	1,631.0 ± 171.7**
Week 14	656.6 ± 17.0	611.5 ± 10.8	668.7 ± 21.3	613.6 ± 11.3	645.3 ± 21.9	617.5 ± 14.9
Leukocytes (10^3/µL)						
Day 5	9.16 ± 0.76	9.41 ± 1.06	10.03 ± 0.68[b]	8.16 ± 0.98	9.19 ± 0.60[c]	9.34 ± 0.93
Day 19	10.55 ± 0.54	9.55 ± 0.67	9.28 ± 0.48	9.18 ± 0.44	8.86 ± 0.56	10.72 ± 0.63
Week 14	9.61 ± 0.20	10.03 ± 0.46	8.60 ± 0.50	8.63 ± 0.48	11.29 ± 0.63	9.72 ± 0.41
Segmented neutrophils (10^3/µL)						
Day 5	0.98 ± 0.16	1.03 ± 0.15	0.90 ± 0.15	1.06 ± 0.14	1.04 ± 0.19	0.97 ± 0.17
Day 19	0.85 ± 0.10	0.75 ± 0.11	1.13 ± 0.14	0.95 ± 0.08	0.73 ± 0.11	0.93 ± 0.11
Week 14	1.53 ± 0.21	1.56 ± 0.22	1.61 ± 0.16	1.54 ± 0.11	1.86 ± 0.28	1.42 ± 0.10

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Drinking Water Study of Sodium Nitrite

	0 ppm	375 ppm	750 ppm	1,500 ppm	3,000 ppm	5,000 ppm
Female (continued)						
Hematology (continued)						
n						
Day 5	9	8	9	9	8	9
Day 19	10	10	10	10	10	10
Week 14	10	10	10	10	9	10
Immature neutrophils (10^3/μL)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.011 ± 0.011	0.000 ± 0.000	0.000 ± 0.000
Day 19	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.010 ± 0.010	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Metamyelocytes (10^3/μL)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 19	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Myelocytes (10^3/μL)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 19	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Promyelocytes (10^3/μL)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 19	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Lymphocytes (10^3/μL)						
Day 5	8.11 ± 0.68	8.23 ± 0.94	9.00 ± 0.73	7.00 ± 0.90	8.18 ± 0.53	8.28 ± 0.78
Day 19	9.33 ± 0.46	8.52 ± 0.62	7.82 ± 0.48	7.98 ± 0.42	7.86 ± 0.51	9.59 ± 0.63
Week 14	7.93 ± 0.21	8.32 ± 0.52	6.93 ± 0.41	6.92 ± 0.38	9.30 ± 0.50	8.16 ± 0.48
Monocytes (10^3/μL)						
Day 5	0.03 ± 0.02	0.01 ± 0.01	0.02 ± 0.02	0.04 ± 0.02	0.10 ± 0.02	0.07 ± 0.04
Day 19	0.29 ± 0.06	0.22 ± 0.07	0.29 ± 0.06	0.22 ± 0.05	0.22 ± 0.04	0.18 ± 0.04
Week 14	0.09 ± 0.03	0.03 ± 0.02	0.02 ± 0.01	0.06 ± 0.04	0.02 ± 0.02	0.08 ± 0.03
Basophils (10^3/μL)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 19	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/μL)						
Day 5	0.04 ± 0.02	0.14 ± 0.04	0.06 ± 0.02	0.04 ± 0.02	0.03 ± 0.02	0.06 ± 0.03
Day 19	0.06 ± 0.02	0.05 ± 0.02	0.08 ± 0.04	0.05 ± 0.02	0.06 ± 0.02	0.01 ± 0.01
Week 14	0.08 ± 0.03	0.13 ± 0.04	0.07 ± 0.03	0.11 ± 0.03	0.11 ± 0.04	0.09 ± 0.04
Methemoglobin (g/dL)						
Day 5	0.02 ± 0.01	0.10 ± 0.05*	0.05 ± 0.01	0.21 ± 0.08**	2.41 ± 0.76**	4.95 ± 0.92**
Day 19	0.03 ± 0.01	0.11 ± 0.03*	0.18 ± 0.04**	2.01 ± 0.49**	3.78 ± 0.79**	6.66 ± 0.36**
Week 14	0.06 ± 0.02	0.14 ± 0.02**	0.16 ± 0.02**	0.48 ± 0.05**[c]	0.99 ± 0.20**	2.27 ± 0.54**
Glutathione, erythrocyte (mg/dL erythrocytes)						
Day 5	83.4 ± 6.6[d]	86.8 ± 6.7[g]	81.5 ± 6.2[d]	87.6 ± 4.3[d]	91.1 ± 4.9[c]	105.0 ± 5.5[d]
Day 19	88.3 ± 5.4	83.0 ± 4.8[d]	79.6 ± 5.5[c]	89.8 ± 4.2[d]	84.0 ± 1.7[e]	98.3 ± 3.8
Week 14	77.9 ± 4.2[d]	79.2 ± 2.1[c]	85.4 ± 2.4[d]	88.3 ± 1.6	84.2 ± 3.4	77.3 ± 2.6[d]
Heinz bodies (10^6/μL)[f]						
Day 5	0.002 ± 0.001	0.001 ± 0.001	0.002 ± 0.001	0.002 ± 0.001	0.006 ± 0.002	0.010 ± 0.002**
Day 19	0.002 ± 0.001	0.002 ± 0.001	0.001 ± 0.001	0.003 ± 0.002	0.002 ± 0.002	0.002 ± 0.001
Week 14	0.300 ± 0.123	0.230 ± 0.117	0.350 ± 0.117	0.210 ± 0.107	0.178 ± 0.118	0.240 ± 0.122

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Drinking Water Study of Sodium Nitrite

	0 ppm	375 ppm	750 ppm	1,500 ppm	3,000 ppm	5,000 ppm
Female (continued)						
Clinical Chemistry						
n						
Day 5	10	9	9	9	10	10
Day 19	10	10	10	10	10	10
Week 14	10	10	10	10	9	10
Urea nitrogen (mg/dL)						
Day 5	22.1 ± 1.1	21.2 ± 0.6	21.3 ± 0.6	20.3 ± 0.7[d]	21.0 ± 0.5	22.5 ± 0.6 .
Day 19	24.4 ± 1.0[c]	24.2 ± 0.7	23.2 ± 0.5	23.9 ± 0.5	24.1 ± 0.6	30.6 ± 0.8**
Week 14	17.8 ± 0.6	19.0 ± 0.4	19.0 ± 0.7	21.7 ± 0.4**	22.3 ± 0.7**	21.5 ± 0.5**
Creatinine (mg/dL)						
Day 5	0.63 ± 0.03[c]	0.62 ± 0.03	0.70 ± 0.04	0.65 ± 0.02[d]	0.71 ± 0.01*[c]	0.73 ± 0.03*[c]
Day 19	0.58 ± 0.04[d]	0.65 ± 0.03*	0.60 ± 0.02	0.69 ± 0.03**	0.73 ± 0.04**	0.81 ± 0.03**
Week 14	0.66 ± 0.02	0.68 ± 0.03	0.67 ± 0.02	0.68 ± 0.03	0.68 ± 0.03	0.69 ± 0.02
Total protein (g/dL)						
Day 5	6.1 ± 0.1	6.2 ± 0.1	6.2 ± 0.1	6.3 ± 0.1	6.2 ± 0.1	6.1 ± 0.1
Day 19	6.1 ± 0.1	6.2 ± 0.1	6.2 ± 0.1	6.3 ± 0.2	6.1 ± 0.1	6.2 ± 0.1
Week 14	6.8 ± 0.1	7.2 ± 0.1	7.0 ± 0.1	7.1 ± 0.1	7.0 ± 0.1	6.7 ± 0.1
Albumin (g/dL)						
Day 5	4.2 ± 0.1	4.4 ± 0.1	4.4 ± 0.1	4.5 ± 0.1*[d]	4.5 ± 0.1	4.4 ± 0.1
Day 19	4.3 ± 0.1	4.5 ± 0.0	4.5 ± 0.0	4.5 ± 0.1	4.4 ± 0.1	4.5 ± 0.1
Week 14	4.5 ± 0.0	4.8 ± 0.1	4.8 ± 0.1	4.8 ± 0.1*	4.7 ± 0.1	4.8 ± 0.1
Alanine aminotransferase (IU/L)						
Day 5	41 ± 4	37 ± 1	40 ± 2[b]	38 ± 2	37 ± 1	44 ± 3
Day 19	38 ± 2	35 ± 1	33 ± 2	37 ± 2	38 ± 2	40 ± 1
Week 14	45 ± 2	42 ± 2	43 ± 2	53 ± 3	53 ± 2*	48 ± 3
Alkaline phosphatase (IU/L)						
Day 5	424 ± 21	423 ± 15	415 ± 14[b]	377 ± 13	345 ± 11**	315 ± 12**
Day 19	350 ± 10	299 ± 22*	340 ± 5	315 ± 16*	288 ± 16**	257 ± 4**
Week 14	178 ± 5	176 ± 8	180 ± 5	167 ± 3	164 ± 3	142 ± 5**
Creatine kinase (IU/L)						
Day 5	344 ± 60[c]	396 ± 94	398 ± 71[d]	397 ± 62	321 ± 54[c]	468 ± 75[d]
Day 19	288 ± 67[e]	267 ± 28	292 ± 40	229 ± 21	383 ± 52	391 ± 42[c]
Week 14	99 ± 22	71 ± 14	67 ± 10	69 ± 14	60 ± 9	109 ± 11
Sorbitol dehydrogenase (IU/L)						
Day 5	11 ± 1	9 ± 1	11 ± 0[b]	10 ± 1	10 ± 1	13 ± 2
Day 19	13 ± 0	13 ± 0	12 ± 1	13 ± 1	14 ± 1	14 ± 1
Week 14	12 ± 5	7 ± 1	6 ± 1	8 ± 1	7 ± 1	10 ± 1
Bile acids (μmol/L)						
Day 5	12.7 ± 2.5[c]	12.4 ± 2.1	21.0 ± 5.9[d]	16.3 ± 5.0[d]	13.6 ± 2.2[c]	17.4 ± 3.5[d]
Day 19	21.1 ± 5.8[c]	15.4 ± 2.3	16.8 ± 3.0	12.9 ± 1.4	14.8 ± 2.5	15.8 ± 3.0
Week 14	17.6 ± 2.2	20.2 ± 3.6	25.1 ± 4.2	30.0 ± 8.6	25.0 ± 3.4	32.0 ± 7.7

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=10
[c] n=9
[d] n=8
[e] n=7
[f] Total number of erythrocytes with Heinz bodies
[g] n=6

TABLE F2
Hemoglobin, Methemoglobin, and Serum and Gastric Nitrosamine Data for Rats on Days 70 and 71 in the 14-Week Drinking Water Study of Sodium Nitrite[a]

