NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 393

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

SODIUM FLUORIDE

(CAS NO. 7681-49-4)

IN F344/N RATS AND B6C3F$_1$ MICE

(DRINKING WATER STUDIES)

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

FOREWORD

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

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

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

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

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ABSTRACT

NaF

SODIUM FLUORIDE
CAS No. 7681-49-4
NaF
Molecular Weight: 41.99

Sodium fluoride is a white, crystalline, water-soluble powder used in municipal water fluoridation systems, in various dental products, and in a variety of industrial applications. Toxicology and carcinogenesis studies were conducted with F344/N rats and B6C3F$_1$ mice of each sex by incorporating sodium fluoride into the drinking water in studies lasting 14 days, 6 months, and 2 years. In addition, genetic toxicology studies were performed with *Salmonella typhimurium*, with mouse L5178Y cells, and with Chinese hamster ovary cells.

14-Day Studies: Rats and mice received sodium fluoride in drinking water at concentrations as high as 800 ppm. (Concentrations are expressed as sodium fluoride; fluoride ion is 45% of the sodium salt by weight.) In the high-dose groups, 5/5 male and 5/5 female rats and 2/5 male mice died; one female rat given 400 ppm in the drinking water also died before the end of the studies. No gross lesions were attributed to sodium fluoride administration.

6-Month Studies: Rats received concentrations of sodium fluoride in drinking water as high as 300 ppm, and mice as high as 600 ppm. No rats died during the studies; however, among the mice, 4/9 high-dose males, 9/11 high-dose females, and 1/8 males in the 300 ppm group died before the end of the studies. Weight gains were less than those of controls for rats receiving 300 ppm and mice receiving 200 to 600 ppm.

The teeth of rats and mice receiving the higher doses of sodium fluoride were chalky white and chipped or showed unusual wear patterns. Mice and male rats given the higher concentrations had microscopic focal degeneration of the enamel organ. Rats receiving 100 or 300 ppm sodium fluoride had minimal hyperplasia of the gastric mucosa of the stomach, and one high-dose rat of each sex had an ulcer. Acute nephrosis and/or lesions in the liver and myocardium were observed in mice that died early, and minimal alterations in bone growth/remodeling were observed in the long bones of mice receiving sodium fluoride at concentrations of 50 to 600 ppm.

The sodium fluoride concentrations selected for the 2-year studies in both rats and mice were 0, 25, 100, and 175 ppm in the drinking water. These concentrations were selected based on the decreased weight gain of rats at 300 ppm and of mice at 200 ppm and above, on the incidence of gastric lesions in rats at 300 ppm in the 6-month studies, and on the absence of significant toxic effects at sodium fluoride concentrations as high as 100 ppm in an earlier 2-year study.

Body Weights and Survival in the 2-Year Studies: Mean body weights of dosed and control groups of rats and mice were similar throughout the 2-year studies. Survival of rats and mice was not affected by sodium fluoride administration. Survival rates after 2 years were: male rats—control, 42/80; 25 ppm, 25/51; 100 ppm, 23/50; 175 ppm, 42/80; female rats—59/80; 31/50; 34/50; 54/81; male mice—58/79; 39/50; 37/51; 65/80; female mice—53/80; 38/52; 34/50; 52/80.

Neoplastic and Nonneoplastic Effects in the 2-Year Studies: The teeth of rats and mice had a dose-

dependent whitish discoloration, and male rats had an increased incidence of tooth deformities and attrition leading on occasion to malocclusion. The teeth of male and, to a lesser degree, female rats had areas of microscopic dentine dysplasia and degeneration of ameloblasts. Dentine dysplasia occurred in both dosed and control groups of male and female mice; the incidence of this lesion was significantly greater in high-dose than in control male mice. Osteosclerosis of long bones was increased in female rats given drinking water containing 175 ppm sodium fluoride. No other significant nonneoplastic lesions in rats or mice appeared related to sodium fluoride administration.

Osteosarcomas of bone were observed in 1/50 male rats in the 100 ppm group and in 3/80 male rats in the 175 ppm group. None were seen in the control or 25 ppm dose groups. One other 175 ppm male rat had an extraskeletal osteosarcoma arising in the subcutaneous tissue. Osteosarcomas occur in historical control male rats at an incidence of 0.5% (range 0-6%). The historical incidence is not directly comparable with the incidences observed in this study because examination of bone was more comprehensive in the sodium fluoride studies than in previous NTP studies of other chemicals, and the diet used in previous studies was not controlled for fluoride content. In the current study, although the pairwise comparison of the incidence in the 175 ppm group versus that in the controls was not statistically significant, osteosarcomas occurred with a statistically significant dose-response trend, leading to the conclusion that a weak association may exist between the occurrence of these neoplasms and the administration of sodium fluoride. No other neoplastic lesions in rats or mice were considered possibly related to chemical administration.

Genetic Toxicology: Sodium fluoride was negative for gene mutation induction in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 with and without S9. In two laboratories, sodium fluoride was tested for induction of trifluorothymidine resistance in mouse L5178Y lymphoma cells; results were positive both with and without S9. Sodium fluoride was tested for cytogenetic effects in Chinese hamster ovary (CHO) cells in two laboratories. In the first laboratory, the sister chromatid exchange (SCE) test was negative with and without S9, and the chromosomal aberration (Abs) test was positive in the absence of S9; in the second laboratory, the SCE test was positive with and without S9, but no induction of Abs was observed. The laboratory that reported a negative result for Abs tested at doses below those shown to be positive in the other laboratory. Similarly, the positive SCE result was obtained at a higher dose and longer harvest time than was used by the laboratory reporting the negative SCE response.

Conclusions: Under the conditions of these 2-year dosed water studies, there was *equivocal evidence of carcinogenic activity** of sodium fluoride in male F344/N rats, based on the occurrence of a small number of osteosarcomas in dosed animals. "Equivocal evidence" is a category for uncertain findings defined as studies that are interpreted as showing a marginal increase of neoplasms that may be related to chemical administration. There was *no evidence of carcinogenic activity* in female F344/N rats receiving sodium fluoride at concentrations of 25, 100, or 175 ppm (11, 45, or 79 ppm fluoride) in drinking water for 2 years. There was *no evidence of carcinogenic activity* of sodium fluoride in male or female mice receiving sodium fluoride at concentrations of 25, 100, or 175 ppm in drinking water for 2 years.

Dosed rats had lesions typical of fluorosis of the teeth and female rats receiving drinking water containing 175 ppm sodium fluoride had increased osteosclerosis of long bones.

*Explanation of Levels of Carcinogenic Activity is on page 8. A summary of peer review comments and the public discussion on this technical report appear on page 10.

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

Variable	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	Control, 25, 100, or 175 ppm in drinking water 7 days per week for 2 years	Control, 25, 100, or 175 ppm in drinking water 7 days per week for 2 years	Control, 25, 100, or 175 ppm in drinking water 7 days per week for 2 years	Control, 25, 100, or 175 ppm in drinking water 7 days per week for 2 years
Body weights	Exposed similar to controls	Exposed similar to controls	Exposed similar to controls	Exposed similar to controls
Survival rates	42/80; 25/51; 23/50; 42/80	59/80; 31/50; 34/50; 54/81	58/79; 39/50; 37/51; 65/80	53/80; 38/52; 34/50; 52/80
Neoplasms	Osteosarcoma of bone (0/80; 0/51; 1/50; 3/80)	None	None	None
Nonneoplastic lesions	Dentine dysplasia, degeneration of ameloblasts, attrition, deformity, and discoloration of teeth	Osteosclerosis, dentine dysplasia, degeneration of ameloblasts, attrition, deformity, and discoloration of teeth	Tooth discoloration Dentine dysplasia	Tooth discoloration
Level of evidence of carcinogenic activity	Equivocal evidence	No evidence	No evidence	No evidence

Genetic toxicology

S. typhimurium (gene mutation):	Negative with and without S9
L5178Y mouse lymphoma:	Positive with and without S9
SCE (CHO cells *in vitro*):	Positive with and without S9[a]
Abs (CHO cells *in vitro*):	Positive without S9[a]

[a] Positive results in this assay were obtained at higher doses than those that produced negative results in another laboratory.

EXPLANATION OF LEVELS OF EVIDENCE

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

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

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

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

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

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the NTP draft Technical Report on sodium fluoride on April 26, 1990 are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members have five major responsibilities in reviewing NTP studies:

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

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SUMMARY OF PEER REVIEW COMMENTS

On April 26, 1990, the draft Technical Report on the toxicology and carcinogenesis studies of sodium fluoride received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. John Bucher, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (equivocal evidence of carcinogenic activity in male rats, no evidence of carcinogenic activity in female rats or in male or female mice).

Dr. Longnecker, a principal reviewer, agreed with the conclusions. He thought this to be a well-written report reflecting a carefully done study. He said the doses chosen were appropriate, yielding clear evidence of biologic effects without severe effects on animal growth.

Dr. Ashby, the second principal reviewer, agreed with the conclusions. However, he considered the definition for *equivocal evidence of carcinogenic activity* to be insufficiently precise for male rats and suggested that a statement from the discussion section be used instead, this being: "Taken together, the current findings are inconclusive, but are weakly supportive of an association between sodium fluoride administration and the occurrence of osteosarcomas in male rats." He noted that the propensity for fluoride to accumulate in bone made this tissue the most likely one for occurrence of a carcinogenic effect, yet the fact that fluoride accumulates in the bone of female rats and male and female mice to a similar extent as in male rats suggested caution in drawing general conclusions. Dr. Ashby commented that sodium fluoride clearly has some genetic activity, but probably by an indirect or secondary effect on chromosome structure. He thought future acquisition of male rat bone marrow genotoxicity data was indicated.

Dr. Garman, the third principal reviewer, agreed with the conclusions. He stated that this was an outstanding report that covered the findings of a thorough, well-conducted study. He speculated that because of a possible link between fracture formation and subsequent development of osteogenic sarcomas in humans and animals, and because increased levels of dietary fluoride may result in increased fragility of certain bones, there might be a connection between osteogenic sarcoma formation and bone remodeling. Dr. Garman suggested that any future studies include measurements of bone tensile strength.

Dr. Silbergeld noted the role of the NTP data in subsequent risk assessment, and pointed out that the doses used were not orders of magnitude above human exposure levels. She supported further research on genotoxicity and on mechanisms of sex differences seen. Dr. Davis underscored the observation of nonneoplastic lesions of the bone in female rats (osteosclerosis) in the absence of bone tumors. Dr. Goodman said the Abstract should point out the extra scrutiny given to the evaluation of bone tissue in this study. Dr. Hayden also commented on the thoroughness of the study and report. Dr. Gold noted that this was an unusual study in that there was not a zero control group, and related to this is the fact that fluoride is a naturally occurring chemical in the standard rodent laboratory diet. She emphasized that both control and dosed animals in all NTP studies received fluoride doses in the laboratory diet that were higher than the low dose tested. Dr. Bucher agreed and said "Control" rather than "zero" would be used in table headings and better defined as to the level of fluoride in the diet of control animals. There was discussion by Dr. McKnight with Dr. J. Haseman, NIEHS, as to why data from paired (age-matched) controls were not used in primary data tables. Dr. Zeise pointed out two rare tumors of the nasal mucosa found in high-dose male rats and suggested these be discussed in the body of the report. She reiterated the need expressed by other Panel members for designing another study with higher top doses. Dr. Zeise noted that the fluoride concentrations in high-dose rats were within the range observed in humans and the differences in pharmacokinetics and deposition of fluoride in bone between humans and animals should be studied. Dr. Carlson inquired about the possible mechanism for induction of the oral cavity tumors. Dr. Bucher responded that there was no overall statistical significance for the oral tumors even if the P values for female rats were combined statistically with the corresponding values for male rats. Additionally, there was a squamous cell carcinoma of the oral cavity in a female control as well as one in a paired male control. Thus, the level of confidence that the oral lesions might be associated with chemical exposure was less than that for the bone lesions. Dr. L. Hart, NIEHS, read into the record comments received from Dr. C. Klaassen, a Panel member who could not be present. Dr. Klaassen thought information in the Abstract about the historical control rate of osteosarcomas in male rats should include not only the mean (0.5%) but also the range (0-6%). Dr. Gallo concluded the initial discussion by emphasizing that there was a major need for looking at the mechanisms of toxic action of fluoride at the various sites in any future studies.