	0 ppm	375 ppm	750 ppm	1,500 ppm	3,000 ppm	5,000 ppm
n	5	5	5	5	5	5
Male						
Hemoglobin (g/dL)						
Day 70 (at 2000 hours)	14.0 ± 0.8	14.4 ± 0.7[b]	14.9 ± 0.2	15.0 ± 0.2	16.1 ± 0.4	14.6 ± 0.8
Day 70 (at 2200 hours)	15.2 ± 0.2	15.4 ± 0.3	15.1 ± 0.2	15.3 ± 0.4[c]	16.7 ± 0.6	15.2 ± 0.5
Day 71 (at 0900 hours)	15.4 ± 0.2	15.4 ± 0.2	15.3 ± 0.1	15.0 ± 0.2	15.9 ± 0.2[b]	14.4 ± 0.1*
Methemoglobin (g/dL)						
Day 70 (at 2000 hours)	0.05 ± 0.02	0.09 ± 0.02[b]	0.12 ± 0.02*	0.44 ± 0.17**	0.47 ± 0.27**	0.54 ± 0.09**
Day 70 (at 2200 hours)	0.02 ± 0.01	0.05 ± 0.01	0.07 ± 0.01**	0.14 ± 0.00**[c]	0.70 ± 0.48**	0.64 ± 0.23**
Day 71 (at 0900 hours)	0.03 ± 0.01	0.09 ± 0.01**	0.10 ± 0.03*	0.54 ± 0.23**	3.50 ± 0.68**[b]	5.13 ± 1.40**
Serum nitrosamine						
Day 70 (at 2000 hours)	—[d]	—	—	—	—	—
Day 70 (at 2200 hours)	—	—	—	—	—	—
Day 71 (at 0900 hours)	—	—	—	—	—	—
Gastric nitrosamine						
Day 70 (at 2000 hours)	—	—	—	—	—	—
Day 70 (at 2200 hours)	—	—	—	—	—	—
Day 71 (at 0900 hours)	—	—	—	—	—	—
Female						
Hemoglobin (g/dL)						
Day 70 (at 2000 hours)	16.2 ± 0.3	15.4 ± 0.2	15.1 ± 0.1	15.8 ± 0.4	17.5 ± 0.2	15.5 ± 0.5[b]
Day 70 (at 2200 hours)	15.7 ± 0.4	15.5 ± 0.3[b]	15.4 ± 0.2	15.8 ± 0.3	16.8 ± 0.2*	16.7 ± 0.0[c]
Day 71 (at 0900 hours)	15.7 ± 0.2	15.2 ± 0.2	15.8 ± 0.1	15.2 ± 0.2	16.5 ± 0.1*	17.2 ± 0.8[b]
Methemoglobin (g/dL)						
Day 70 (at 2000 hours)	0.04 ± 0.02	0.21 ± 0.08*	0.39 ± 0.12**	0.60 ± 0.11**	0.57 ± 0.20**	2.76 ± 0.75**[b]
Day 70 (at 2200 hours)	0.27 ± 0.09	0.12 ± 0.02[b]	0.26 ± 0.06[b]	0.26 ± 0.05	0.50 ± 0.10	0.44 ± 0.07[c]
Day 71 (at 0900 hours)	0.09 ± 0.02	0.19 ± 0.05*	1.16 ± 0.30**	1.06 ± 0.09**	4.39 ± 0.79**	3.32 ± 1.78**[b]
Serum nitrosamine						
Day 70 (at 2000 hours)	—	—	—	—	—	—
Day 70 (at 2200 hours)	—	—	—	—	—	—
Day 71 (at 0900 hours)	—	—	—	—	—	—
Gastric nitrosamine						
Day 70 (at 2000 hours)	—	—	—	—	—	—
Day 70 (at 2200 hours)	—	—	—	—	—	—
Day 71 (at 0900 hours)	—	—	—	—	—	—

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=4
[c] n=3
[d] Undetectable by thermal energy analyzer. Nitrosamine includes *N*-nitrosodimethylamine, *N*-nitrosodiethylamine, *N*-nitrosodipropylamine, *N*-nitrosodibutylamine, *N*-nitrosopiperidine, *N*-nitrosopyrrolidine, and *N*-nitrosomorpholine concentrations.

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

TABLE G1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Drinking Water Study of Sodium Nitrite 230
TABLE G2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Drinking Water Study of Sodium Nitrite 232

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Drinking Water Study of Sodium Nitrite[a]

	0 ppm	375 ppm	750 ppm	1,500 ppm	3,000 ppm	5,000 ppm
Male						
n	10	10	10	10	10	10
Necropsy body wt	372 ± 5	357 ± 7	360 ± 9	366 ± 4	347 ± 6*	316 ± 8**
Heart						
Absolute	1.109 ± 0.014	1.056 ± 0.023	1.106 ± 0.034	1.123 ± 0.019	1.113 ± 0.021	1.078 ± 0.039
Relative	0.298 ± 0.004	0.296 ± 0.005	0.307 ± 0.006	0.307 ± 0.005	0.321 ± 0.004**	0.340 ± 0.006**
R. Kidney						
Absolute	1.273 ± 0.016	1.293 ± 0.036	1.276 ± 0.033	1.319 ± 0.021	1.328 ± 0.030	1.250 ± 0.029
Relative	0.342 ± 0.003	0.362 ± 0.007*	0.354 ± 0.003*	0.360 ± 0.004*	0.382 ± 0.005**	0.396 ± 0.006**
Liver						
Absolute	13.140 ± 0.412[b]	13.252 ± 0.394	13.098 ± 0.351	13.222 ± 0.187	12.593 ± 0.367	11.086 ± 0.343**
Relative	3.522 ± 0.066[b]	3.712 ± 0.085	3.638 ± 0.051	3.610 ± 0.048	3.622 ± 0.066	3.509 ± 0.075
Lung						
Absolute	1.796 ± 0.051	1.785 ± 0.075	1.675 ± 0.069	1.756 ± 0.082	1.746 ± 0.057	1.575 ± 0.056
Relative	0.483 ± 0.016	0.499 ± 0.016	0.465 ± 0.014	0.479 ± 0.022	0.502 ± 0.010	0.497 ± 0.008
Spleen						
Absolute	0.822 ± 0.006	0.793 ± 0.019	0.829 ± 0.018	0.849 ± 0.015	0.881 ± 0.019	0.818 ± 0.025
Relative	0.221 ± 0.003	0.222 ± 0.003	0.230 ± 0.003	0.232 ± 0.003*	0.254 ± 0.004**	0.259 ± 0.004**
R. Testis						
Absolute	1.686 ± 0.127	1.515 ± 0.024	1.539 ± 0.022	1.575 ± 0.016	1.553 ± 0.018	1.497 ± 0.019
Relative	0.452 ± 0.032	0.425 ± 0.005	0.429 ± 0.009	0.430 ± 0.006	0.448 ± 0.009	0.476 ± 0.009
Thymus						
Absolute	0.366 ± 0.018	0.363 ± 0.013	0.367 ± 0.011	0.396 ± 0.010	0.385 ± 0.019	0.328 ± 0.015
Relative	0.098 ± 0.005	0.102 ± 0.003	0.102 ± 0.004	0.108 ± 0.003	0.111 ± 0.006	0.104 ± 0.006

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Drinking Water Study of Sodium Nitrite

	0 ppm	375 ppm	750 ppm	1,500 ppm	3,000 ppm	5,000 ppm
Female						
n	10	10	10	10	9	10
Necropsy body wt	207 ± 4	207 ± 2	200 ± 3	207 ± 3	194 ± 3*	185 ± 6**
Heart						
Absolute	0.711 ± 0.018	0.716 ± 0.013	0.700 ± 0.020	0.734 ± 0.015	0.713 ± 0.009	0.742 ± 0.009
Relative	0.344 ± 0.004	0.345 ± 0.005	0.350 ± 0.006	0.355 ± 0.005	0.369 ± 0.006*	0.406 ± 0.014**
R. Kidney						
Absolute	0.778 ± 0.017	0.758 ± 0.017	0.768 ± 0.012	0.793 ± 0.013	0.819 ± 0.022	0.841 ± 0.017**
Relative	0.376 ± 0.003	0.365 ± 0.006	0.385 ± 0.003	0.383 ± 0.005	0.423 ± 0.008**	0.460 ± 0.017**
Liver						
Absolute	6.376 ± 0.178	6.814 ± 0.164	6.730 ± 0.200	6.730 ± 0.119	6.324 ± 0.133	6.155 ± 0.167
Relative	3.086 ± 0.061	3.286 ± 0.073	3.371 ± 0.078	3.256 ± 0.041	3.268 ± 0.063	3.364 ± 0.141
Lung						
Absolute	1.281 ± 0.066	1.214 ± 0.043	1.273 ± 0.054	1.301 ± 0.044	1.284 ± 0.063	1.160 ± 0.024
Relative	0.621 ± 0.032	0.585 ± 0.020	0.636 ± 0.020	0.628 ± 0.014	0.662 ± 0.028	0.633 ± 0.021
Spleen						
Absolute	0.532 ± 0.009	0.523 ± 0.006	0.514 ± 0.007	0.552 ± 0.014	0.612 ± 0.013**	0.654 ± 0.013**
Relative	0.258 ± 0.004	0.252 ± 0.003	0.258 ± 0.003	0.267 ± 0.005	0.317 ± 0.006**	0.357 ± 0.013**
Thymus						
Absolute	0.276 ± 0.011	0.276 ± 0.011	0.272 ± 0.008	0.284 ± 0.006	0.279 ± 0.014	0.270 ± 0.006
Relative	0.134 ± 0.006	0.133 ± 0.005	0.137 ± 0.004	0.138 ± 0.002	0.144 ± 0.007	0.148 ± 0.006

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as g organ weight/g body weight as a percentage (mean ± standard error).
[b] n=9

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Drinking Water Study of Sodium Nitrite[a]

	0 ppm	375 ppm	750 ppm	1,500 ppm	3,000 ppm	5,000 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	34.6 ± 0.8	34.4 ± 0.8	33.5 ± 0.7	33.4 ± 1.0	31.7 ± 1.0*	30.7 ± 0.8**
Heart						
Absolute	0.166 ± 0.006	0.173 ± 0.005	0.168 ± 0.007	0.166 ± 0.007	0.162 ± 0.003	0.169 ± 0.008
Relative	0.480 ± 0.019	0.502 ± 0.012	0.502 ± 0.014	0.499 ± 0.017	0.515 ± 0.018	0.552 ± 0.030*
R. Kidney						
Absolute	0.296 ± 0.007	0.291 ± 0.004	0.284 ± 0.008	0.285 ± 0.008	0.288 ± 0.007	0.291 ± 0.008
Relative	0.859 ± 0.023	0.851 ± 0.024	0.850 ± 0.017	0.856 ± 0.019	0.912 ± 0.026	0.952 ± 0.018**
Liver						
Absolute	1.630 ± 0.042	1.530 ± 0.142	1.652 ± 0.041	1.450 ± 0.046	1.648 ± 0.058	1.616 ± 0.075
Relative	4.718 ± 0.107	4.400 ± 0.388	4.944 ± 0.114	4.349 ± 0.079	5.200 ± 0.108	5.257 ± 0.168
Lung						
Absolute	0.295 ± 0.013	0.267 ± 0.020	0.273 ± 0.013	0.277 ± 0.014	0.269 ± 0.011	0.276 ± 0.017
Relative	0.852 ± 0.031	0.772 ± 0.049	0.815 ± 0.030	0.836 ± 0.047	0.860 ± 0.052	0.898 ± 0.043
Spleen						
Absolute	0.071 ± 0.003	0.071 ± 0.002	0.072 ± 0.002	0.074 ± 0.002	0.080 ± 0.003	0.106 ± 0.005**
Relative	0.206 ± 0.007	0.209 ± 0.007	0.217 ± 0.006	0.221 ± 0.007	0.253 ± 0.009**	0.344 ± 0.013**
R. Testis						
Absolute	0.124 ± 0.003	0.123 ± 0.002	0.117 ± 0.002	0.121 ± 0.002	0.117 ± 0.003	0.122 ± 0.002
Relative	0.358 ± 0.010	0.358 ± 0.007	0.350 ± 0.004	0.364 ± 0.010	0.372 ± 0.011	0.398 ± 0.008**
Thymus						
Absolute	0.062 ± 0.003	0.060 ± 0.004	0.051 ± 0.005	0.050 ± 0.003	0.050 ± 0.004	0.052 ± 0.003
Relative	0.181 ± 0.010	0.174 ± 0.012	0.152 ± 0.015	0.150 ± 0.005	0.158 ± 0.014	0.170 ± 0.009
Female						
Necropsy body wt	30.1 ± 0.9	31.4 ± 1.0	31.8 ± 1.2	31.3 ± 1.0	31.7 ± 1.1	28.2 ± 0.6
Heart						
Absolute	0.143 ± 0.005	0.139 ± 0.006	0.159 ± 0.006	0.156 ± 0.005	0.164 ± 0.006*	0.168 ± 0.006**
Relative	0.477 ± 0.021	0.443 ± 0.017	0.502 ± 0.022	0.501 ± 0.020	0.521 ± 0.020	0.598 ± 0.021**
R. Kidney						
Absolute	0.198 ± 0.004	0.196 ± 0.005	0.208 ± 0.005	0.201 ± 0.004	0.214 ± 0.005*	0.212 ± 0.004*
Relative	0.659 ± 0.014	0.627 ± 0.012	0.657 ± 0.014	0.644 ± 0.013	0.677 ± 0.016	0.753 ± 0.006**
Liver						
Absolute	1.454 ± 0.030	1.504 ± 0.031	1.617 ± 0.053	1.487 ± 0.035	1.682 ± 0.041**	1.575 ± 0.042**
Relative	4.853 ± 0.112	4.822 ± 0.120	5.096 ± 0.091	4.785 ± 0.143	5.328 ± 0.096**	5.597 ± 0.137**
Lung						
Absolute	0.296 ± 0.009	0.293 ± 0.017	0.311 ± 0.013	0.289 ± 0.014	0.274 ± 0.018	0.254 ± 0.019
Relative	0.989 ± 0.037	0.938 ± 0.050	0.986 ± 0.049	0.934 ± 0.053	0.871 ± 0.061	0.899 ± 0.061
Spleen						
Absolute	0.090 ± 0.003	0.090 ± 0.003	0.098 ± 0.002	0.096 ± 0.003	0.125 ± 0.004**	0.149 ± 0.008**
Relative	0.300 ± 0.010	0.290 ± 0.012	0.312 ± 0.012	0.311 ± 0.015	0.396 ± 0.014**	0.531 ± 0.028**
Thymus						
Absolute	0.061 ± 0.004	0.064 ± 0.004	0.065 ± 0.004	0.066 ± 0.003	0.065 ± 0.003	0.056 ± 0.003
Relative	0.204 ± 0.012	0.204 ± 0.009	0.206 ± 0.013	0.211 ± 0.006	0.208 ± 0.012	0.198 ± 0.011