Dr. John A. Yiamouyiannis, Director, Safe Water Foundation, Delaware, Ohio, stated that occurrence of a rare form of liver cancer, hepatocholangiocarcinoma, in fluoride-treated male and female mice in the NTP studies provided clear evidence of carcinogenic activity in mice. Further, he said a dose-dependent relationship between fluoride and the number of male rats with oral squamous cell tumors and a dose-dependent relationship between oral squamous cell metaplasia and tumors in female rats along with the increased incidence of osteosarcomas in male rats supported a finding of clear evidence of carcinogenic activity of fluoride in rats.

Dr. James W. Bawden, University of North Carolina School of Dentistry, representing the American Association for Dental Research and the American Association of Dental Schools, (a) contended that plasma fluoride levels reported for the six-month studies in rats were in error due to the assay method used; (b) expressed concern about the terms "low," "mid," and "high" used to describe the doses used in the study, stating that a comparison of plasma levels of fluoride from animals in the study with those observed in humans would support terming the doses as "high," "very high," and "extremely high," (c) questioned the appropriateness and relevance of the rat model, noting that in humans osteosarcoma as a primary lesion is predominately associated with long bones and occurs almost exclusively in young people; and (d) agreed with the NTP conclusions. He opined that the results of the NTP study do not indicate that the fluoridation of municipal water supplies is ill advised.

Dr. Robert d'Amato, Procter & Gamble Company, described their chronic carcinogenicity studies with sodium fluoride in Swiss CD mice and Sprague-Dawley rats. The high dose for the rat study was 2 to 3 times greater than the NTP study high dose on a body weight basis. The mouse studies, not yet reported, showed dose-related increases in the incidences of osteomas, but were flawed by a C-type retroviral infection in all groups. He speculated that increased incidences of osteomas (observed in the mouse study) might be due to a biological interaction between virus and fluoride ion. Their rat study indicated no evidence that sodium fluoride altered the incidences of preneoplastic or neoplastic lesions at any site in either sex. The results of the rat study have been accepted for publication in the *Journal of the National Cancer Institute*. Dr. d'Amato said the results of their studies supported the wide body of data which indicates that sodium fluoride does not cause cancer and that human lifetime exposure to fluoride via dentrifice usage, as well as from the environment, is safe.

Ms. Susan Pare, Center for Health Action, questioned the objectivity of a study apparently designed to confirm a negative and stated that it had taken 13 years from the decision to do carcinogenesis studies on sodium fluoride to the present, leading her to wonder about the efficiency of the test system. Ms. Pare commented on the lack of a "true" control diet, i.e., one free of fluoride, and the difficulties this could cause in comparisons with other studies. She contended that rare liver cancers originally diagnosed in exposed mice had been reclassified. Finally, she objected to "sweeping" statements in NTP news releases and the Technical Report about the effectiveness of water fluoridation against tooth decay.

A statement was read into the record from Dr. James A. Popp, Chemical Industry Institute of Toxicology, responding to comments attributed to him in written material provided to the NTP by Ms. Pare prior to the meeting which stated that Dr. Popp had expressed to a "reliable source" that the evidence in the NTP studies linking fluoride to osteosarcomas in rats was "clear". Dr. Popp had been a member of the Pathology Working Group evaluating the studies. In his statement, Dr. Popp said that he did not recall making such a comment, and added that "without complete information I believe it is impossible for me or any other member of the Pathology Working Group to make a determination of the appropriate level of evidence assignment for the sodium fluoride study."

Dr. John R. Lee, Marin County, California, representing the Center for Health Action spoke to the need for further studies which he thought should include (a) adequate controls, (b) better assessment of age-related nephropathy which can lead to decreased excretion of fluoride, (c) more balanced treatment in reporting of the deleterious effects of fluoride and considering the risks as well as the benefits of fluoride, (d) lumping subcutaneous and bone osteosarcomas together, and (e) a better evaluation of the genetic toxicology.

Dr. Melvin Reuber, representing the Safe Water Foundation, Delaware, Ohio, commented on some of the tumors observed in the NTP studies as follows: (a) in commenting on the hepatocholangiomas and hepatoblastomas observed in mice, he said more sections of liver should have been cut; (b) the osteosclerosis reported should be considered a preneoplastic lesion; (c) squamous dysplasia should be considered a preneoplastic lesion; and (d) neoplasms of the Zymbal's gland, skin, and kidney received insufficient pathologic evaluation. Dr. Reuber claimed there were discrepancies between the diagnoses made by the original laboratory pathologist for several lesions and the diagnoses made by the laboratory performing pathology quality assurance.

Dr. Gary M. Whitford, Department of Oral Biology, Medical College of Georgia, suggested that statements in the Report about *in vitro* genotoxic effects of fluoride should note that the concentrations are much higher than the likely levels of fluoride in the human body. Dr. Whitford summarized the findings from a recently completed chronic toxicity study in which Sprague-Dawley rats were administered fluoride in the form of dentifrices. He concluded that administration of 0.25 or 2.5 mg fluoride/kg for 18 months caused no consistent evidence of toxicity of any kind that distinguished these dosed groups from the control groups. All animals in the high-dose groups, 12.5 mg/kg, died, usually in renal failure, between the sixth and twelfth months.

Dr. John W. Stamm, School of Dentistry, University of North Carolina, representing the American Dental Association (ADA), stated that the ADA disagreed with the NTP's conclusions for male rats based on four issues: (a) the criteria used by the NTP to assess strength of experimental evidence appeared to depart from the norms used by the NTP and NCI over many years; (b) the NTP interpretation appeared to have given insufficient attention to the relative contributions of increased and decreased incidences of tumors in the rat studies; (c) a recent suggestion that some NIEHS investigators themselves may regard compounds categorized as "equivocal" to be more properly seen as noncarcinogenic; and (d) extensive epidemiological studies in humans have consistently shown no link between water fluoridation and cancer.

Dr. Edward Remmers, American Council on Science and Health (ACSH), noted that the ACSH had held a press conference on April 24, 1990, to present their pro-fluoridation position for drinking water. He asked the Panel to acknowledge that high-dose rodent studies are not infallible predictors of cancer risk in humans, and to reject the recommendation of those who allege that the EPA should classify fluoride as a "probable human carcinogen." Dr. Remmers concluded by reporting that the ACSH planned a press conference in the fall of 1990 on the limits of extrapolating cancer risk from animals to humans and on the possibility of considering seeking Congressional redress of the increasing misuse of animal studies to needlessly terrify the American consumer about safe technologies and products.

Dr. Gold noted that younger animals received a higher dose because they drink a larger amount of water in proportion to their body weight than older animals. Dr. Zeise questioned whether a high enough dose was used in mice. Dr. Bucher replied that the primary factor considered in selection of sodium fluoride concentrations for 2-year studies in mice was a reduction in body weight gain at higher doses in the 6-month studies. Dr. Zeise asked for a statement to the effect that mice could have tolerated higher doses. Dr. Bucher agreed saying that based on the 2-year results it appeared that mice might have been able to tolerate higher doses. Dr. Haseman agreed to Dr. McKnight's request that statistical analyses including the paired control data for the more important tumors be added to the tables.

Dr. Goodman moved that the conclusion in male rats be changed to *no evidence of carcinogenic activity* based on the following points: (1) the number of osteosarcomas observed in male rats was within the historical control range; (2) scrutiny of bone and bone tissue was more rigorous than in previous studies; (3) fluoride accumulation was similar in all four experiments, and actually highest in female rats where there were no tumors; and (4) there was no statistical difference in pairwise comparisons between control and treated male rat groups. Dr. Davis seconded the motion. Discussion against the motion noted that the tumors at issue (osteosarcomas) were found in a target organ for fluoride (bone), they are uncommon tumors, and a further supporting factor was the observation of a subcutaneous osteosarcoma. The motion was defeated by 10 no votes to 1 yes vote (Dr. Goodman).

Dr. Longnecker moved that the draft Technical Report on sodium fluoride be accepted with the editorial changes and revisions as discussed by the Panel and with the conclusions as written for male rats, *equivocal evidence of carcinogenic activity*, and for female rats and male and female mice, *no evidence of carcinogenic activity*. He asked that the statement cited by Dr. Ashby be added to the conclusions. Dr. Ashby seconded the motion. In discussion, there was concern that "weakly supportive" was too positive when viewed in the context of the NTP definition of equivocal evidence. Dr. Gold stated that the uncertain nature of the findings in male rats needed to be emphasized, and after further discussion, she proposed that the definition for equivocal evidence be included in the conclusions. Dr. Longnecker and Dr. Ashby agreed. The statement which would be inserted after the first sentence of the conclusions read: "Equivocal evidence is a category for uncertain findings demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related." The motion to add this sentence was accepted by nine yes votes to two no votes (Drs. Silbergeld and Zeise).

Dr. Ashby moved that the proposed conclusions be accepted. Dr. Gold seconded the motion, which was accepted unanimously with 11 votes.

INTRODUCTION

NaF

SODIUM FLUORIDE
CAS No. 7681-49-4
NaF
Molecular Weight: 41.99

CHEMICAL AND PHYSICAL PROPERTIES, PRODUCTION, USE, AND HUMAN EXPOSURE TO FLUORIDES

Fluorine is estimated to be the seventeenth most abundant element (Murray, 1986). Because of its extreme reactivity, it is nearly always found as the fluoride ion or combined in inorganic complexes. Various fluoride compounds occur naturally and are recovered or released during the manufacture of rock phosphate fertilizer, aluminum smelting, and during the combustion of coal. Fluoride is part of the minerals fluorspar and cryolite (Walton, 1988). Seawater contains 0.8 to 1.4 ppm fluoride (Murray, 1986). The fluoride content of freshwaters differs widely in different geographical locations and is dependent on the fluoride content of the local soils and rock formations (Janssen *et al.*, 1989).

Sodium fluoride is a white, free-flowing crystalline powder, typically prepared by neutralizing aqueous solutions of hydrofluoric acid with sodium carbonate or sodium hydroxide or by fusing cryolite with sodium hydroxide. The compound is soluble in water, generally forming a solution with a nearly neutral pH (Bellack, 1974; International Program on Chemical Safety, 1984; Windholz *et al.*, 1983).