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as g organ weight/g body weight as a percentage (mean ± standard error).

APPENDIX H
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

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TABLE H1
Summary of Reproductive Tissue Evaluations for Male Rats in the 14-Week Drinking Water Study of Sodium Nitrite[a]

	0 ppm	375 ppm	1,500 ppm	5,000 ppm
n	10	10	10	10
Weights (g)				
Necropsy body wt	372 ± 5	357 ± 7	366 ± 4	316 ± 8**
L. Cauda epididymis	0.2030 ± 0.0066	0.1976 ± 0.0044	0.1860 ± 0.0042	0.1900 ± 0.0050
L. Epididymis	0.5110 ± 0.0133	0.5017 ± 0.0067	0.4922 ± 0.0090	0.4745 ± 0.0072*
L. Testis	1.5359 ± 0.0609	1.4418 ± 0.0719	1.6062 ± 0.0145	1.5386 ± 0.0249
Spermatid measurements				
Spermatid heads (10^7/g testis)	9.471 ± 0.562	10.722 ± 1.046	10.268 ± 0.733	9.309 ± 0.488
Spermatid heads (10^7/testis)	14.310 ± 0.540	14.865 ± 0.645	16.560 ± 1.282	14.325 ± 0.773
Spermatid count (mean/10^{-4} mL suspension)	71.550 ± 2.702	74.325 ± 3.227	82.800 ± 6.412	71.625 ± 3.863
Epididymal spermatozoal measurements				
Motility (%)	89.45 ± 1.85	91.09 ± 1.38	83.18 ± 2.15*	73.42 ± 4.15**
Concentration (10^6/g cauda epididymal tissue)	366 ± 15[b]	370 ± 14	366 ± 14	391 ± 15

* Significantly different ($P \le 0.05$) from the control group by Williams' test (epididymis weight) or Shirley's test (motility)
** Significantly different ($P \le 0.01$) from the control group by Williams' test (body weight) or Shirley's test (motility)
[a] Data are presented as mean ± standard error. Differences from the control group are not significant by Dunnett's test (cauda epididymis and testis weights) or Dunn's test (spermatid measurements, epididymal spermatozoal concentration).
[b] n=9

TABLE H2
Estrous Cycle Characterization for Female Rats in the 14-Week Drinking Water Study of Sodium Nitrite[a]

	0 ppm	375 ppm	750 ppm	3,000 ppm
n	10	10	10	9
Necropsy body wt (g)	205 ± 4	207 ± 2	200 ± 3	194 ± 3*
Estrous cycle length (days)	5.100 ± 0.125	4.850 ± 0.076	5.050 ± 0.117	5.278 ± 0.121
Estrous stages (% of cycle)				
Diestrus	40.8	40.0	42.5	42.6
Proestrus	15.0	15.0	12.5	15.7
Estrus	23.3	25.0	25.8	21.3
Metestrus	20.8	20.0	18.3	20.4
Uncertain diagnoses	0.0	0.0	0.8	0.0

* Significantly different ($P \le 0.05$) from the control group by Williams' test
[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the control group for estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, exposed females do not differ significantly from the control females in the relative length of time spent in the estrous stages.

TABLE H3
Summary of Reproductive Tissue Evaluations for Male Mice in the 14-Week Drinking Water Study of Sodium Nitrite[a]

	0 ppm	375 ppm	1,500 ppm	5,000 ppm
n	10	10	10	10
Weights (g)				
Necropsy body wt	34.6 ± 0.8	34.4 ± 0.8	33.4 ± 0.9	30.7 ± 0.8**
L. Cauda epididymis	0.0287 ± 0.0035	0.0254 ± 0.0032	0.0273 ± 0.0038	0.0256 ± 0.0032
L. Epididymis	0.0613 ± 0.0060	0.0549 ± 0.0027	0.0587 ± 0.0040	0.0601 ± 0.0074
L. Testis	0.1222 ± 0.0039	0.1216 ± 0.0049	0.1236 ± 0.0034	0.1167 ± 0.0027
Spermatid measurements				
Spermatid heads (10^7/g testis)	18.274 ± 0.635	17.016 ± 0.891	18.566 ± 0.702	18.012 ± 1.017
Spermatid heads (10^7/testis)	2.228 ± 0.092	2.060 ± 0.111	2.287 ± 0.091	2.094 ± 0.112
Spermatid count (mean/10^{-4} mL suspension)	69.625 ± 2.864	64.350 ± 3.485	71.500 ± 2.853	65.425 ± 3.519
Epididymal spermatozoal measurements				
Motility (%)	73.89 ± 4.14	71.74 ± 3.63	67.86 ± 1.57	39.23 ± 7.41**
Concentration (10^6/g cauda epididymal tissue)	527 ± 93	685 ± 74	457 ± 106	717 ± 99

** Significantly different ($P \leq 0.01$) from the control group by Williams' test (body weight) or Shirley's test (motility)
[a] Data are presented as mean ± standard error. Differences from the control group are not significant by Dunnett's test (tissue weights) or Dunn's test (spermatid measurements, epididymal spermatozoal concentration).

TABLE H4
Estrous Cycle Characterization for Female Mice in the 14-Week Drinking Water Study of Sodium Nitrite[a]

	0 ppm	375 ppm	1,500 ppm	5,000 ppm
n	10	10	10	10
Necropsy body wt (g)	30.1 ± 0.9	31.4 ± 1.0	31.3 ± 1.0	28.2 ± 0.6
Estrous cycle length (days)	4.188 ± 0.132[b]	4.400 ± 0.125	4.667 ± 0.118*[c]	4.813 ± 0.091**[b]
Estrous stages (% of cycle)				
Diestrus	37.5	29.2	30.8	32.5
Proestrus	20.8	20.8	19.2	18.3
Estrus	25.0	30.8	35.8	33.3
Metestrus	16.7	19.2	14.2	15.8

* Significantly different ($P \leq 0.05$) from the control group by Shirley's test
** $P \leq 0.01$
[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the control group for necropsy cycle length are not significant by Dunn's test. By multivariate analysis of variance, exposed females do not differ significantly from the control females in the relative length of time spent in the estrous stages.
[b] Estrous cycle was longer than 12 days or unclear in 2 of 10 animals.
[c] Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.

APPENDIX I
DETERMINATIONS OF PLASMA NITRITE AND BLOOD METHEMOGLOBIN CONCENTRATIONS

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TABLE I1
Plasma Nitrite and Blood Methemoglobin Concentrations at 2 Weeks in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite[a]

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
n	2	2	2	2
Plasma Nitrite (μg/mL)				
Time of collection				
0600	—[b]	—	—	4.500[c]
1200	—	—	—	—
2100	—	—	2.100[c]	9.000 ± 2.000
2400	—	2.000[c]	4.200 ± 0.300	—
0300	—	—	—	8.100 ± 2.900
Blood Methemoglobin (g/dL)				
Time of collection				
0600	0.250 ± 0.050	0.150 ± 0.050	1.200 ± 0.400	2.750 ± 1.150
1200	0.150 ± 0.050	0.250 ± 0.050	0.400 ± 0.100	0.650 ± 0.150*
2100	0.350 ± 0.050	0.550 ± 0.050	1.650 ± 0.250*	3.850 ± 0.550*
2400	0.400 ± 0.100	0.700 ± 0.000	2.350 ± 0.550	0.500 ± 0.000
0300	0.400 ± 0.000	0.500 ± 0.100	0.800 ± 0.200	2.300 ± 0.700*

* Significantly different from the control group ($P \leq 0.05$) by Shirley's test
[a] Mean ± standard error
[b] Both samples in this group were below the estimated limit of quantitation (1.7 μg/mL).
[c] n=1

TABLE I2
Plasma Nitrite and Blood Methemoglobin Concentrations at 2 Weeks in Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite[a]

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
n	2	2	2	2
Plasma Nitrite (μg/mL)				
Time of collection				
0600	—[b]	—	7.400[c]	9.700 ± 2.300
1200	—	—	—	—
2100	—	—	3.500[c]	3.450 ± 1.350
2400	—	—	—	4.086 ± 0.079
0300	—	—	2.900[c]	6.600[c]
Blood Methemoglobin (g/dL)				
Time of collection				
0600	0.250 ± 0.050	0.250 ± 0.150	1.650 ± 0.050	6.350 ± 1.550
1200	0.250 ± 0.050	0.200 ± 0.100	0.200 ± 0.100	0.600 ± 0.200
2100	0.350 ± 0.050	0.600 ± 0.200	2.650 ± 0.150*	3.850 ± 0.750*
2400	0.500 ± 0.000	0.500 ± 0.000	1.900 ± 0.400	4.350 ± 1.050*
0300	0.400 ± 0.100	0.700 ± 0.100	2.250 ± 0.450	3.850 ± 2.550

* Significantly different from the control group ($P \leq 0.05$) by Shirley's test
[a] Mean ± standard error
[b] Both samples in this group were below the estimated limit of quantitation (1.7 μg/mL).
[c] n=1

TABLE I3
Plasma Nitrite and Blood Methemoglobin Concentrations at 3 Months in Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
n	2	2	2	2
Plasma Nitrite (µg/mL)				
Time of collection				
0600	—[b]	—	—	1.800[c]
1200	—	—	—	4.200[c]
2100	—	—	2.000[c]	3.000[c]
2400	—	—	—	4.500 ± 1.100
0300	—	—	—	—
Blood Methemoglobin (g/dL)				
Time of collection				
0600	0.700 ± 0.000	0.750 ± 0.050	2.100 ± 0.700	4.400 ± 1.900*
1200	0.300 ± 0.000	0.300 ± 0.000	0.400 ± 0.000	2.450 ± 0.050*
2100	0.350 ± 0.050	0.600 ± 0.000	1.450 ± 0.250	1.350 ± 0.750
2400	0.450 ± 0.050	0.600 ± 0.000	0.900 ± 0.100*	3.400 ± 0.600*
0300	0.300 ± 0.000	0.400 ± 0.000	0.650 ± 0.350	1.150 ± 0.750

* Significantly different from the control group ($P \leq 0.05$) by Shirley's test
[a] Mean ± standard error
[b] Both samples in this group were below the estimated limit of quantitation (1.7 µg/mL).
[c] n=1

TABLE I4
Plasma Nitrite and Blood Methemoglobin Concentrations at 3 Months in Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
n	2	2	2	2
Plasma Nitrite (μg/mL)				
Time of collection				
0600	—[b]	—	—	2.400[c]
1200	—	—	—	—[c]
2100	—	—	—	3.000[c]
1200	—	—	—	—[c]
0300	—	—	—	2.700[c]
Blood Methemoglobin (g/dL)				
Time of collection				
0600	0.450 ± 0.050	0.500 ± 0.100	0.550 ± 0.050	3.550 ± 1.050
1200	0.150 ± 0.050	0.300 ± 0.000	0.400 ± 0.000*	0.900 ± 0.400*
2100	0.200 ± 0.000	0.650 ± 0.250	3.650 ± 0.550*	2.250 ± 0.050
2400	0.350 ± 0.150	0.450 ± 0.150	1.150 ± 0.550	2.400 ± 1.200
0300	0.300 ± 0.100	0.450 ± 0.050	1.600 ± 0.300	3.000 ± 2.300

* Significantly different from the control group ($P \leq 0.05$) by Dunn's or Shirley's test
[a] Mean ± standard error
[b] Both samples in this group were below the estimated limit of quantitation (1.7 μg/mL).
[c] n=1

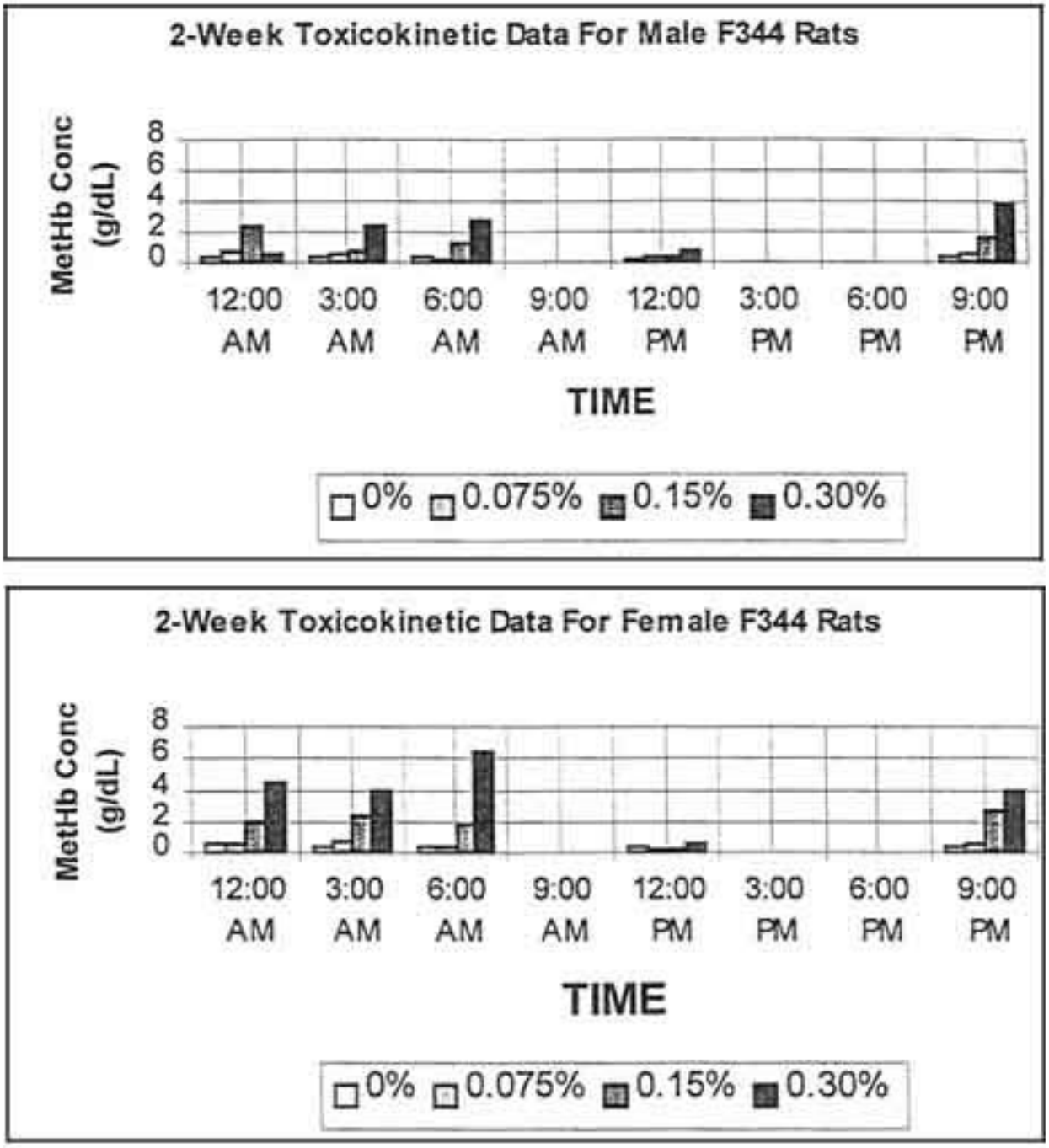

FIGURE I1
Blood Methemoglobin Concentrations at 2 Weeks in Male and Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite
(0% = 0 ppm, 0.075% = 750 ppm, 0.15% = 1,500 ppm, 0.30% = 3,000 ppm)

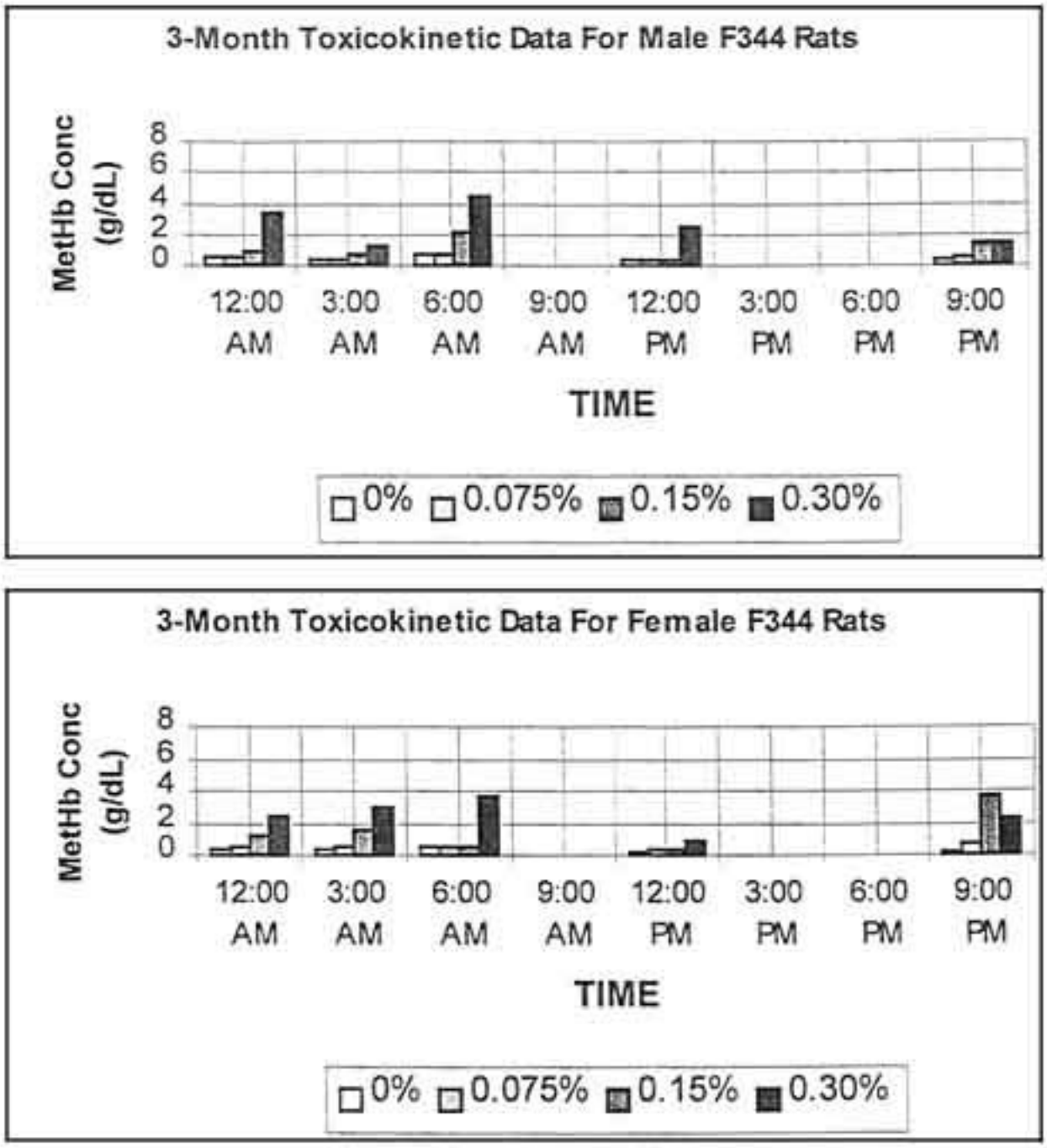

FIGURE 12
Blood Methemoglobin Concentrations at 3 Months in Male and Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite
(0% = 0 ppm, 0.075% = 750 ppm, 0.15% = 1,500 ppm, 0.30% = 3,000 ppm)

TABLE I5
Plasma Nitrite and Blood Methemoglobin Concentrations at 18 Months in Aged Male Rats after a Single Gavage Dose of 40 mg/kg Sodium Nitrite[a]

Time after Dosing (minutes)	Concentration
Plasma Nitrite (µg/mL)	
2	—[b]
5	2.500[c]
10	8.000
30	8.950 ± 2.050
60	6.300
Methemoglobin (g/dL)	
2	1.333 ± 0.176
5	2.167 ± 0.328
10	2.700 ± 0.208
30	4.200 ± 0.300
60	5.100 ± 1.100

[a] Mean ± standard error. Three animals were bled at 2, 5, and 10 minutes and two animals were bled at 30 and 60 minutes for blood methemoglobin measurements.
[b] All samples in this group were below the estimated limit of quantitation (1.7 µg/mL).
[c] Two samples in this group were below the estimated limit of quantitation (1.7 µg/mL).

TABLE I6
Plasma Nitrite and Blood Methemoglobin Concentrations at 18 Months in Aged Female Rats after a Single Gavage Dose of 40 mg/kg Sodium Nitrite[a]

Time after Dosing (minutes)	Concentration
Plasma Nitrite (µg/mL)	
2	—[b]
5	3.500 ± 0.200
10	6.067 ± 0.578
30	8.133 ± 0.561
60	6.350 ± 0.550
Methemoglobin (g/dL)	
2	1.333 ± 0.203
5	2.933 ± 0.145
10	2.700 ± 0.265
30	5.200 ± 0.058
60	5.650 ± 0.150

[a] Mean ± standard error. Three animals were bled at 2, 5, 10, and 30 minutes and two animals were bled at 60 minutes for blood methemoglobin measurements.
[b] All samples in this group were below the estimated limit of quantitation (1.7 µg/mL).