Sodium fluoride is used in a variety of industrial and consumer applications. It is an ingredient in vitreous enamel and glass mixes. It is used as a steel degassing agent, in electroplating, in fluxes, as a wood preservative, in the manufacture of paper, and for disinfecting fermentation apparatus in distilleries and breweries. Sodium fluoride is also used as an insecticide, fungicide, and rodenticide (Windholz *et al.*, 1983). Sodium fluoride was the first fluoride compound used in the fluoridation of drinking water. Although it is the most expensive of the three chemicals commonly used for this purpose (the other two are sodium silicofluoride and hydrofluosilicic acid), sodium fluoride is still recommended for use by small municipal water systems because of the simplicity of the equipment required (Murray, 1986). For this purpose, sufficient sodium fluoride is added to bring the fluoride content of the water to 0.7 to 1.2 mg/L (Bellack, 1974).

In 1981, 35 countries either permitted or required fluoridation of drinking water, and an estimated 210 million people were provided fluoridated water. An additional 103 million people live in areas where optimal fluoride concentrations occur naturally (Murray, 1986). Various fluoride compounds including sodium fluoride are added to tooth pastes (1,000 to 1,500 mg fluoride/kg), mouth rinses (1,000 mg fluoride/kg), fluoride tablets (0.25 mg fluoride/tablet), and gels (4,000 to 6,000 mg fluoride/kg) (Janssen *et al.*, 1989).

ABSORPTION, DISTRIBUTION, AND EXCRETION

Solutions of fluoride salts are rapidly and nearly completely absorbed from the gastrointestinal tract. Low pH in the stomach favors formation of non-ionized hydrofluoric acid, which is irritating but more easily absorbed than is the fluoride ion (Carlson *et al.*, 1960; Taves and Guy, 1979). The presence of food can retard absorption, especially foods rich in calcium, which binds to fluoride (Trautner and Einwag, 1989).

Following absorption from the gut, fluoride is found in low concentrations in plasma and soft tissues; however, bone and teeth accumulate fluoride. Typically about 99% of the total body burden is contained in the skeleton. Uptake into bone is rapid. One metabolism study using intravenously administered radioactive fluoride indicated a half-time of 13 minutes for deposition into bone (Charkes *et al.*, 1978). Studies have found that about 40%-50% of an increase in fluoride intake is incorporated into bone (Largent and Heyroth, 1949; Spencer *et al.*, 1981). Kinetic studies have demonstrated two compartments for fluoride in bone: an "exchangeable" compartment where fluoride concentrations fluctuate and tend to buffer changes in plasma and tissue levels; and a "nonexchangeable" compartment where fluoride is released only during bone remodeling (Hall *et al.*, 1977). Bone fluoride concentrations vary with age and depend upon total intake. Weatherell (1966) reported bone fluoride concentrations of 200 to 800 mg/kg (ash) in subjects 20 to 30 years of age and 1,000 to 2,500 mg/kg in persons 70 to 80 years old. Zipkin *et al.* (1958) reported bone fluoride concentrations in four groups of individuals with average ages of 56 to 76 who lived in areas with fluoride concentrations in drinking water of 0.1, 1, 2.6, or 4 ppm. The relationship between bone fluoride concentrations and water fluoride content was linear; bone fluoride ranged from about 800 to 7,000 ppm ash with increasing water fluoride.

In the adult, the fluoride content of tooth enamel is reported to be 900 to 1,000 mg/kg in persons living in areas with low fluoride concentrations in the drinking water, about 1,500 mg/kg for people in areas with artificial fluoridation, and about 2,700 mg/kg for people in areas with 3 ppm fluoride in the drinking water (Berndt and Stearns, 1979). The average concentration in dentin is approximately four times higher than that in the enamel (Murray, 1986).

Fluoride is excreted primarily in the urine; some appears in the sweat and feces. Fluoride will cross the placenta, but fluoride levels in breast milk are usually low. Children who are actively forming bone excrete a lower proportion of fluoride than adults, reflecting a higher degree of uptake into the bone matrix (Zipkin *et al.*, 1958; International Program on Chemical Safety, 1984).

Mechanism and Effects of Fluoride Accumulation in Bone and Teeth

The chemical mechanisms responsible for uptake of fluoride into bone and teeth are similar, but uptake into teeth can be through either topical or systemic exposure (International Program on Chemical Safety, 1984). Fluoride ions replace hydroxyl ions in bone apatite or are incorporated into growing apatite crystals. Fluoride can also bind to enamel matrix proteins (Eanes and Reddi, 1979; Bawden *et al.*, 1987).

The effects of increased fluoride concentrations in teeth include a reduction in the incidence of caries (Murray, 1986). Some of the proposed mechanisms accounting for this effect include an increased acid resistance of fluoride-containing enamel (Brown *et al.*, 1977), an increased degree of remineralization in acid damaged areas (McCann and Brudevold, 1966), increased deposition of enamel-protecting salivary proteins acting as a pellicle (Moreno *et al.*, 1982), and decreased acid production by plaque bacteria (Edgar *et al.*, 1970).

Fluoride administration stimulates net deposition of bone (Kleerekoper and Parfitt, 1983). Osteoblastic osteoid formation and mitogenesis are stimulated, as is apparent osteoclastic bone resorption (in some studies); however, there is a greater increase in formation than resorption, leading to a net increase in bone mass (Baylink *et al.*, 1970; Farley *et al.*, 1983; Marie and Hott, 1986). Consequently, sodium fluoride has been used to treat osteoporosis (Kleerekoper and Parfitt, 1983), with daily doses for adults ranging from approximately 50 to 100 mg (0.7 to 1.4 mg sodium fluoride/kg, or 0.3 to 0.6 mg fluoride/kg) (Farley *et al.*, 1987) along with supplemental calcium. The efficacy of this therapy is still under investigation. Recent studies suggest that fluoride treatment increases cancellous bone mass, but decreases cortical bone mass and may actually increase skeletal fragility in osteoporosis patients (Riggs *et al.*, 1990).

Acute and Chronic Toxic Effects

With increasing ingestion of fluoride, toxic effects range from minor ones, such as discoloration of teeth associated with mild dental fluorosis, through severe dental and skeletal fluorosis, to acute lethality. In laboratory animals, single lethal doses of soluble fluorides (as fluoride ion) are 20 to 100 mg/kg body weight (International Program on Chemical Safety, 1984). The acute lethal dose for humans is estimated to be about 50 mg/kg (Hodge, 1983). Plasma concentrations of fluoride associated with lethality in young rats range from 8 to 10 mg/L (de Lopez *et al.*, 1976). A variety of clinical signs are associated with acute intoxication, but none are specific for fluoride (International Program on Chemical Safety, 1984).

Fluoride is known to affect the activity of numerous enzymes. It inhibits erythrocyte enolase (Feig *et al.*, 1971) and initially decreases protein and ultimately deoxyribonucleic acid (DNA) synthesis in a variety of cell and organ culture systems (Hongslo and Holland, 1979; reviewed by Holland, 1979c). Fluoride stimulates the activity of adenylate cyclase (Tada *et al.*, 1975) and leads to an influx of calcium and efflux of potassium from erythrocytes (McIvor and Cummings, 1987) and hepatocytes (Hughes and Barritt, 1987). However, the acute lethal effects of fluoride are probably due to binding to calcium and magnesium, depleting the serum of these ions (Hodge, 1983).

Chronic exposure to fluoride can result in dental fluorosis and can affect bone, liver, and kidney at higher concentrations. Taylor *et al.* (1961) reported a loss of normal tooth coloration in Wistar rats maintained on drinking water containing 25 ppm or higher amounts of fluoride (as sodium fluoride); at 50 to 100 ppm, incisors were chalky white and brittle after 6 months of treatment. Exposure of weanling Wistar rats to 380 ppm fluoride (as sodium fluoride) for 6 weeks resulted in swelling and necrosis of proximal and distal renal tubules, necrosis of hepatocytes, and degeneration and vacuolation of ameloblasts in the enamel organ of the teeth (Lim *et al.*, 1975). Taylor *et al.* (1961) also demonstrated kidney toxicity, described as increased interstitial nephritis and dilation of tubules at the corticomedulary junction in rats maintained for 6 months on water containing 100 ppm fluoride. Taylor *et al.* (1961) found similar lesions in rats ingesting water containing 200 to 500 ppm fluoride for 5 days, and they attributed deaths to fluoride at concentrations as low as 150 ppm. Preweanling Sprague-Dawley rats were found to be more resistant to the nephrotoxic effects of sodium fluoride than were their adult counterparts (Daston *et al.*, 1985). Weber and Reid (1969) observed deaths in mice of an unspecified strain that were fed diets containing 1,500 or 2,000 ppm sodium fluoride for 3 weeks.

Dental and skeletal fluorosis have been extensively studied in humans exposed to fluoride in drinking water and in the workplace. Dental fluorosis is a disturbance of enamel formation that occurs prior to eruption of the tooth in which maturation of the enamel is delayed and mineralization may be inhibited. Brownish-black discoloration, pitting, and attrition can occur. In areas with fluoride concentrations of 1 to 2 ppm in the drinking water, dental fluorosis, when observed, is typically mild, resulting in white opaque areas covering less than half of the tooth surface. Moderate and severe forms of fluorosis, which involve staining and pitting of teeth, occur with increasing frequency in people who drink water containing concentrations greater than 2 ppm fluoride (Driscoll *et al.*, 1983; International Program on Chemical Safety, 1984).

Skeletal fluorosis with radiological and clinical symptoms has been observed in people drinking water containing fluoride in excess of 10 ppm (Pandit *et al.*, 1940). Other investigators have reported more subtle radiologic skeletal changes (osteosclerosis) in subjects ingesting water containing fluoride at concentrations of 4 to 8 ppm for prolonged periods (Leone *et al.*, 1955; Stevenson and Watson, 1957). Several stages of advanced skeletal fluorosis have been described radiographically. When bone fluoride contents measure 4,000 to 6,000 mg/kg of dry fat-free bone (or approximately 8,000 to 12,000 mg fluoride/kg ash), the vertebra and pelvis become more dense (Smith and Hodge, 1959; Zipkin *et al.*, 1958). Subsequently, bone contours and trabeculae become uneven and blurred, the bones of the extremities show thickening of the compact bone and irregular periosteal growth (exostoses and osteophytes), and ligaments and muscle insertions become calcified (Roholm, 1937; International Program on Chemical Safety, 1984). Characteristic changes seen upon bone biopsy include linear formation defects, porosity of cortical bone, increased trabecular bone volume, and newly formed periosteal bone (Baud *et al.*, 1978; Boillat *et al.*, 1981). Polyarthralgia is a common early complaint, and pain can increase to the point of limiting movement of the vertebral column and lower limbs. Ossification of ligaments and bony spurs may lead to fusion of the spine and contractures of the hips and knees, a condition known as "crippling fluorosis" (Roholm, 1937; International Program on Chemical Safety, 1984).

Toxic effects are also seen in the skeletons of animals given diets or water containing excessive amounts of fluoride. Qiu *et al.* (1987), using a tetracycline double-labeling method, demonstrated inhibition of bone formation in rats of an unspecified strain that were maintained for 250 days on drinking water containing 50 or 80 ppm sodium fluoride. Exposure of beagle dogs to 0.7 mg/kg sodium fluoride per day for 6 months resulted in apparent toxic effects to both osteoblasts and osteoclasts, leading to the speculation that, with time, total bone cellular activity declines, tending to preserve prior gains in bone mass (Snow and Anderson, 1986). Increased fragility of the parietal, frontal, and femoral bones and exostotic anomalies of the sagittal crest and jaw bones were observed in adult male mink fed diets containing 194 or 350 ppm fluoride (as sodium fluoride) for 350 days. Increased mortality was seen at the higher dose (Aulerich *et al.*, 1987).

Reproductive and Developmental Toxicity

In general, existing studies in laboratory animals and epidemiological studies in humans have been judged inadequate to determine whether fluoride exposure represents a hazard to reproduction or development (International Agency for Research on Cancer, 1982; International Program on Chemical Safety, 1984; Janssen *et al.*, 1989). Messer *et al.* (1973) found reduced fertility in female Swiss Webster mice during 25-week studies with drinking water concentrations of fluoride (as sodium fluoride) that were lethal (200 ppm) or caused significant effects on maternal weight gain (100 ppm). No effects on fertility of two generations of mice were seen with dams given water containing 50 ppm fluoride. Aulerich *et al.* (1987), in a small study with mink maintained for 7 months on diets containing up to 350 ppm fluoride (as sodium fluoride), found no effects on reproduction; however, postnatal mortality of kits maintained on the same diet for 6 weeks was high. Dunipace *et al.* (1989) found no increase in abnormal sperm morphology in B6C3F$_1$ mice maintained for 21 weeks on drinking water containing up to 75 ppm fluoride (as sodium fluoride).

Genetic Toxicity

Sodium fluoride has been tested extensively for gene mutation induction in *Salmonella typhimurium* by standard plate and preincubation tests, with and without S9 activation, and the results have uniformly been negative (Gocke *et al.*, 1981; Martin *et al.*, 1979; Moriya *et al.*, 1983; Haworth *et al.*, 1983; Li *et al.*, 1987a; Tong *et al.*, 1988). However, in a suspension assay, Nikiforova *et al.* (1982) found increases in histidine-revertant colonies in strains TA98 and TA1535; the reported increases in TA1535, but not TA98, appear to be artifactual results of increased cell killing. Any conclusions drawn from this report are tentative due to the use of histidine-containing agar for plating treated cells. No gene conversion or aneuploidy induction was observed in *Saccharomyces* (Litton Bionetics, 1975; Martin *et al.*, 1979) or *Neurospora* (Griffiths, 1981; NIEHS, 1983) treated with sodium fluoride or potassium fluoride, respectively. No gene mutations at the HGPRT locus were detected in cultured rat liver epithelial cells treated with up to 160 μg/mL sodium fluoride (Tong *et al.*, 1988). However, a recent report showed that sodium fluoride induces gene mutations at the TK and HGPRT loci in cultured lymphoblastoid cells treated with 100 to 600 μg/mL sodium fluoride for 28 hours, and at the TK locus in cells treated with 65 μg/mL for up to 20 days (Crespi *et al.*, 1990). Induction of trifluorothymidine resistance was observed in mouse L5178Y lymphoma cells treated with 300 to 600 μg/mL sodium fluoride, with or without induced rat liver S9 (Cole *et al.*, 1986; Caspary *et al.*, 1987); the authors speculate that chromosomal aberrations may have been responsible for this response. Sodium fluoride-induced unscheduled DNA synthesis was reported in Syrian hamster embryo cells at cytotoxic concentrations (Tsutsui *et al.*, 1984), but these results were not confirmed by other investigators who controlled for the formation of Mg^{++}, F^-, and ^{3}H-thymidine triphosphate complexes and used doses that did not induce high levels of toxicity (Skare *et al.*, 1986; Tong *et al.*, 1988). DNA synthesis inhibition occurs following exposure of cells to sodium fluoride, but this is believed to be the result of sodium fluoride effects on protein synthesis, which results in a decrease in cellular proteins necessary for DNA synthesis (Holland, 1979a,b; Imai *et al.*, 1983).

Several reports on the effects of sodium fluoride and other fluoride-containing compounds in *Drosophila* have been published. Most of these were designed to study the effect of sodium fluoride on the activity of known mutagens and employed inadequate controls to allow assessment of the effect of sodium fluoride alone. However, there are a few papers which allow critical analysis of the mutagenicity of fluorides in *Drosophila*. Two studies reported clear, dose-related increases in sex-linked recessive lethal mutations in male *Drosophila*: in the first study, hydrogen fluoride was administered by inhalation (Gerdes, 1971); in the second study, sodium fluoride or stannous fluoride were administered by feeding in a glucose solution (Mitchell and Gerdes, 1973). In addition, sodium fluoride was observed to induce whole chromosome loss and partial chromosome loss, an indication of breakage, in postmeiotic germ cells of males (Vogel, 1973).

Clastogenic activity of sodium fluoride in mammalian cells has been demonstrated *in vitro*, but this appears to be highly protocol-dependent (Li *et al.*, 1988; Aardema *et al.*, 1989). In those studies where a positive response was obtained, sodium fluoride exposure resulted in induction of chromatid deletions and increases in achromatic regions (gaps). The induction of chromosomal aberrations by sodium fluoride treatment has been reported in a variety of cultured mammalian cell types, including Chinese hamster "don" (Bale and Mathew, 1987) and Chinese hamster ovary (Aardema *et al.*, 1989; NTP, unpublished) cells, red muntjac cells (He *et al.*, 1983), and human lymphocytes (Kishi and Tonomura, 1984; Luchnick *et al.*, 1985; Albanese, 1987), and fibroblasts (Tsutsui *et al.*, 1984; Scott and Roberts, 1987). It would appear, given the currently available data, that the lowest effective concentration in cultured human lymphocytes and fibroblasts, as well as Chinese hamster ovary cells, is in the range of 10-20 μg/mL. In contrast, other reports (Slacik-Erben and Obe, 1976; Voroshilin *et al.*, 1973; Kralisz and Saymaniak, 1978) cite a lack of aberration induction in human leukocytes treated *in vitro*, as does a report in Chinese hamster lung cells (Ishidate, 1987). The negative results reported by Slacik-Erben and Obe (1976) and Kralisz and Symaniak (1978) must be qualified because the doses tested did not approach toxic levels. NTP studies (unpublished; Table H4) using Chinese hamster ovary cells showed no aberration induction in one study and a positive response in a second study that used higher doses. Induction of sister chromatid exchanges has not been observed in mammalian cell cultures (Kishi and Tonomura, 1984; Thomson *et al.*, 1985; Li *et al.*, 1987b; Tong *et al.*, 1988), with the exception of the NTP Chinese hamster ovary cell results included in this report (Table H3) and those of Tsutsui *et al.* (1984), who reported a dose-related increase in sister chromatid exchanges in Syrian hamster embryo cells treated with 20-80 μg/mL sodium fluoride without S9, and He *et al.* (1983), who reported a weak induction of sister chromatid exchanges at the highest dose tested (3.0 mM sodium fluoride).

As with the *in vitro* cytogenetics test results, results from *in vivo* tests for chromosomal effects of sodium fluoride are mixed. The published data are generally weak and the descriptions of experimental protocols often fail to provide dose selection criteria and toxicity information, thus precluding accurate assessment of the adequacy of the test concentrations employed. Induction of sister chromatid exchanges, chromosomal aberrations, and micronuclei was reported in the bone marrow of mice administered 40 mg/kg sodium fluoride by gavage or intraperitoneal injection (Ma *et al.*, 1986; Pati and Bhunya, 1987). In contrast, no clastogenic effects were seen in bone marrow of mice administered 50 ppm sodium fluoride in dosed feed for 6 weeks (Kram *et al.*, 1978), 50 ppm sodium fluoride in drinking water for several generations (Martin *et al.*, 1979), or 100 ppm sodium fluoride in drinking water for 6 weeks (Martin *et al.*, 1979). A study on sperm morphology in mice exposed intraperitoneally to sodium fluoride for 5 days and then sampled 35 days later reported a significant dose-dependent increase in abnormal sperm (Pati and Bhunya, 1987). Mohamed and Chandler (1982) reported significant increases in chromosomal aberrations in mouse bone marrow and germ cells following exposure in drinking water to as little as 1 ppm sodium fluoride. However, because of very high frequencies of aberrant cells in the control animals and uncertainty regarding the nature of the aberrations scored, the validity of these findings is questionable. Another study, conducted under similar conditions and utilizing the same exposure levels, found no evidence of chromosomal aberration induction by sodium fluoride in testicular tissue of mice (Martin *et al.*, 1979). Recently, results were reported from a bone marrow sister chromatid exchanges study in which sodium fluoride (1, 10, 50, 75 ppm) was administered to male Chinese hamsters in drinking water for 24 weeks (Li *et al.*, 1989); no significant increases in sister chromatid exchanges were observed, even though fluoride concentrations in bone and plasma increased with sodium fluoride dose. Likewise, there was no apparent effect on rate of cell proliferation as measured by the relative numbers of first, second, and third metaphase cells in the bone marrow preparations. In summary, the evidence for chromosomal effects in mice is questionable because it derives from one study in which the data are uninterpretable (Mohamed and Chandler, 1972), a second study obtained as an abstract with no data (Ma *et al.*, 1986), and a third study which included gaps in the analysis of aberrations and relied largely on these for the conclusions that sodium fluoride was clastogenic (Pati and Bhunya, 1987). The significance of gaps is not understood and this lesion is not normally used in aberration analysis.

Sodium fluoride has been tested in several laboratories for induction of morphological transformation of Syrian hamster embryo cells, and positive, dose-related increases in the frequencies of transformed colonies (on the order of 1% at the higher doses) were observed within a concentration range of 10 to 125 μg/mL (Tsutsui *et al.*, 1984; Jones *et al.*, 1988a; Lasne *et al.*, 1988). Sodium fluoride was also tested for induction of morphological transformation in the BALB/c-3T3 cell line. In this cell line, sodium fluoride was shown to be inactive at similar concentrations to those used in the Syrian hamster embryo cell experiments (Lasne *et al.*, 1988; NTP unpublished). In addition, sodium fluoride demonstrated promoter activity in Syrian hamster embryo cells when used in conjunction with benzo[a]pyrene in a two-step exposure study (Jones *et al.*, 1988a). Neoplastic transformation was observed in Syrian hamster embryo cells treated with 75 or 100 μg/mL sodium fluoride for 24 hours, washed, and subcultured 35 to 50 times (corresponding to 120 to 270 doublings). Subcutaneous injection of 1 x 10^6 cells from this treatment into newborn Syrian hamsters produced anaplastic fibrosarcomas at the site of injection after 28 to 39 days with one of two cultures treated with 75 μg/mL sodium fluoride and both cultures treated with 100 μg/mL sodium fluoride (Tsutsui *et al.*, 1984).

Chlorophyll mutations were not produced by sodium fluoride treatment of barley or rice (Bale and Hart, 1973a,b; Narahari, 1978). Induction of chromosomal aberrations was reported in *Allium* (Galal and Abd-Alla, 1976), *Vicia faba* (Hakeem and Shehab, 1970; Galal and Abd-Alla, 1976), and *Hordeum vulgare* (Bale, 1972).