TABLE I7
Plasma Nitrite and Blood Methemoglobin Concentrations at 12 Months in Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite[a]

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
n	2	2	2	2
Plasma Nitrite (μg/mL)				
Time of collection				
0600	—[b]	—	2.140[c]	4.251 ± 1.095
1200	—	—	—	—
2100	—	—	2.329[c]	1.883[c]
2400	—	—	2.515[c]	17.111 ± 14.689
0300	—	—	—	2.370[c]
Blood Methemoglobin (g/dL)				
Time of collection				
0600	0.200 ± 0.000	0.200 ± 0.000	0.300 ± 0.000	0.750 ± 0.050
1200	0.200 ± 0.000	0.200 ± 0.000	0.200 ± 0.000	0.250 ± 0.050
2100	0.100 ± 0.000	0.150 ± 0.050	0.250 ± 0.050	0.200 ± 0.000
2400	0.300 ± 0.000	0.300 ± 0.100	0.200 ± 0.000	0.450 ± 0.050
0300	0.250 ± 0.050	0.200 ± 0.000	0.200 ± 0.000	0.300 ± 0.100

[a] Mean ± standard error
[b] Both samples in this group were below the estimated limit of quantitation (1.7 μg/mL).
[c] n=1

TABLE I8
Blood Methemoglobin Concentrations at 12 Months in Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite[a]

	0 ppm	750 ppm	1,500 ppm	3,000 ppm
n	2	2	2	2
Time of collection				
0600	0.200 ± 0.000	0.200 ± 0.000	0.200 ± 0.100	0.250 ± 0.050
1200	0.400[b]	0.300 ± 0.000	0.300 ± 0.000	0.300 ± 0.000
2100	0.200 ± 0.000	0.200 ± 0.000	0.200 ± 0.000	0.200 ± 0.000
2400	0.150 ± 0.050	0.250 ± 0.050	0.250 ± 0.050	0.250 ± 0.050
0300	0.200 ± 0.000	0.300 ± 0.100	0.200 ± 0.000	0.250 ± 0.050

[a] Data are given in g/dL as mean ± standard error. All plasma nitrite samples were below the estimated limit of quantitation (1.7 μg/mL).
[b] n=1

TABLE I9
Plasma Nitrite and Blood Methemoglobin Concentrations at 18 Months in Aged Male Mice after a Single Gavage Dose of 62.5 mg/kg Sodium Nitrite[a]

Time after Dosing (minutes)	Concentration
Plasma Nitrite (μg/mL)	
2	22.233 ± 6.082
5	23.967 ± 5.206
10	32.267 ± 4.018
30	13.533 ± 0.717
60	8.933 ± 0.921
Methemoglobin (g/dL)	
2	1.100 ± 0.208
5	1.833 ± 0.088
10	2.000 ± 0.289
30	1.600 ± 0.058
60	0.800 ± 0.153

[a] Mean ± standard error. Three animals were bled at each time point.

TABLE I10
Plasma Nitrite and Blood Methemoglobin Concentrations at 18 Months in Aged Female Mice after a Single Gavage Dose of 62.5 mg/kg of Sodium Nitrite[a]

Time after Dosing (minutes)	Concentration
Plasma Nitrite (μg/mL)	
2	27.100 ± 4.637
5	64.933 ± 6.199
10	50.800 ± 3.293
30	45.933 ± 6.583
60	43.967 ± 11.737
Methemoglobin (g/dL)	
2	1.533 ± 0.376
5	2.900 ± 0.361
10	3.433 ± 0.393
30	3.833 ± 0.857
60	5.000 ± 0.231

[a] Mean ± standard error. Three animals were bled at each time point.

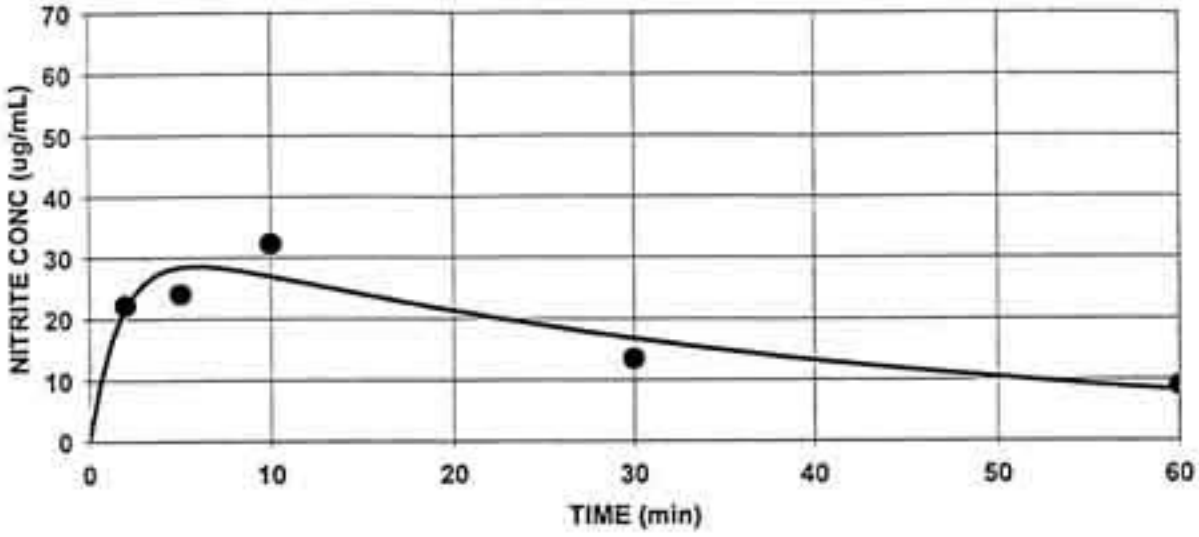

FIGURE 13
Plasma Nitrite Concentrations at 18 Months in Aged Male Mice after a Single Gavage Dose of 62.5 mg/kg Sodium Nitrite

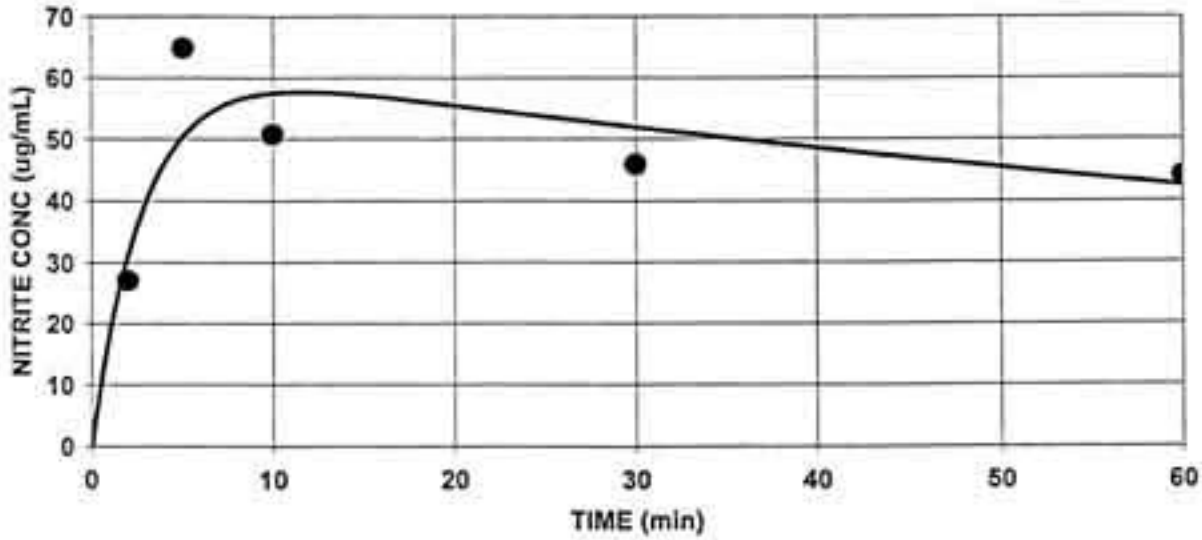

FIGURE 14
Plasma Nitrite Concentrations at 18 Months in Aged Female Mice after a Single Gavage Dose of 62.5 mg/kg Sodium Nitrite

APPENDIX J
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF SODIUM NITRITE

Sodium nitrite was obtained from J.T. Baker, Inc. (Phillipsburg, NJ), in two lots (A42340 and H05714). Lot A42340 was used during the 14-week and 2-year studies and lot H05714 was used during the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the sodium nitrite studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the chemical, a white crystalline solid, were identified as sodium nitrite by infrared and ultraviolet/visible spectroscopy. The infrared spectra were consistent with the literature spectra (*Sadtler Standard Spectra*; *Aldrich*, 1985) of sodium nitrite; the ultraviolet/visible spectra were consistent with the structure of sodium nitrite. The infrared spectrum is presented in Figure J1. The melting point ranges of 281.2° to 282.7° C determined for lot A42340 and 281.1° to 281.6° C for lot H05714 were in agreement with a value of 281° C cited in the literature (Klein and McDonald, 1982).

The purity of both lots was determined by elemental analyses, weight loss on drying, spark source mass spectrometry, and high-performance liquid chromatography (HPLC). The purity of lot A42340 was also analyzed by differential scanning calorimetry, a United States Pharmacopeia (USP) XXI titrimetric assay, and American Chemical Society (ACS) tests for chloride and sulfate. Elemental analyses of lot A42340 were performed by the analytical chemistry laboratory and Lancaster Laboratories (Lancaster, PA); elemental analyses of lot H05714 were performed by Galbraith Laboratories, Inc. (Knoxville, TN). Spark source mass spectrometry was performed by the analytical chemistry laboratory for lot A42340 and by Accu-Labs Research, Inc. (Golden, CO), for lot H05714. Lot A42340 was analyzed with HPLC by system A, and lot H05714 was analyzed with HPLC by system B (Table J1).

For lot A42340, elemental analyses for sodium and nitrogen were in agreement with the theoretical values for sodium nitrite. Weight loss on drying indicated 0.006% ± 0.002% water. Differential scanning calorimetry determined a melting point of 280.8° C and indicated that the purity was greater than 99 molar percent. Spark source mass spectrometry identified sodium as the major component; the concentration of impurities was less than 87 ppm. The USP method of titration with potassium permanganate to a colorimetric endpoint indicated a purity of 100.4% ± 0.4%. ACS tests on lot A42340 for chloride and sulfate produced less turbidity than tests on a standard solution, indicating less than 0.005% chloride ion and less than 0.01% sulfate ion. HPLC indicated a major peak and a single impurity with an area of 0.2% relative to the major peak area (system A). The cumulative data indicated a purity greater than 99%.

For lot H05714, elemental analyses for sodium and nitrogen were in agreement with the theoretical values for sodium nitrite. There was no weight loss on drying. HPLC by system B indicated one major peak and one impurity with an area of 0.15% relative to the major peak area. Spark source mass spectrometry identified sodium as the major component and no major contaminants; traces of calcium, fluorine, potassium, phosphorus, and iron were detected. The overall purity of lot H05714 was determined to be 99% or greater.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory. Permanganate titration was performed by reacting sodium nitrite with an excess of standard potassium permanganate (USP XIX). These studies indicated that sodium nitrite was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C.

To ensure stability, the bulk chemical was stored at 5° C, protected from light, in closed containers under an inert atmospere during the 14-week study and in Nalgene® containers at room temperature, protected from light, during the 2-year studies. Stability was monitored by the study laboratory with infrared and ultraviolet/visible spectroscopy and HPLC by system C (14-week studies) and with ultraviolet spectroscopy (2-year studies). No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared every 2 weeks (14-week studies) or approximately every 4 weeks (2-year studies) by mixing sodium nitrite with water (Table J2). Formulations were stored in glass carboys at room temperature for up to 3 weeks for the 14-week studies and in Nalgene® tanks at room temperature for up to 35 days for the 2-year studies.

Stability studies of a 0.075 mg/mL dose formulation were performed by the analytical chemistry laboratory using ultraviolet/visible spectrophotometry by measuring absorbance at 347 nm of an aliquot of the sample treated with a salt solution (sodium sulfate and sodium acetate) and a color reagent (hydrochloric acid, resorcinol and zinconyl chloride). Stability was confirmed for at least 35 days for dose formulations stored at 5° C or at room temperature in the dark.

Periodic analyses of the dose formulations of sodium nitrite were conducted by the study laboratory using ultraviolet/visible spectroscopy as described for the stability study. During the 14-week studies, the dose formulations were analyzed at the beginning, midpoint, and end of the studies; animal room samples of these dose formulations were also analyzed (Table J3). All 32 dose formulations analyzed were within 10% of the target concentrations; all 30 animal room samples for rats and 22 of 25 for mice were also within 10% of the target concentrations. During the 2-year studies, the dose formulations were analyzed approximately every 8 to 12 weeks; animal room samples were also analyzed periodically (Table J4). All 39 of the 2-year dose formulations analyzed were within 10% of the target concentrations. All 12 animal room samples for rats and for mice were within 10% of the target concentrations. Results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table J5).