There are a number of possible reasons for the conflicting data found in the cytogenetics literature. These reasons include: the fact that gaps can be produced as an artifact of slide preparation and are the major aberration induced by sodium fluoride; gaps are not scored uniformly among laboratories and may be confused with breaks; the DNA damage produced by ineffective repair may be the cause of the beaded, clumped chromosomes which often are seen in sodium fluoride-treated cells, and this distorted appearance further complicates scoring of aberrations; cell exposures and harvest times must be carefully planned to allow for cells to progress though the G2 stage of the cell cycle in the presence of sodium fluoride (this is the stage most sensitive to the induction of aberrations) and be harvested during the metaphase immediately following this period. Another confounding factor could be the induction of chromosome damage through an ionic imbalance induced by the reaction of fluoride ion with ions in the culture media or in the cells, which could then interfere with DNA synthesis or repair. A number of these effects have been addressed elsewhere (Aardema *et al.*, 1989; Brusick, 1986; Ashby and Ishidate, 1986; Li *et al.*, 1988). Finally, some papers dealing with the genetic effects of sodium fluoride have not been included in this review because, in the opinion of the reviewers, they were deficient in one or more of the following categories: insufficient data to support the conclusion, inadequate experimental design, faulty hypotheses, and improper endpoints. Lack of such essential information precludes judgment on the adequacy of the study data.

In summary, sodium fluoride is mutagenic in cultured mammalian cells and produces transformation of Syrian hamster embryo cells *in vitro*. The reports of *in vitro* cytogenetic studies are mixed, but the preponderance of the evidence indicates that sodium fluoride can induce chromosome aberrations and sister chromatid exchanges in cultured mammalian cells. These mutagenic and clastogenic effects in cultured cells are supported by positive effects in *Drosophila* germ cell tests that measure point mutations and chromosome breakage. *In vivo* tests in rodents for chromosome aberrations provide mixed results that cannot readily be resolved because of differences in protocols and insufficient detail in some study reports to allow a thorough analysis.

The mechanism(s) by which these effects result from exposure to sodium fluoride is not known. Possibilities include (1) disturbance of nucleotide pool balances through formation of $Mg^{++}:F^-$: nucleotide triphosphate complexes (Larsen and Klenow, 1969), (2) alteration or inactivation of essential DNA processing enzymes through the binding of fluoride ions to cofactors such as Mg^{++} or Ca^{++}, and, perhaps more remotely, (3) disruption of calcium-dependent transmembrane processes (Hughes and Barritt, 1987) or (4) disruption of chromatin structure through hydrogen bonding analogous to that shown with uracil (Clark and Taylor, 1981). Such indirect or "secondary" effects on chromosome structure are attractive in light of the fact that there is no apparent direct mechanism for sodium fluoride to induce these effects, the reported difficulties in demonstrating reproducibility of effects, the observance of threshold doses, and the lack of clear dose-effect relationships.

CARCINOGENICITY

Previous studies of sodium fluoride in animals are inadequate to allow an evaluation of its carcinogenic activity to be made (International Agency for Research on Cancer, 1987; Janssen *et al.*, 1989).

Kanisawa and Schroeder (1969) gave groups of 54 male and 54 female weanling Swiss CD1 mice drinking water containing 0 or 10 ppm sodium fluoride for life. No effect on body weight of males was noted, but treated females weighed somewhat more than controls. The average life span of females was not affected, but treated males lived 1 to 2 months longer than controls. There was no difference in the total tumor incidences observed in treated and control groups at the end of the study.

Tannenbaum and Silverstone (1949) fed groups of 50 female DBA mice diets containing either 0 or 900 mg/kg sodium fluoride for 90 weeks. Treated animals had reduced body weight and fewer mammary tumors than controls. Taylor (1954) reported partial results of a series of 12 experiments in which a total of 645 DBA and C3H female mice were given drinking water containing amounts of fluoride up to 10 ppm for periods of 7 to 17 months. Sixty-three percent of the mice receiving 10 ppm died of mammary gland carcinomas compared to 50% of controls. Taylor and Taylor (1965) reported increased growth of implanted mammary adenocarcinoma tumor suspensions in DBA mice in 8- to 10-day experiments when the animals received sodium fluoride in the drinking water or by subdermal injection.

The NTP is aware of an industry-sponsored study as yet unreported in which groups of Sprague-Dawley rats and ICR Swiss mice received sodium fluoride in the feed at concentrations sufficient to achieve daily doses of 0, 4, 10, or 25 mg/kg.*

In 1975, Burk and Yiamouyiannis reported to the United States Congress results of an epidemiological study in which they concluded that cancer mortality rates from 1950 to 1970 were increasing more rapidly in cities with fluoridated water than in cities with nonfluoridated water (Burk and Yiamonyiannis, 1975; Yiamouyiannis and Burk, 1977; Graham *et al.*, 1987). Other epidemiological studies from the United States, Australia, Austria, Canada, New Zealand, and the United Kingdom have failed to show an association between cancer mortality in humans and the fluoride content of drinking water (Hoover *et al.*, 1976; USDHHS, 1981; IARC, 1982; Clemmesen, 1983; Knox, 1985). However, Bundock *et al.* (1985) interpret several of these studies differently, finding an association between fluoridated water and increased cancer mortality. The International Agency for Research on Cancer (IARC) has concluded that none of the studies reported up to their initial review in February 1981 had "provided any evidence that an increased level of fluoride in water was associated with an increase in cancer mortality"; this conclusion was reaffirmed in a subsequent review in March 1987 (IARC, 1982, 1987).

STUDY RATIONALE

Concern over the possibility that fluoride might have carcinogenic activity prompted the National Cancer Institute, the Environmental Protection Agency, and the National Institute for Dental Research to nominate sodium fluoride for study by the National Toxicology Program. The drinking water route of administration was chosen to mimic human exposure to fluoridated water. The studies reported in this document include 14-day, 6-month, and 2-year studies with rats and mice maintained on various

*The results of the rat study were published after the peer review of this report (Maurer *et al*, 1990). The authors concluded that the study provided no evidence to suggest sodium fluoride was carcinogenic in either sex of rats.

concentrations of fluoridated or deionized water. The diet used for the 14-day and 6-month studies was a low fluoride, semisynthetic diet; the 2-year studies were performed using an NIH-07 diet specially formulated to contain less than 10 ppm fluoride. Although 2-year studies using the low fluoride, semisynthetic diet were also performed, they were considered inadequate because the diet was determined to be nutritionally deficient (see Appendix M).

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF SODIUM FLUORIDE

Sodium fluoride was obtained from Apache Chemical, Inc. (Seward, IL) in two lots. One lot was used for the 14-day and 6-month studies (lot no. A-06255) and another for the 2-year studies (lot no. A022085). Identity, purity, and stability analyses were conducted on these lots by Midwest Research Institute (Kansas City, MO). Details of these analyses are presented in Appendix J. The study chemical, a white crystalline powder, was identified as sodium fluoride and was found to be at least 99% pure, as determined by elemental analysis, Karl Fischer water analysis, spark source mass spectrometry, and titration of acidic components. During the 2-year studies, the stability of the bulk chemical was monitored by Galbraith Laboratories (Knoxville, TN). No degradation of the study material was detected throughout the studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Throughout all studies, dose formulations were prepared by mixing appropriate amounts of sodium fluoride with deionized water. Stability studies indicated that sodium fluoride at a concentration of 25 ppm in deionized water was stable under simulated animal dosing conditions for up to 3 weeks when stored in the dark at room temperature (25° C). Details of the preparation and storage of dose formulations of sodium fluoride are presented in Appendix J.

During the 2-year studies, the study laboratory conducted periodic dose formulation analyses, utilizing a potentiometric method with a fluoride ion electrode as described in Appendix J. These analyses were performed weekly on all dose formulations during approximately the first 6 months of the 2-year studies and then every 8 weeks for the duration of these studies (Appendix J, Tables J2, J3, and J4). These analyses indicated that all dose formulations were within ±10% of target concentrations throughout the studies. Results of periodic referee analyses performed by Midwest Research Laboratory were in agreement with the results from the study laboratory (Appendix J, Table J5). Analyses of deionized water for pH and fluoride concentration were all within acceptable limits of pH≥5 (except on four occasions) and fluoride concentration ≤0.1 ppm.

14-DAY STUDIES

Short-term toxicity studies of sodium fluoride were conducted in rodents to determine appropriate doses for longer studies. Male and female F344/N rats were obtained from the Charles River Laboratories (Portage, MI) and were observed for 6 days; male and female $B6C3F_1$ mice were obtained from the same source and were observed for 25 days. The rats and mice were 5 weeks old when placed on study. Animals were assigned to cages, then cages were assigned to control or dose groups by random number tables.

Groups of five rats and mice of each sex received 0, 50, 100, 200, 400, or 800 ppm sodium fluoride in deionized water *ad libitum* for 14 consecutive days. Animals were housed five per cage, with semisynthetic low fluoride (12.7 to 14 ppm) feed available *ad libitum*. Water consumption was recorded every 3 days for rats, every 4 days for mice. The rats and mice were observed twice daily for morbidity, mortality, and signs of toxicity; they were weighed at the beginning of the studies, at the end of the first week, and at necropsy. Details of study design and animal maintenance are presented in Table 1. All animals were necropsied, and tissues were examined for gross lesions. Microscopic examination of tissues was not performed.

6-MONTH STUDIES

Six-month studies were conducted to evaluate the cumulative toxic effects of continuous exposure to sodium fluoride and to determine appropriate doses for the 2-year studies. The male and female rats and mice for these studies were bred at the study laboratory. Breeder F344 rats (Harlan Industries, Indianapolis, IN) and C57BL/N6 female and C3H/HeN male mice (Charles River Laboratories, Wilmington, DE) were placed on a low fluoride diet (≤2.1 ppm fluoride) 1 month before monogamous pairing (Appendix K). Progeny that survived to weaning were distributed to weight classes and assigned to cages by a random number table; cages were then assigned to dose and control groups by a second table of random numbers. Rats were 5 to 6 weeks old when placed on study, and mice were 4 to 6 weeks old. The weight range of animals used in the 6-month studies was somewhat larger than is typical in NTP studies because insufficient numbers of animals were derived from the breeding program to allow the usual culling of animals of high or low weights.

Groups of ten rats of each sex were administered 0, 10, 30, 100, or 300 ppm sodium fluoride in deionized drinking water *ad libitum* for 6 months. Groups of 8 to 12 mice of each sex received 0, 10, 50, 100, 200, 300, or 600 ppm sodium fluoride in deionized drinking water *ad libitum* for 6 months. The study design called for ten mice of each sex per dose group; however, on the second day of dosing, one male and five female mice were found to have been missexed, and they were placed with the group of the correct sex at the same dose level. All test animals receiving water supplemented with sodium fluoride were provided with a low fluoride (≤2.1 ppm), semisynthetic diet throughout the study. Three control groups were included in the studies of male rats and male and female mice: one received deionized drinking water and a low fluoride, semisynthetic diet; the second received sodium chloride-supplemented deionized drinking water and a low fluoride, semisynthetic diet; and the third received deionized drinking water and a standard NIH-07 diet. The first two of these control groups were included in the female rat study.

Animals were housed five per cage, with feed and water available *ad libitum*. They were observed twice daily for morbidity and mortality, and signs of toxicity were recorded. Individual weights were recorded weekly throughout the studies. Water consumption was recorded daily by cage; diet consumption was recorded every other week for the first 13 weeks and for a 1-week period during each of the last 3 months. Table 1 summarizes further experimental details.

At termination of the studies, the fluoride concentrations in urine, blood, and bone were determined from samples collected from five male and five female rats and from all surviving mice from all groups (except the control group given sodium chloride-supplemented deionized drinking water and a low fluoride, semisynthetic diet); samples from the same animals were included in all three evaluations. Methodological details are presented in Appendix I.