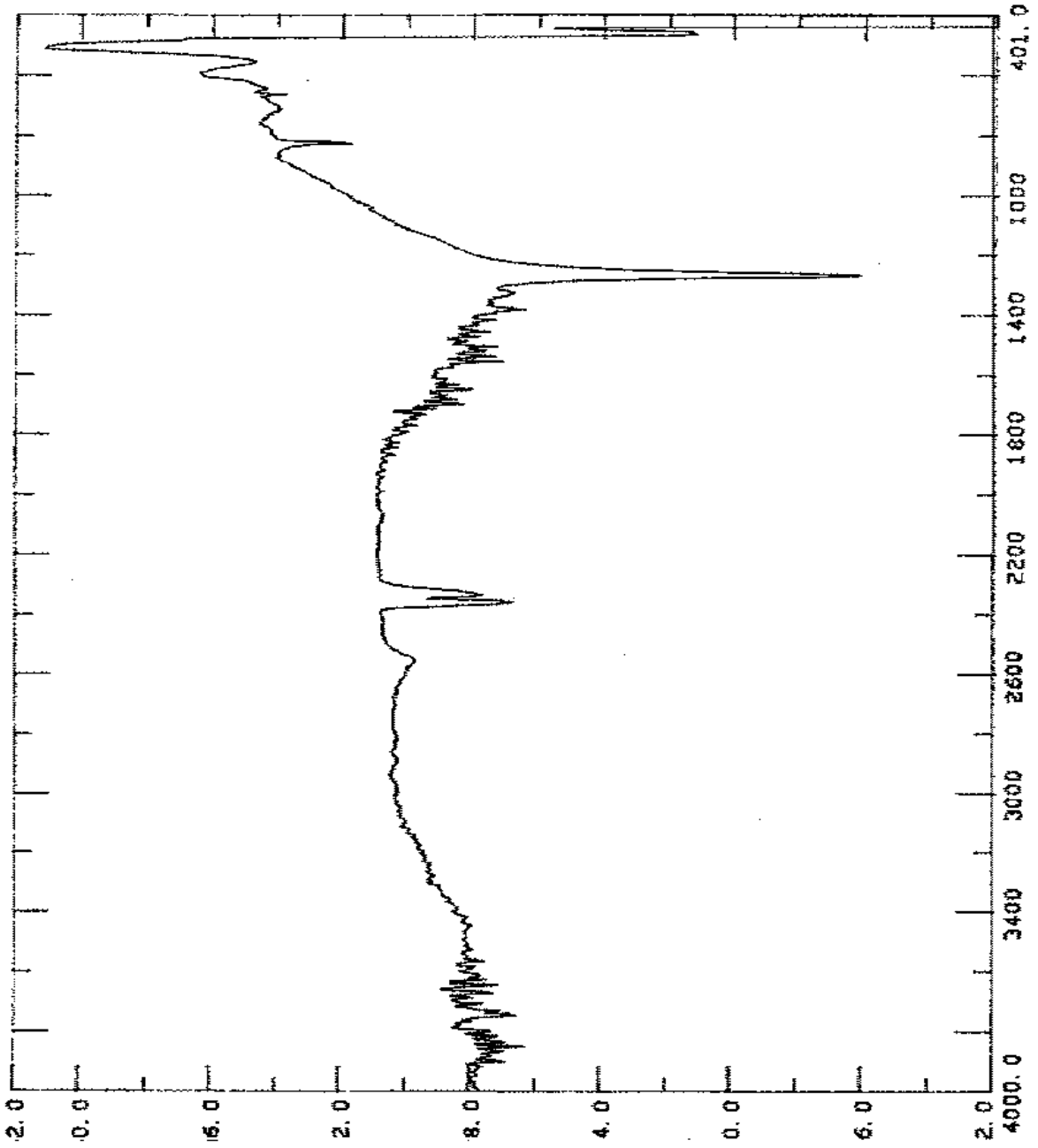

FIGURE J1
Infrared Absorption Spectrum of Sodium Nitrite

TABLE J1
High-Performance Liquid Chromatography Systems Used in the Drinking Water Studies of Sodium Nitrite[a]

Detection System	Column	Solvent System
System A Ultraviolet (230 nm)	Whatman Partisil 10 SAX, 250 mm × 4.6 mm (Whatman, Inc., Clifton, NJ)	0.0125 M potassium dihydrogen phosphate, pH 4.5; flow rate 1.0 mL/minute
System B Dionex CDM-3 Conductivity Detector (300 μS)	Dionex AS4A-SC, 250 mm × 4.0 mm, 13 μm (Dionex Corp., Sunnyvale, CA)	1.5 mM sodium carbonate/1.2 mM sodium bicarbonate, in water; flow rate 2 mL/minute
System C Waters Model 430 Conductivity Detector	Waters IC-PAK Anion, 5 cm × 4.6 mm (Waters-Millipore, Milford, MA)	Water containing (in 1 L) approximately 4.3 mL glycerin, 20 mL n-butanol, 120 mL acetonitrile, 0.3 g sodium gluconate, 0.3 g boric acid, and 0.4 g sodium tetraborate decahydrate; flow rate 0.9 mL/minute

[a] Chromatographs were manufactured by Waters-Millipore (Milford, MA) and Dionex Corp. (Sunnyvale, CA).

TABLE J2
Preparation and Storage of Dose Formulations in the Drinking Water Studies of Sodium Nitrite

14-Week Studies	2-Year Studies
Preparation Sodium nitrite was mixed with charcoal-filtered deionized water (pH 6.8-7.0) with a stir-bar and then further diluted with water. Dose formulations were prepared every 2 weeks.	Sodium nitrite was mixed with tap water with an automatic stirrer, then further diluted and stirred for an additional 5 minutes. A 2-L portion was removed from the bottom of the preparation and returned to the top; the formulation was then stirred for 5 minutes. Dose formulations were prepared approximately every 4 weeks.
Chemical Lot Number Lot A42340	Lots A42340 and H05714
Maximum Storage Time 3 weeks	35 days
Storage Conditions Stored in glass carboys at room temperature	Stored in Nalgene® tanks at room temperature
Study Laboratory Microbiological Associates, Inc. (Bethesda, MD)	Battelle Columbus Laboratories (Columbus, OH)
Referee Laboratory Midwest Research Institute (Kansas City, MO)	None

Table J3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Drinking Water Studies of Sodium Nitrite

Date Prepared	Date Analyzed	Target Concentration (%)	Determined Concentration[a] (%)	Difference from Target (%)
Rats				
1 August 1989	3 August 1989	0.0375	0.0361	−4
		0.0375	0.0358	−5
		0.075	0.0726	−3
		0.075	0.0724	−3
		0.15	0.139	−7
		0.15	0.159	+6
		0.15	0.137	−9
		0.30	0.286	−5
		0.30	0.295	−2
		0.50	0.532	+6
		0.50	0.541	+8
		0.50	0.534	+7
	24 August 1989[b]	0.0375	0.0349	−7
		0.0375	0.0342	−9
		0.075	0.0698	−7
		0.075	0.0708	−6
		0.15	0.139	−7
		0.15	0.139	−7
		0.30	0.273	−9
		0.30	0.291	−3
		0.50	0.500	0
		0.50	0.490	−2
12 September 1989	13 September 1989	0.0375	0.0384	+2
		0.0375	0.0378	+1
		0.075	0.0768	+2
		0.075	0.0770	+3
		0.15	0.153	+2
		0.15	0.155	+3
		0.30	0.310	+3
		0.30	0.311	+4
		0.50	0.524	+5
		0.50	0.513	+3
	5 October 1989[b]	0.0375	0.0389	+4
		0.0375	0.0386	+3
		0.075	0.0776	+3
		0.075	0.0763	+2
		0.15	0.155	+3
		0.15	0.164	+9
		0.30	0.307	+2
		0.30	0.316	+5
		0.50	0.523	+5
		0.50	0.523	+5

TABLE J3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Drinking Water Studies of Sodium Nitrite

Date Prepared	Date Analyzed	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
24 October 1989	25 October 1989	0.0375	0.0403	+7
		0.0375	0.0405	+8
		0.075	0.0828	+10
		0.075	0.0779	+4
		0.15	0.162	+8
		0.15	0.162	+8
		0.30	0.330	+10
		0.30	0.327	+9
		0.50	0.528	+6
		0.50	0.525	+5
	15 November 1989[b]	0.0375	0.0397	+6
		0.0375	0.0403	+7
		0.075	0.0763	+2
		0.075	0.0786	+5
		0.15	0.162	+8
		0.15	0.159	+6
		0.30	0.318	+6
		0.30	0.307	+2
		0.50	0.520	+4
		0.50	0.512	+2
Mice				
1 August 1989	3 August 1989	0.0375	0.0361	−4
		0.0375	0.0358	−5
		0.075	0.0726	−3
		0.075	0.0724	−3
		0.15	0.139	−7
		0.15	0.159	+6
		0.15	0.137	−9
		0.30	0.286	−5
		0.30	0.295	−2
		0.50	0.532	+6
		0.50	0.541	+8
		0.50	0.534	+7
	24 August 1989[b]	0.0375	0.0348	−7
		0.0375	0.0340	−9
		0.075	0.0714	−5
		0.075	0.0710	−5
		0.15	0.138	−8
		0.15	0.156	+4
		0.30	0.282	−6
		0.30	0.282	−6
		0.50	0.478	−4
		0.50	0.500	0

TABLE J3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Drinking Water Studies of Sodium Nitrite

Date Prepared	Date Analyzed	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
12 September 1989	13 September 1989	0.0375	0.0384	+2
		0.0375	0.0378	+1
		0.075	0.0768	+2
		0.075	0.0770	+3
		0.15	0.153	+2
		0.15	0.155	+3
		0.30	0.310	+3
		0.30	0.311	+4
		0.50	0.524	+5
		0.50	0.513	+3
	5 October 1989[b]	0.0375	0.0303	−19
		0.0375	0.0556	+48
		0.075	0.0590	−21
		0.075	0.0771	+3
		0.15	0.160	+7
		0.15	0.161	+7
		0.30	0.280	−7
		0.30	0.307	+2
		0.50	0.535	+7
		0.50	0.516	+3
	11 October 1989[b]	0.0375	0.0282	−25
		0.0375	0.0537	+43
		0.075	0.0598	−20
24 October 1989	25 October 1989	0.0375	0.0403	+7
		0.0375	0.0405	+8
		0.075	0.0828	+10
		0.075	0.0779	+4
		0.15	0.162	+8
		0.15	0.162	+8
		0.30	0.330	+10
		0.30	0.327	+9
		0.50	0.528	+6
		0.50	0.525	+5
	15 November 1989[b]	0.0375	0.0376	0
		0.075	0.0781	+4
		0.15	0.160	+7
		0.30	0.318	+6
		0.50	0.471	−6

[a] Results of duplicate analyses
[b] Animal room samples

TABLE J4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of Sodium Nitrite

Date Prepared	Date Analyzed	Target Concentration (%)	Determined Concentration[a] (%)	Difference from Target (%)
Rats				
1 August 1995	3 August 1995	0.075	0.07639	+2
		0.15	0.1534	+2
		0.30	0.3062	+2
	22 August 1995[b]	0.075	0.07438	−1
		0.15	0.1530	+2
		0.30	0.3047	+2
20 September 1995	21-22 September 1995	0.075	0.07480	0
		0.15	0.1548	+3
		0.30	0.2928	−2
13 December 1995	14 December 1995	0.075	0.07819	+4
		0.15	0.1577	+5
		0.30	0.3154	+5
7 February 1996	7 February 1996	0.075	0.07550	+1
		0.15	0.1524	+2
		0.30	0.3027	+1
	15 March 1996[b]	0.075	0.07495	0
		0.15	0.1484	−1
		0.30	0.2951	−2
3 April 1996	3 April 1996	0.075	0.07803	+4
		0.15	0.1578	+5
		0.30	0.3148	+5
26 June 1996	26 June 1996	0.075	0.07964	+6
		0.15	0.1572	+5
		0.30	0.3057	+2
21 August 1996	22 August 1996	0.075	0.07635	+2
		0.15	0.1518	+1
		0.30	0.3049	+2
	30 September 1996[b]	0.075	0.07991	+7
		0.15	0.1563	+4
		0.30	0.3127	+4
16 October 1996	16 October 1996	0.075	0.07684	+2
		0.15	0.1491	−1
		0.30	0.3125	+4
8 January 1997	9 January 1997	0.075	0.07751	+3
		0.15	0.1546	+3
		0.30	0.3083	+3

TABLE J4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of Sodium Nitrite

Date Prepared	Date Analyzed	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
5 March 1997	6 March 1997	0.075	0.07682	+2
		0.15	0.1535	+2
		0.30	0.3057	+2
	15 April 1997[b]	0.075	0.08139	+9
		0.15	0.1547	+3
		0.30	0.3112	+4
30 April 1997	1 May 1997	0.075	0.07732	+3
		0.15	0.1537	+2
		0.30	0.3031	+1
23 July 1997	23 July 1997	0.075	0.07385	−2
		0.15	0.1561	+4
		0.30	0.2984	−1
Mice				
25 July 1995	26 July 1995	0.075	0.07694	+3
		0.15	0.1551	+3
		0.30	0.3035	+1
	9 August 1995[b]	0.075	0.07705	+3
		0.15	0.1550	+3
		0.30	0.3040	+1
1 August 1995	3 August 1995	0.075	0.07639	+2
		0.15	0.1534	+2
		0.30	0.3062	+2
20 September 1995	21-22 September 1995	0.075	0.07480	0
		0.15	0.1548	+3
		0.30	0.2928	−2
13 December 1995	14 December 1995	0.075	0.07819	+4
		0.15	0.1577	+5
		0.30	0.3154	+5
7 February 1996	7 February 1996	0.075	0.07550	+1
		0.15	0.1524	+2
		0.30	0.3027	+1
	15 March 1996[b]	0.075	0.07319	−2
		0.15	0.1450	−3
		0.30	0.2891	−4

TABLE J4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of Sodium Nitrite

Date Prepared	Date Analyzed	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
3 April 1996	3 April 1996	0.075	0.07803	+4
		0.15	0.1578	+5
		0.30	0.3148	+5
26 June 1996	26 June 1996	0.075	0.07964	+6
		0.15	0.1572	+5
		0.30	0.3057	+2
21 August 1996	22 August 1996	0.075	0.07635	+2
		0.15	0.1518	+1
		0.30	0.3049	+2
	30 September 1996[b]	0.075	0.08076	+8
		0.15	0.1583	+6
		0.30	0.3081	+3
16 October 1996	16 October 1996	0.075	0.07684	+2
		0.15	0.1491	−1
		0.30	0.3125	+4
8 January 1997	9 January 1997	0.075	0.07751	+3
		0.15	0.1546	+3
		0.30	0.3083	+3
5 March 1997	6 March 1997	0.075	0.07682	+2
		0.15	0.1535	+2
		0.30	0.3057	+2
	15 April 1997[b]	0.075	0.07688	+3
		0.15	0.1534	+2
		0.30	0.3109	+4
30 April 1997	1 May 1997	0.075	0.07732	+3
		0.15	0.1537	+2
		0.30	0.3031	+1
23 July 1997	23 July 1997	0.075	0.07385	−2
		0.15	0.1561	+4
		0.30	0.2984	−1

[a] Results of duplicate analyses
[b] Animal room samples

TABLE J5
Results of Referee Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Drinking Water Studies of Sodium Nitrite

Date Prepared	Target Concentration (%)	Determined Concentration (%)	
		Study Laboratory[a]	Referee Laboratory[b]
1 August 1989	0.3	0.286	0.282 ± 0.000
12 September 1989	0.075	0.0768	0.0788 ± 0.0002

[a] Results of duplicate analyses
[b] Results of triplicate analyses (mean ± standard error)

APPENDIX K
WATER AND COMPOUND CONSUMPTION IN THE 2-YEAR DRINKING WATER STUDIES OF SODIUM NITRITE

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TABLE K1
Water and Compound Consumption by Male Rats in the 2-Year Drinking Water Study of Sodium Nitrite

Week	0 ppm		750 ppm			1,500 ppm			3,000 ppm		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	16.4	107	17.8	107	125	18.1	107	256	13.4	107	375
2	17.0	144	17.7	144	92	18.2	143	192	14.7	134	329
6	19.3	259	18.9	254	56	18.0	254	106	15.9	242	197
10	18.9	314	17.7	307	43	16.9	304	84	13.6	288	142
14	19.5	354	18.0	348	39	16.3	341	72	14.2	322	133
18	18.3	381	16.7	376	33	15.3	367	63	13.5	349	116
22	18.0	406	17.6	399	33	17.1	392	66	14.9	369	121
26	17.9	426	17.5	416	32	16.9	410	62	15.1	385	118
30	17.4	438	17.2	435	30	16.2	423	57	15.0	400	112
34	18.9	450	17.5	446	29	17.9	435	62	16.0	412	116
38	18.5	458	17.0	460	28	16.8	443	57	15.7	418	113
42	17.4	466	16.6	462	27	16.5	450	55	15.4	422	109
46	17.2	478	16.1	474	26	16.1	463	52	15.2	433	105
50	17.2	487	16.3	486	25	16.5	470	53	14.9	437	102
54	17.5	492	16.2	487	25	16.7	473	53	14.5	441	98
58	16.9	491	16.6	495	25	16.6	477	52	14.9	445	101
62	17.7	499	16.8	495	25	17.0	481	53	15.2	448	102
66	17.7	499	16.6	494	25	16.9	480	53	15.9	444	107
70	17.9	499	17.0	499	25	16.9	481	53	16.3	452	108
74	18.4	501	17.8	498	27	17.6	477	55	16.2	449	109
78	18.1	501	17.7	497	27	18.0	481	56	15.5	446	104
82	18.5	502	17.5	493	27	17.5	479	55	16.1	445	108
86	17.5	497	17.3	495	26	17.5	481	55	15.4	445	104
90	17.7	494	16.8	499	25	17.1	480	54	14.5	441	98
94	17.6	495	16.8	496	25	17.2	481	54	14.6	440	100
98	17.5	492	16.2	488	25	16.8	480	52	14.4	442	98
102	17.9	496	16.7	485	26	18.0	483	56	15.0	441	102
Mean for weeks											
1-13	17.9	206	18.0	203	79	17.8	202	159	14.4	193	261
14-52	18.0	435	17.1	430	30	16.6	420	60	15.0	395	115
53-102	17.8	497	16.9	494	26	17.2	480	54	15.3	445	103

[a] Grams of water consumed per animal per day
[b] Milligrams of sodium nitrite consumed per kilogram body weight per day

TABLE K2
Water and Compound Consumption by Female Rats in the 2-Year Drinking Water Study of Sodium Nitrite

Week	0 ppm		750 ppm			1,500 ppm			3,000 ppm		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	13.1	96	13.0	95	103	13.7	96	215	12.0	95	377
2	14.9	118	14.4	116	94	14.3	115	186	11.9	111	324
6	14.7	168	15.0	164	68	13.4	164	123	11.0	159	207
10	13.9	187	13.2	182	55	12.2	183	101	10.0	177	169
14	12.8	201	12.2	196	46	11.4	195	88	9.3	188	148
18	13.0	212	12.2	206	45	11.4	204	84	9.7	197	147
22	13.6	220	12.7	214	45	11.7	212	83	10.5	204	155
26	13.5	227	12.2	221	41	12.0	218	83	10.2	211	145
30	12.2	238	11.3	231	37	11.0	227	73	9.6	217	133
34	12.7	245	11.9	236	38	11.5	234	74	10.1	224	136
38	12.6	254	11.8	245	36	11.2	241	70	10.2	231	132
42	12.6	260	11.6	251	35	11.2	246	68	10.1	235	129
46	12.1	271	11.4	259	33	10.8	252	65	9.8	241	122
50	11.9	281	11.2	269	31	11.1	264	63	10.2	250	122
54	12.0	286	11.2	276	31	11.2	270	62	10.1	256	119
58	11.8	293	11.8	284	31	11.4	276	62	10.1	261	116
62	11.9	302	11.8	291	30	11.5	287	60	11.7	265	132
66	12.9	307	12.1	293	31	12.0	288	63	11.3	269	126
70	13.1	315	12.8	305	31	12.5	299	63	11.7	276	127
74	13.4	319	13.1	312	31	13.0	305	64	11.6	279	125
78	13.5	329	13.5	319	32	13.4	313	64	12.0	285	126
82	13.6	332	12.9	320	30	12.8	314	61	11.6	287	121
86	13.5	333	13.7	325	32	13.3	319	62	12.1	291	125
90	13.5	339	13.1	327	30	12.6	323	58	11.3	290	117
94	14.1	346	13.4	330	31	12.7	326	58	12.2	302	121
98	14.8	350	13.6	333	31	13.2	332	60	12.1	308	118
102	14.4	344	14.4	337	32	13.6	332	61	12.6	312	121
Mean for weeks											
1-13	14.1	142	13.9	139	80	13.4	139	156	11.2	135	269
14-52	12.7	241	11.8	233	39	11.3	229	75	10.0	220	137
53-102	13.3	323	12.9	312	31	12.5	307	61	11.6	283	123

[a] Grams of water consumed per animal per day
[b] Milligrams of sodium nitrite consumed per kilogram body weight per day

TABLE K3
Water and Compound Consumption by Male Mice in the 2-Year Drinking Water Study of Sodium Nitrite

Week	0 ppm		750 ppm			1,500 ppm			3,000 ppm		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
2	3.2	23.7	3.4	23.7	106	3.3	23.6	211	2.9	23.4	368
6	3.1	29.5	3.1	29.6	78	3.2	29.1	164	2.7	28.3	288
10	3.1	34.9	3.2	34.5	69	3.0	33.7	133	2.7	32.7	247
14	3.2	39.1	3.1	38.9	60	3.1	37.7	124	2.9	36.2	244
18	3.8	43.2	3.5	42.9	62	3.4	41.9	123	3.3	40.2	247
22	3.3	45.6	3.1	44.9	52	3.1	44.0	106	2.9	42.1	209
26	3.6	47.5	3.3	46.6	53	3.1	45.7	102	3.0	44.6	203
30	3.3	49.6	3.2	48.9	48	3.1	48.3	96	3.0	46.9	195
34	3.4	50.8	3.1	50.1	47	3.1	49.2	95	3.0	48.4	188
38	3.6	50.6	3.2	49.7	49	3.3	48.7	101	3.1	48.1	193
42	3.7	50.9	3.4	49.9	51	3.2	48.4	101	3.1	48.6	191
46	3.8	50.8	3.3	49.4	50	3.3	48.3	102	3.0	48.6	186
50	3.9	50.3	3.7	49.0	57	3.4	48.0	107	3.1	48.3	195
54	3.8	51.3	3.4	50.5	50	3.3	49.2	102	3.0	49.5	180
58	3.7	51.1	3.3	49.6	50	3.5	49.3	105	3.2	49.8	194
62	3.7	51.4	3.5	50.4	52	3.4	49.4	103	3.1	49.5	189
66	3.8	50.7	3.5	49.8	53	3.6	49.0	109	3.2	48.8	200
70	3.9	50.0	3.6	49.7	55	3.6	48.8	110	3.3	48.7	206
73	3.8	49.4	3.6	49.5	54	3.7	48.8	114	3.3	48.1	207
78	4.1	49.4	3.8	49.1	58	3.9	48.2	120	3.5	47.6	222
82	4.0	48.7	3.8	48.4	59	4.0	48.2	125	3.5	46.6	223
86	4.1	47.2	3.9	46.9	63	3.9	46.8	124	3.6	45.4	235
90	3.8	46.4	3.5	46.4	57	3.7	46.1	120	3.2	44.7	216
94	4.0	44.7	3.4	44.4	57	3.7	44.5	123	3.3	44.1	221
98	3.7	43.0	3.5	43.7	61	3.6	43.6	126	3.1	42.8	221
102	4.0	40.2	3.6	41.3	65	3.6	41.4	131	3.3	41.0	244
Mean for weeks											
2-13	3.1	29.4	3.2	29.3	84	3.2	28.8	169	2.8	28.1	301
14-52	3.6	47.8	3.3	47.0	53	3.2	46.0	106	3.1	45.2	205
53-102	3.9	48.0	3.6	47.7	56	3.6	47.2	116	3.3	46.7	212