Complete necropsies with tissue collection were performed on all animals. Microscopic examination was conducted on tissues from all control animals, all animals dying spontaneously, and all animals in the two highest dose groups (Table 1).

2-Year Studies

Study Design

Groups of 100 rats and mice of each sex received 0 or 175 ppm sodium fluoride and groups of 70 rats and mice of each sex received 25 or 100 ppm sodium fluoride in deionized drinking water *ad libitum* for up to 103 weeks. Interim sacrifices of ten animals of each sex per dose group from each species occurred at 24 weeks for mice, at 27 weeks for rats, and at 66 weeks for both species. An additional group of 50 animals of each sex and species was included to provide paired (age-matched) controls. These animals received deionized drinking water. During every study week that one or more animals from any group receiving sodium fluoride-supplemented water was found dead or killed in a moribund condition, one animal of the same species and sex was chosen at random from the paired control group and killed.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ mice used in these studies were obtained from the National Cancer Institute's Frederick Cancer Research Facility (Frederick, MD). Rats and mice were 4 weeks old upon arrival at the study laboratory. After all animals were quarantined for 12 to 13 days, a complete necropsy was performed on 20 rats of each sex and on three male and two female mice to assess their health status. Serologic analyses were performed on samples drawn from five animals of each sex and species on two different dates during quarantine and on sentinel animals at

6, 12, and 18 months. Details of animal health monitoring are presented in Appendix N. The rodents were placed on study when they were 6 weeks old.

Animal Maintenance

Rats were housed five per cage; mice were housed individually. Specially formulated low fluoride feed and deionized water were available *ad libitum*. Feed analyses are presented in Appendix K. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed twice a day for morbidity and mortality. Clinical signs and body weights were recorded once a week for the first 13 weeks of the studies and once a month thereafter. Once every 4 weeks, diet consumption and water consumption were measured for 7 consecutive days.

Clinical pathology studies conducted during the 2-year studies included: fluoride concentrations in bone (rats and mice), serum (rats), and urine (rats); hematology and serum clinical chemistry (calcium, phosphorous, alkaline phosphatase) analyses (rats and mice); urinalysis and urine concentration (rats); and a study to assess the bioavailability of fluoride contained in the diet (male rats). Details of these analyses are presented in Table 1; methodology is detailed in Appendix I.

A necropsy was performed on all animals including those found dead. Lateral and dorsal-ventral view radiographs were taken of all animals at necropsy. During necropsy, all organs and tissues were examined for grossly visible lesions; histopathologic examinations were performed on the tissues listed in Table 1 and on all grossly detectable lesions and tissue masses in all dose groups. Tissues and organs from all dose groups were fixed in 10% neutral buffered formalin, processed using standard procedures, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The tissues listed in Table 1 were examined microscopically for all animals found dead or killed before scheduled sacrifice, on all control and high-dose animals at the 24-week and 27-week interim sacrifices, on all animals at the 66-week interim sacrifice, and on all animals at terminal sacrifice. The organs that were subjected to a more extensive histopathologic analysis than is normally performed in NTP studies were bones (right femur, right tibia, right humerus, thoracic vertebrae, maxilla, and mandible) and teeth (incisors).

After pathology evaluations were completed by the laboratory pathologist and the pathology data entered into the Toxicology Data Management System (TDMS), the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The tissue sections, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. The bones and teeth of all rats and mice and the livers of all mice were reviewed microscopically by the quality assessment pathologist. In addition, proliferative lesions of the oral mucosa of male and female rats, proliferative lesions of the adrenal and thyroid glands of male rats, and all malignant lymphomas of female mice were reviewed.

The quality assessment report and slides were submitted to the Pathology Working Group (PWG) chairpersons, who reviewed microscopically selected lesions of bone and teeth in rats; bone, teeth, bone marrow, and liver in mice and any others about which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. All bone tumors, oral cavity tumors, representative examples of potential chemical-related nonneoplastic lesions of bone and teeth and differences in diagnosis between the laboratory and quality assessment pathologists, were selected by the PWG chairpersons for review by the PWG. The PWG included the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without knowledge of dose group or previously rendered diagnoses. When the consensus opinion of the PWG differed from that of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are evaluated separately or are combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

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

Calculation of Incidence

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

Analysis of Tumor Incidence

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

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

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

The primary statistical analyses of tumor incidence utilized the base two-year study groups. Supplementary analyses which included the 2 interim sacrifice and paired control groups were also carried out, and the results of these analyses are reported in the text and in Appendixes A3, B3, C3, and D3 in those instances in which inclusion of these animals may have affected the interpretation of study results.

Analysis of Continuous Variables

For all end points, dosed groups were compared with the control group using the nonparametric multiple comparison test of Dunn (1964) or Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose response trends and to determine whether Dunn's or Shirley's test was more appropriate for pairwise comparisons.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can often be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the

NTP historical control data base (Haseman *et al.*, 1984, 1985) are included for those tumors appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

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

GENETIC TOXICOLOGY

The genetic toxicity of sodium fluoride was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, to induce trifluorothymidine resistance in mouse L5178Y lymphoma cells, and to induce sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells. The methods and materials employed in these studies are given in Appendix H.

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Sodium Fluoride

14-Day Studies	6-Month Studies	2-Year Studies
Study Laboratory		
Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)	Batelle Columbus Laboratories (Columbus, OH)
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Charles River Laboratories (Portage, MI)	Battelle Columbus Laboratories (Columbus, OH) Rats: Progeny of F/344 breeders from Harlan Industries (Indianapolis, IN) Mice: Progeny of C57BL/N6 female and C3H/HEN male breeders from Charles River Laboratories (Wilmington, DE)	Frederick Cancer Research Facility (Frederick, MD)
Time Held Before Study		
Rats: 6 days Mice: 25 days	Rats: 5-6 weeks Mice: 4-6 weeks	Rats: 12 days Mice: 13 days
Age When Placed on Study		
Rats: 5 weeks Mice: 5 weeks	Rats: 5-6 weeks Mice: 4-6 weeks	Rats: 6 weeks Mice: 6 weeks
Date of First Dose		
Rats: 19 July 1979 Mice: 18 July 1979	Rats: 6 October 1980 Mice: 6 October 1980	Rats: 7 October 1985 Mice: 28 October 1985
Duration of Dosing		
14 days (7 days/week)	26 weeks (7 days/week)	103 weeks (7 days/week)
Date of Last Dose		
Rats: 2 August 1979 Mice: 31 July 1979	Rats: 6-7 April 1981 Mice: 8-9 April 1981	24-week interim sacrifice: Mice, 10-11 April 1986 27-week interim sacrifice: Rats, 8-9 April 1986 66-week interim sacrifice: Rats, 8-9 January 1987; Mice, 28-29 January 1987 105-week scheduled termination: Rats, 27 September 1987; Mice, 19 October 1987
Necropsy Dates		
Rats: 3 August 1979 Mice: 2 August 1979	Rats: 6-7 April 1981 Mice: 8-9 April 1981	24-week interim sacrifice: Mice, 10-11 April 1986 27-week interim sacrifice: Rats, 8-9 April 1986 66-week interim sacrifice: Rats, 8-9 January 1987; Mice, 28-29 January 1987 105-week scheduled termination: Rats, 5-9 October 1987; Mice, 26-30 October 1987 and 2-3 November 1987

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Sodium Fluoride (continued)

14-Day Studies	6-Month Studies	2-Year Studies
Age at Necropsy		
Rats: 7 weeks Mice: 7 weeks	Rats: 31-32 weeks Mice: 30-32 weeks	24-week interim sacrifice: Mice, 30 weeks 27-week interim sacrifice: Rats, 32 weeks 66-week interim sacrifice: 71 weeks 105-week scheduled termination: Rats, 110 weeks; Mice, 111 weeks
Size of Study Groups		
5 males and 5 females	Rats: 10 males and 10 females Mice: 8-12/sex/group	Base studies: 80, 50, 50, and 80 males and females of each species for control, low-dose, mid-dose, and high-dose groups; 10 additional animals per sex for each species and dose group for each interim evaluation (24 weeks for mice, 27 weeks for rats, 66 weeks for both rats and mice). Paired (age-matched) controls: 50 males and 50 females of each species
Method of Animal Distribution		
Animals randomized to cages, then cages randomized to test and control groups by random number tables.	Animals assigned to weight classes, then randomized to cages; cages randomized to test and control groups by random number tables.	Animals assigned to weight classes, then randomized to test and control groups by partitioning algorithm using Xybion® Pathology/Toxicology Data System.
Animals per Cage		
5	5	Rats: 5 Mice: 1
Method of Animal Identification		
Not specified	Not specified	Toe mark
Diet		
Formulated semisynthetic low fluoride diet, available *ad libitum*	Formulated semisynthetic low fluoride diet, Biomix #1409 (Bioserv, Frenchtown, NJ); one control group of male rats and one control group of male and female mice were fed NIH-07 Rat and Mouse Ration pellets (Zeigler Bros, Gardners, PA); all feed available *ad libitum*	NIH-07 Rat and Mouse Pellets Low Fluoride (Ziegler Brothers, Gardners, PA); available *ad libitum*
Maximum Storage Time for Feed		
Not specified	Not specified	159 days postmilling (rats) 166 days postmilling (mice)

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Sodium Fluoride (continued)

14-Day Studies	6-Month Studies	2-Year Studies
Water		
Deionized water; supplied in glass bottles with rubber stoppers and stainless steel sipper tubes (Lab Products, Rochelle Park, NJ) that were changed every 3 days for rats, every 4 days for mice; available *ad libitum*	Deionized water; tap water (City of Columbus, OH) deionized at study laboratory with Millipore Bed Deionizer (Continental Water Systems, Cleveland, OH); one control group of male and female rats and mice received sodium chloride-supplemented deionized water; supplied in glass bottles with rubber stoppers and stainless steel sipper tubes (Lab Products, Rochelle Park, NJ) that were changed once daily; available *ad libitum*	Deionized water; tap water (City of Columbus, OH) deionized at study laboratory with equipment from Peck Water Systems (North Canton, OH); supplied in glass bottles with rubber stoppers and stainless steel sipper tubes (Lab Products, Maywood NJ) that were changed twice weekly; available *ad libitum*
Cages		
Polycarbonate (Lab Products, Rochelle Park, NJ)	Same as 14-day studies	Same as 14-day studies; cages and racks rotated every other week
Bedding		
Absorb-Dri (Lab Products, Rochelle Park, NJ); changed twice/week	Same as 14-day studies	Beta-Chip® hardwood chips (Northeastern Products, Warrensburg, NY); changed twice/week
Cage Filters		
DuPont 2024 spun-bonded polyester (Snow Filtration, Cincinnati, OH); changed every other week	Same as 14-day studies	Same as 14-day studies
Animal Room Environment		
Temperature: 21°-23° C Humidity: 40%-60% Fluorescent light: 12 hours/day Room air changes: 15/hour	Temperature: 22°-24° C Humidity: 40%-60% Fluorescent light: 12 hours/day Room air changes: 15/hour	Temperature: 19.4°-26.1° C Humidity: 22%-76% Fluorescent light: 12 hours/day Room air changes: 10/hour
Doses		
0, 50, 100, 200, 400, or 800 ppm sodium fluoride in deionized water, available *ad libitum*	Rats: 0, 10, 30, 100, or 300 ppm sodium fluoride in deionized water, available *ad libitum* Mice: 0, 10, 50, 100, 200, 300, or 600 ppm sodium fluoride in deionized water, available *ad libitum* 3 control groups: (1) male and female rats and mice: deionized water and low fluoride, semisynthetic diet; (2) male and female rats and mice: sodium chloride-supplemented water and low fluoride, semisynthetic diet; (3) male rats and male and female mice: deionized water and standard NIH-07 diet.	0, 25, 100, or 175 ppm sodium fluoride in deionized water, available *ad libitum*

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Sodium Fluoride (continued)

14-Day Studies	6-Month Studies	2-Year Studies
Type and Frequency of Observation		
Observed twice daily for mortality and morbidity; weighed initially, at the end of the first week, and at termination; clinical observations recorded daily. Water consumption by cage recorded every 3 days for rats, every 4 days for mice.	Observed twice daily for mortality and morbidity; weighed initially, once weekly, and at termination; clinical observations recorded daily. Feed consumption recorded every other week for first 13 weeks and for 1 week during each of last 3 months. Water consumption recorded daily.	Observed twice daily for mortality and morbidity; weighed initially, weekly through week 13, monthly thereafter; clinical observations recorded weekly through week 13, monthly thereafter. Every 4 weeks, feed and water consumption recorded for a 1-week period.
Supplemental Studies		
None	Fluoride concentrations in bone, blood, urine: In rats, 24-hour urine samples collected 7 days prior to necropsy from 5/sex/group (except control group receiving sodium-chloride-supplemented deionized water) were analyzed; in mice, 24-hour urine samples collected 7 days prior to necropsy from all surviving mice (except control group receiving sodium-chloride-supplemented deionized water) were pooled for analysis. Blood (pooled in mice) and bone (humerus) determinations made on the same animals at scheduled termination.	Studies to assess the bioavailability of fluoride contained in the diet were conducted in male rats at approximately 6, 12, and 18 months on study. Other clinical pathology studies were conducted at the interim evaluations of both rats and mice. Urinalysis in rats at 27-week and 66-week evaluations included measuring volume, specific gravity, protein, glucose, calcium, inorganic phosphorus, and fluoride, as well as microscopic examination of sediment. Urine concentration studies in rats at 27-week and 66-week evaluations measured volume and specific gravity. Hematology measures for rats (27 weeks and 66 weeks) and mice (24 weeks and 66 weeks) included red blood cell count, hemoglobin, hematocrit, white blood cell count with differential, platelet count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte count, and erythrocyte morphology. Clinical chemistry analyses for rats (27 weeks and 66 weeks) and mice (24 weeks and 66 weeks) included serum calcium, inorganic phosphorus, alkaline phosphatase, and serum fluoride. The left humerus of all animals killed at all interim sacrifices and of ten randomly selected animals from each group at terminal sacrifice was evaluated for fluoride concentration. The incisors of designated animals at all scheduled sacrifices were evaluated for attrition and mottling. Lateral and dorsal-ventral view radiographs were taken of all animals at necropsy.

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Sodium Fluoride (continued)

14-Day Studies	6-Month Studies	2-Year Studies
Necropsy and Histologic Examinations		
Necropsy and tissue collection performed on all animals.	Necropsy and tissue collection performed on all animals. In addition to tissue masses, gross lesions, and associated regional lymph nodes, the following organs and/or tissues were examined histologically for all males and females in the control groups and in the two highest dose groups of both species (100 ppm, 300 ppm in rats; 300 ppm, 600 ppm in mice): adrenals, bone (femur, tibia), brain (frontal cortex and basal ganglia, parietal cortex and thalamus, cerebellum and pons), esophagus, eyes (when grossly abnormal), gallbladder (mice only), heart, kidney, large intestines (colon, liver, lung with bronchi, lymph nodes (mandibular), mammary glands, ovaries, pancreas, parathyroid, pituitary, prostate, salivary gland, small intestines, spinal cord (when neurologic signs were present), spleen, stomach, teeth (incisors), testes, thymus, thyroid, trachea, urinary bladder, and uterus.	Necropsy performed on all animals; complete histopathologic examination performed on all animals dying spontaneously or terminated because of moribund condition. In addition to tissue masses, gross lesions, and associated regional lymph nodes, the following organs and/or tissues were included in complete histopathological examinations: adrenals, bone (femur, humerus, mandible, maxilla, tibia, and vertebra), bone marrow, brain (frontal cortex and basal ganglia, parietal cortex and thalamus, cerebellum and pons), clitoral gland, epididymis, esophagus, eyes (when grossly abnormal), gallbladder (mice only), heart, kidney, large intestines (cecum, colon, rectum), liver, lung with bronchi, lymph nodes (mandibular, mesenteric), mammary glands, nasal cavity and turbinates, ovaries, pancreas, parathyroid, pharynx (when grossly abnormal), pituitary, preputial gland, prostate, salivary gland, sciatic nerve (when neurologic signs were present), seminal vesicles, skeletal muscle (thigh), skin, small intestines (duodenum, ileum, jejunum), spinal cord (when neurologic signs were present), spleen, stomach (including forestomach and glandular stomach), teeth, testes, thymus, thyroid, trachea, urinary bladder, and uterus. For all interim sacrifices, weights were recorded for liver, right kidney, left kidney, and brain. At 24-week and 27-week interim sacrifices, complete histopathologic examination (including supplemental examination of right tibia, right humerus, thoracic vertebrae [7,8,9], maxilla, mandible, and incisors) performed on all animals in the 0 and 175 ppm dose groups; gross lesions examined in animals in the 25 and 100 ppm dose groups. At 66-week interim sacrifice, complete histopathologic examination (including supplemental examination of bones and teeth) performed on all animals. At 105-week scheduled termination, complete histopathologic examination (including supplemental examination of bones and teeth) performed on all animals.

RESULTS

Rats

14-Day Studies

Groups of five rats of each sex received 0, 50, 100, 200, 400, or 800 ppm sodium fluoride in deionized water *ad libitum* for 14 consecutive days. Survival and body weights are given in Table 2. One female from the second highest dose group (400 ppm) died on day 6; all male rats in the high-dose group (800 ppm) died by day 7; and all female rats in the high-dose group died by day 10. All groups, male and female, surviving to the end of the studies gained weight except the group receiving 400 ppm. In this group, 4/5 males lost from 5%-31% of their initial body weight, and 3/4 females lost from 10%-29% of their initial body weight.

The following signs of toxicity were noted in all animals in the two highest dose groups: dehydration and lethargy by day 4 and hunched posture by day 5. In addition, reduced water consumption was recorded among the two highest dose groups. Daily water consumption recorded by cage for males and females in the second highest dose group (400 ppm) was approximately 70% that of controls; for high-

Table 2
Survival and Mean Body Weights of Rats in the 14-Day Drinking Water Studies of Sodium Fluoride

Dose (ppm)	Survival[a]	Mean Body Weights (g) Initial[b]	Final	Change[c]	Final Weight Relative to Controls (%)
Male					
Control	5/5	86 ± 5	167 ± 6	81 ± 3	100
50	5/5	79 ± 3	151 ± 4	72 ± 2	91
100	5/5	75 ± 4	146 ± 5*	71 ± 1*	88
200	5/5	77 ± 3	140 ± 6**	62 ± 4**	84
400	5/5	80 ± 3	69 ± 6**	-11 ± 5**	41
800	0/5[d]	79 ± 2	–[e]	–	–
Female					
Control	5/5	80 ± 4	133 ± 2	53 ± 3	100
50	5/5	74 ± 3	128 ± 3	53 ± 4	96
100	5/5	79 ± 4	128 ± 2	49 ± 2	96
200	5/5	77 ± 5	128 ± 4	51 ± 3	96
400	4/5[f]	80 ± 4	79 ± 14**	0 ± 15**	59
800	0/5[g]	77 ± 3	–	–	–

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Number surviving/number initially on study
[b] Initial group mean body weight given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Mean body weight change of survivors given as mean ± standard error
[d] Day of death: 5,6,6,6,7
[e] No data reported due to 100% mortality in this group
[f] Day of death: 6
[g] Day of death: 7,8,8,9,10

dose males (800 ppm), water consumption was approximately 50% that of controls, and for high-dose females, approximately 25%.

No significant gross lesions were seen at necropsy in any groups of rats. Tissues from the animals were not evaluated microscopically.

6-Month Studies

Groups of ten rats of each sex were administered 0, 10, 30, 100, or 300 ppm sodium fluoride in deionized water *ad libitum* for 26 weeks. Survival and body weight data are presented in Table 3. There were no deaths throughout these studies. Body weight gain was depressed only in the highest dose groups.

Signs of dental fluorosis were observed in all high-dose animals. From week 6 to the end of the studies, their teeth appeared chalky white and had an unusual wear pattern. During weeks 6 to 17, the upper incisors grew quite long, while the occlusal surface of the lower incisors was worn to the gum line. So that feed consumption would not be affected, the upper incisors were trimmed periodically, allowing the lower incisors to grow to a normal length. Unusual chipping of incisors was observed from week 17 through the end of the studies. In addition, all high-dose animals had rough hair coats during the last 9 weeks of the studies.

Average weekly feed consumption was approximately 13% less in high-dose males and 18% less in high-dose females compared to controls. Somewhat

TABLE 3
Survival and Mean Body Weights of Rats in the 6-Month Drinking Water Studies of Sodium Fluoride

Dose (ppm)	Survival[a]	Mean Body Weights (g)			Final Weight Relative to Controls (%)
		Initial[b]	Final	Change[c]	
Male					
Control[d]	10/10	78 ± 7	444 ± 7	366 ± 8	100
Control[e]	10/10	78 ± 7	450 ± 7	372 ± 10	101
Control[f]	10/10	80 ± 7	420 ± 7*	339 ± 8*	94
10	10/10	76 ± 7	425 ± 9	349 ± 7	96
30	10/10	83 ± 7	437 ± 7	354 ± 10	98
100	10/10	76 ± 6	433 ± 7	357 ± 5	97
300	10/10	81 ± 7	371 ± 10**	290 ± 8**	83
Female					
Control[d]	10/10	72 ± 6	236 ± 7	163 ± 8	100
Control[e]	10/10	67 ± 6	234 ± 4	167 ± 6	99
10	10/10	75 ± 7	232 ± 3	156 ± 6	98
30	10/10	69 ± 7	234 ± 6	166 ± 7	99
100	10/10	69 ± 7	235 ± 4	166 ± 8	100
300	10/10	70 ± 7	212 ± 3**	141 ± 6	90

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test; control group received semisynthetic, low fluoride diet and deionized water.
** $P \leq 0.01$
a Number surviving/number initially on study
b Initial group mean body weight given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
c Mean body weight change of survivors given as mean ± standard error
d Control group receiving semisynthetic, low fluoride diet and deionized water
e Control group receiving semisynthetic, low fluoride diet and sodium chloride-supplemented deionized water
f Control group receiving standard NIH-07 diet and deionized water

reduced water consumption averages were also recorded (8% less than controls in high-dose males and 19% less than controls in high-dose females).

At termination of the studies, the fluoride content of bone, plasma, and urine was determined from samples collected from five male and female rats from each group (except the control group receiving sodium chloride-supplemented deionized drinking water and a semisynthetic, low fluoride diet). Results are presented in Appendix I (Table I1).

The fluoride content of bone and urine increased with increasing fluoride concentration in the drinking water. The fluoride content of plasma was significantly increased over that in control rats maintained on the low fluoride, semisynthetic diet only in the high-dose groups (300 ppm) and in the group of male rats maintained on the standard NIH-07 diet (Appendix I).