[a] Grams of water consumed per animal per day
[b] Milligrams of sodium nitrite consumed per kilogram body weight per day

TABLE K4
Water and Compound Consumption by Female Mice in the 2-Year Drinking Water Study of Sodium Nitrite

Week	0 ppm		750 ppm			1,500 ppm			3,000 ppm		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	2.9	18.9	2.8	18.9	113	2.7	18.8	211	2.3	18.9	370
2	3.0	19.4	3.0	19.7	114	3.0	19.5	227	2.3	19.4	364
6	2.9	23.7	3.0	23.9	93	2.8	23.9	174	2.5	23.2	325
10	3.1	28.2	2.8	28.4	74	2.8	28.2	149	2.5	26.9	281
14	2.9	31.4	3.0	32.6	69	2.7	31.5	129	2.9	30.3	282
18	3.1	35.6	2.8	37.8	55	2.7	36.5	110	2.4	34.4	208
22	2.8	40.0	2.4	41.7	44	2.4	40.6	88	2.2	38.2	177
26	2.5	43.2	2.4	44.9	40	2.3	43.7	80	2.2	41.1	163
30	2.6	46.6	2.3	47.4	36	2.3	46.2	74	2.3	43.3	158
34	2.4	49.2	2.2	49.6	34	2.3	48.8	71	2.3	45.4	151
38	2.6	51.1	2.5	51.1	36	2.4	50.0	73	2.4	46.9	153
42	2.6	53.4	2.4	53.3	34	2.3	52.3	65	2.3	48.8	139
46	2.4	54.2	2.2	54.6	30	2.1	54.0	59	2.1	50.8	125
50	2.5	55.3	2.2	55.6	30	2.2	54.8	61	2.1	52.5	120
54	2.2	56.1	2.2	55.3	30	2.2	55.2	59	2.0	53.0	111
58	2.6	56.7	2.6	57.0	34	2.5	56.6	67	2.3	54.2	126
62	2.3	58.8	2.2	58.2	28	2.1	58.4	54	2.0	56.1	106
66	2.4	58.3	2.3	57.5	31	2.3	57.4	61	2.0	55.4	111
70	2.7	57.7	2.3	56.8	30	2.3	56.5	62	2.1	54.4	117
73	2.5	56.1	2.3	56.1	30	2.3	55.0	62	2.1	53.7	116
78	2.8	55.5	2.6	56.3	35	2.6	55.0	71	2.3	53.8	131
82	2.8	55.0	2.6	55.6	35	2.4	54.2	67	2.3	54.2	126
86	2.8	53.5	2.5	53.7	35	2.5	53.5	71	2.2	53.2	123
90	3.2	52.6	2.6	52.8	37	2.7	53.1	75	2.2	51.2	127
94	3.1	52.1	2.5	52.1	36	2.6	52.3	76	2.1	49.6	128
98	2.8	52.0	2.4	51.4	36	2.5	51.4	72	2.1	49.3	129
102	2.8	51.1	2.3	50.7	34	2.6	50.7	77	2.0	48.9	124
Mean for weeks											
1-13	3.0	22.5	2.9	22.7	98	2.8	22.6	190	2.4	22.1	335
14-52	2.6	46.0	2.4	46.9	41	2.4	45.8	81	2.3	43.2	168
53-102	2.7	55.0	2.4	54.9	33	2.4	54.6	67	2.1	52.8	121

[a] Grams of water consumed per animal per day
[b] Milligrams of sodium nitrite consumed per kilogram body weight per day

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

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TABLE L1
Ingredients of NTP-2000 Rat and Mouse Ration

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

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

TABLE L2
Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]

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

[a] Per kg of finished product

TABLE L3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	13.8 ± 0.72	12.7 – 16.2	23
Crude fat (% by weight)	8.1 ± 0.33	7.5 – 8.7	23
Crude fiber (% by weight)	9.5 ± 0.59	7.8 – 10.3	23
Ash (% by weight)	5.0 ± 0.16	4.8 – 5.4	23
Amino Acids (% of total diet)			
Arginine	0.732 ± 0.050	0.670 – 0.800	6
Cystine	0.220 ± 0.011	0.210 – 0.240	6
Glycine	0.683 ± 0.048	0.620 – 0.740	6
Histidine	0.333 ± 0.020	0.310 – 0.350	6
Isoleucine	0.522 ± 0.054	0.430 – 0.590	6
Leucine	1.065 ± 0.070	0.960 – 1.130	6
Lysine	0.705 ± 0.066	0.620 – 0.790	6
Methionine	0.402 ± 0.042	0.350 – 0.460	6
Phenylalanine	0.600 ± 0.042	0.540 – 0.640	6
Threonine	0.512 ± 0.056	0.430 – 0.590	6
Tryptophan	0.125 ± 0.015	0.110 – 0.150	6
Tyrosine	0.410 ± 0.037	0.360 – 0.460	6
Valine	0.628 ± 0.052	0.550 – 0.690	6
Essential Fatty Acids (% of total diet)			
Linoleic	3.98 ± 0.325	3.59 – 4.54	6
Linolenic	0.30 ± 0.048	0.21 – 0.35	6
Vitamins			
Vitamin A (IU/kg)	5,018 ± 1,421	2,780 – 8,140	23
Vitamin D (IU/kg)	1,000[a]		
α-Tocopherol (ppm)	77.2 ± 10.94	62.2 – 87.1	6
Thiamine (ppm)[b]	9.4 ± 2.19	6.0 – 15.0	23
Riboflavin (ppm)	5.6 ± 1.24	4.20 – 7.70	6
Niacin (ppm)	73.1 ± 4.13	66.4 – 78.8	6
Pantothenic acid (ppm)	24.2 ± 2.92	21.4 – 29.1	6
Pyridoxine (ppm)[b]	9.37 ± 2.50	6.7 – 12.4	6
Folic acid (ppm)	1.70 ± 0.43	1.26 – 2.32	6
Biotin (ppm)	0.349 ± 0.18	0.225 – 0.704	6
Vitamin B_{12} (ppb)	83.4 ± 67.1	30.0 – 174.0	6
Choline (ppm)	3,082 ± 232	2,700 – 3,400	6
Minerals			
Calcium (%)	0.958 ± 0.051	0.858 – 1.050	23
Phosphorus (%)	0.577 ± 0.022	0.548 – 0.640	23
Potassium (%)	6.660 ± 0.026	0.627 – 0.691	6
Chloride (%)	0.356 ± 0.031	0.300 – 0.392	6
Sodium (%)	0.193 ± 0.020	0.160 – 0.212	6
Magnesium (%)	0.197 ± 0.010	0.185 – 0.213	6
Sulfur (%)	0.182 ± 0.023	0.153 – 0.209	6
Iron (ppm)	158 ± 15.2	135 – 173	6
Manganese (ppm)	51.8 ± 4.05	46.2 – 56.0	6
Zinc (ppm)	53.2 ± 5.68	45.0 – 61.1	6
Copper (ppm)	6.49 ± 0.786	5.38 – 7.59	6
Iodine (ppm)	0.487 ± 0.204	0.233 – 0.843	6
Chromium (ppm)	0.763 ± 0.620	0.330 – 2.000	6
Cobalt (ppm)	0.53 ± 0.720	0.20 – 2.0	6

[a] From formulation
[b] As hydrochloride

TABLE L4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.26 ± 0.11	0.10 – 0.50	23
Cadmium (ppm)	0.05 ± 0.01	0.04 – 0.10	23
Lead (ppm)	0.14 ± 0.10	0.06 – 0.4	23
Mercury (ppm)	<0.02		23
Selenium (ppm)	0.18 ± 0.68	0.10 – 0.40	23
Aflatoxins (ppb)	<5.00		23
Nitrate nitrogen (ppm)[c]	13.2 ± 5.79	4.80 – 31.90	23
Nitrite nitrogen (ppm)[c]	0.85 ± 0.672	0.30 – 3.20	23
BHA (ppm)[d]	1.3 ± 1.04	0.01 – 5.00	23
BHT (ppm)[d]	1.2 ± 0.96	0.01 – 5.00	23
Aerobic plate count (CFU/g)[e]	156,770 ± 306,635	7,700 – 1,000,000	10
Coliform (MPN/g)[e]	17 ± 20	3 – 70	10
Escherichia coli (MPN/g)	<10		23
Salmonella (MPN/g)	Negative		23
Total nitrosoamines (ppb)[f]	6.5 ± 4.10	2.1 – 20.9	23
N-Nitrosodimethylamine (ppb)[f]	3.5 ± 2.50	1.0 – 9.4	23
N-Nitrosopyrrolidine (ppb)[f]	2.9 ± 2.70	1.0 – 14.5	23
Pesticides (ppm)			
α-BHC	<0.01		23
β-BHC	<0.02		23
γ-BHC	<0.01		23
δ-BHC	<0.01		23
Heptachlor	<0.01		23
Aldrin	<0.01		23
Heptachlor epoxide	<0.01		23
DDE	<0.01		23
DDD	<0.01		23
DDT	<0.01		23
HCB	<0.01		23
Mirex	<0.01		23
Methoxychlor	<0.05		23
Dieldrin	<0.01		23
Endrin	<0.01		23
Telodrin	<0.01		23
Chlordane	<0.05		23
Toxaphene	<0.10		23
Estimated PCBs	<0.20		23
Ronnel	<0.01		23
Ethion	<0.02		23
Trithion	<0.05		23
Diazinon	<0.10		23
Methyl chlorpyrifos	0.053 ± 0.051	0.010 – 0.160	22
Methyl parathion	<0.02		23
Ethyl parathion	<0.02		23
Malathion	0.138 ± 0.195	0.020 – 0.830	23
Endosulfan I	<0.01		23
Endosulfan II	<0.01		23
Endosulfan sulfate	<0.03		23

[a] CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] Nonirradiated samples; microbial counts for irradiated samples were below the detection limit.
[f] All values were corrected for percent recovery.

APPENDIX M
SENTINEL ANIMAL PROGRAM

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SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from randomly selected rats and mice during the 14-week and 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
14-Week Study	
ELISA	
PVM (pneumonia virus of mice)	Study termination
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
2-Year Study	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM	1, 6, 12, and 18 months, study termination
RCV/SDA	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
M. arthritidis	Study termination
Hemagglutination Inhibition	
H-1	1, 6, 12, and 18 months, study termination
KRV	1, 6, 12, and 18 months, study termination

MICE

14-Week Study

ELISA

Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
Mouse adenoma virus	Study termination
MHV (mouse hepatitis virus)	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination

Immunofluorescence Assay

EDIM (epizootic diarrhea of infant mice)	Study termination
MVM (minute virus of mice)	Study termination

Hemagglutination Inhibition

K (papovavirus)	Study termination
Polyoma virus	Study termination

2-Year Study

ELISA

Ectromelia virus	1, 6, 12, and 18 months, study termination
EDIM	1, 6, 12, and 18 months, study termination
GDVII	1, 6, 12, and 18 months, study termination
LCM	1, 6, 12, and 18 months, study termination
Mouse adenoma virus-FL	1, 6, 12, and 18 months, study termination
MHV	1, 6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	1, 6, 12, and 18 months, study termination
Reovirus 3	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination

Immunofluorescence Assay

Ectromelia virus	Study termination
EDIM	6 months
GDVII	Study termination
LCM	Study termination
Mouse adenoma virus-FL	Study termination
MCMV (mouse cytomegalovirus)	Study termination
MHV	6 months, study termination
PVM	1 month, study termination

Hemagglutination Inhibition

K	1, 6, 12, and 18 months, study termination
MVM	1, 6, 12, and 18 months, study termination
Polyoma virus	1, 6, 12, and 18 months, study termination

RESULTS

All test results were negative.