The principal pathological effects associated with the administration of sodium fluoride for 6 months were observed in the incisor teeth and stomach. The incisor teeth were chosen for examination because they are continuously growing and, therefore, contain all specialized components of the dental epithelium. Paraffin-embedded sagittal sections of upper incisors were unsatisfactory for critical examination. Therefore, the incisors were embedded in glycol methacrylate, sectioned sagittally, and stained with hematoxylin and eosin. Five male rats receiving 300 ppm sodium fluoride had focal or multifocal degeneration of the enamel organ, primarily in the maturation zone near the apical end of the incisor tooth (Table 4). The columnar ameloblasts were flattened or lost (atrophy), and the cells of the stratum intermedium were disorganized and contained less cytoplasm and fewer secretory vacuoles (Plates 1 and 2). In a few animals, small aggregates

TABLE 4
Incidence of Lesions of the Tooth and Stomach in Rats in the 6-Month Studies of Sodium Fluoride

Organs and Diagnoses	Control[a]	Control[b]	Control[c]	30 ppm	100 ppm	300 ppm
Male						
Incisor tooth, enamel organ[d]	(2)	(2)	(2)	(0)	(5)	(6)
Degeneration[e]	0	0	0	0	0	5
Glandular stomach	(10)	(10)	(10)	(10)	(10)	(10)
Inflammatory, infiltrate, lymphocytic	3	2	1	2	0	7
Inflammation, acute	0	0	0	0	0	2
Hyperplasia	0	0	0	0	5	10
Necrosis	0	0	0	0	0	10
Female						
Incisor tooth, enamel organ	(2)	(2)	(0)	(0)	(5)	(4)
Degeneration[e]	0	0	0	0	0	0
Glandular stomach	(10)	(10)	(10)	(10)	(10)	(10)
Inflammatory, infiltrate, lymphocytic	0	3	0	1	0	4
Hyperplasia	0	0	0	0	2	9
Necrosis	0	0	0	0	0	9

[a] Control group received semisynthetic, low-fluoride diet and deionized water.
[b] Control group received semisynthetic, low-fluoride diet and sodium chloride-supplemented deionized water.
[c] Control group received standard NIH-07 diet and deionized water.
[d] The number in parentheses is the number of animals examined microscopically. More than one lesion may occur within the same organ.
[e] The study pathologist used the term "dysplasia" for this lesion.

of enamel-like material were trapped within the cell layers. These changes collectively were diagnosed as dysplasia by the laboratory pathologist.

On gross examination, the mucosa of the glandular stomach of most male rats receiving 300 ppm sodium fluoride appeared thickened, and focal or multifocal punctate hemorrhages were observed in 4/10 males and 1/10 females. Similar but less severe alterations were observed in some rats receiving 100 ppm sodium fluoride. A perforated ulcer of the glandular stomach was seen in a 300 ppm female, and multiple, small, nonperforated ulcers were seen in one 300 ppm male. Histologically, a subtle focal to diffuse hyperplasia of the mucosal epithelium of the glandular stomach was observed in 10/10 male and 9/10 female rats receiving 300 ppm (Table 4). It was accompanied by minimal individual cell necrosis (apoptosis) and was most evident in the pyloric region. In affected rats, the number of mucous cells in the epithelium was slightly decreased relative to that in controls, the columnar cells stained more basophilic, and the number of mitotic figures at the base of the gastric pits was increased relative to that in controls. The epithelium lining the gastric pits contained one or several cells with pyknotic nuclei, fragments of nuclear debris, or residual bodies. Nearly all rats receiving 300 ppm sodium fluoride had focal basal cell hyperplasia of the stratified squamous epithelium adjacent to the limiting ridge (junction of the glandular stomach and forestomach). Hyperplasia of the mucosal epithelium of the glandular stomach also was observed in half the males and in two females receiving 100 ppm sodium fluoride, but individual cell necrosis was not.

Dose Selection Rationale: Two factors were of primary importance in the selection of the sodium fluoride drinking water concentrations for the 2-year studies in rats. These were the notably lower weight gains of male and female rats given 300 ppm in the 6-month studies and the occurrence of what were considered potentially life-threatening lesions in the stomach of rats receiving 300 ppm. For these reasons, the concentrations selected for the first 2-year sodium fluoride studies in rats were 0, 10, 30, and 100 ppm. Upon completion of the first 2-year sodium fluoride studies (Appendix M), it was determined that study animals could tolerate higher concentrations. Thus, the drinking water concentrations selected for the second 2-year sodium fluoride studies were 0, 25, 100, and 175 ppm.

2-Year Studies

Groups of 100 rats of each sex received 0 or 175 ppm sodium fluoride and groups of 70 rats of each sex received 25 or 100 ppm sodium fluoride in deionized water *ad libitum* for up to 103 weeks. Interim sacrifices of ten animals per sex per group occurred at 27 weeks and 66 weeks. An additional group of 50 animals of each sex received deionized water and provided age-matched controls for early deaths of rats given sodium fluoride.

Body Weights

Group mean body weights and mean body weights relative to control values are presented by week on study in Tables 5 and 6. Growth curves, plotting mean body weights against week on test, are shown in Figure 1. No significant chemically related differences in body weights were observed.

Feed, Water, and Compound Consumption

Average daily feed consumption for control and treated groups ranged from 17.2 to 17.4 g for males and 11.2 to 11.3 g for females (data on file at NIEHS). Administration of sodium fluoride in drinking water at the concentrations used in these studies had no effect on feed consumption.

Deionized drinking water was the vehicle for administering sodium fluoride to rats. Average daily water consumption for control and treated groups ranged from 19.8 to 21.2 g for males and 13.1 to 13.6 g for females (Appendix L, Tables L1 and L2). Administration of sodium fluoride in drinking water at the concentrations used in these studies had no effect on water consumption. Estimated daily ingestion of the chemical throughout the studies is presented in Table L1 for male rats and in Table L2 for female rats. When averaged over the 2-year studies, the daily amounts of sodium fluoride ingested were 1.3 mg/kg for low-dose males, 5.2 mg/kg for mid-dose males, 8.6 mg/kg for high-dose males, 1.3 mg/kg for low-dose females, 5.5 mg/kg for mid-dose females, and 9.5 mg/kg for high-dose females.

Clinical Signs

While numerous clinical signs were recorded during these studies, most occurred with such low frequency or with such similarity across dosed and control

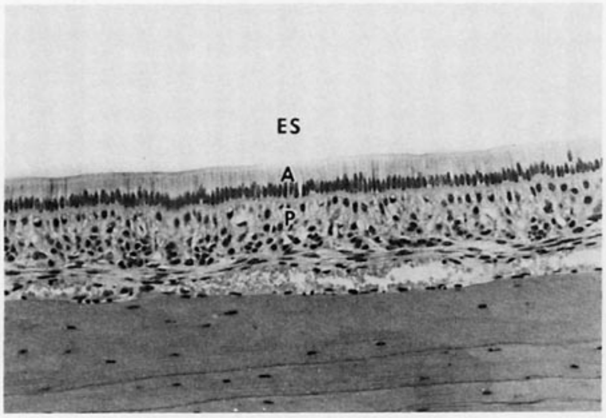


Plate 1
Maturation zone of the enamel organ of the incisor tooth from a control male. The maturation zone is characterized by a well-defined layer of tall columnar ameloblasts (A) overlying the maximally developed papillary layer (P). The enamel is mature at this level and is completely removed during decalcification leaving the enamel space (ES). H&E, 150×

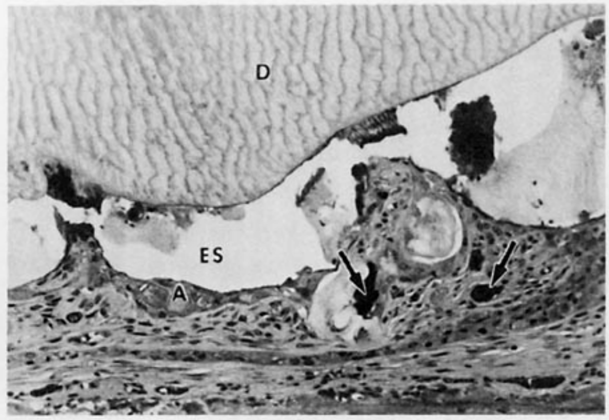


Plate 2
Maturation zone of the enamel organ of the incisor tooth from a male rat receiving 300 ppm sodium fluoride for six months. There is marked atrophy of the layer of ameloblasts. Note the clumps of immature enamel within the enamel organ (arrows) and within the enamel space. Dentin (D). H&E, 150×

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Drinking Water Study of Sodium Fluoride

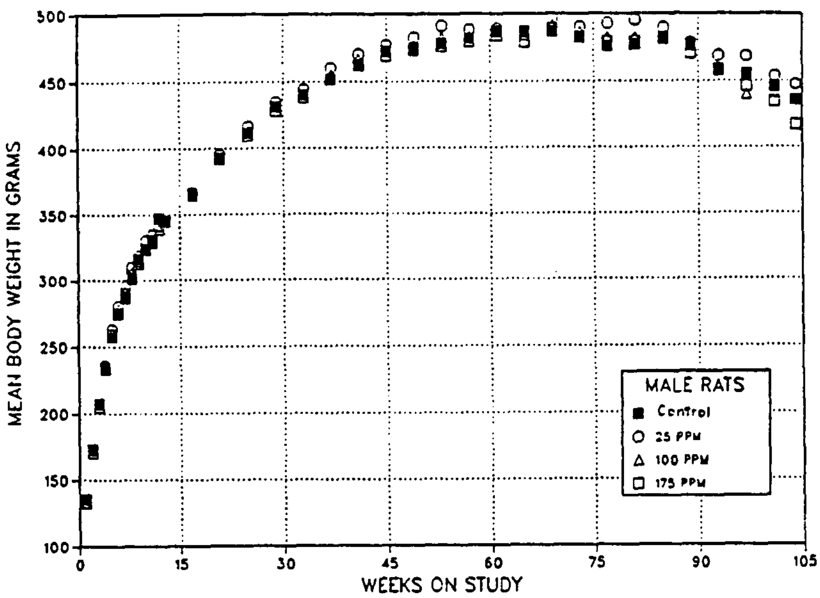
Study Week	Control Av.Wt. (g)	Control No. of Surv.[a]	25 ppm Av.Wt. (g)	25 ppm (%)	25 ppm No. of Surv.[a]	100 ppm Av.Wt. (g)	100 ppm (%)	100 ppm No. of Surv.[a]	175 ppm Av.Wt. (g)	175 ppm (%)	175 ppm No. of Surv.[a]
1	136	80	133	98	51	133	98	50	133	98	80
2	174	80	172	99	51	173	100	50	170	98	80
3	208	80	207	100	51	208	100	50	205	98	80
4	236	79[b]	237	101	51	236	100	50	233	99	80
5	258	80	264	102	51	262	101	50	259	100	80
6	276	80	281	102	51	280	101	50	275	100	80
7	287	80	296	103	51	292	102	50	290	101	80
8	302	80	310	103	51	308	102	50	304	101	80
9	316	79	319	101	51	316	100	50	313	99	80
10	325	79	331	102	51	325	100	50	324	100	80
11	330	79	335	101	51	329	100	50	331	100	80
12	342	79	341	100	51	340	99	50	341	100	80
13	346	79	342	99	51	343	99	50	341	98	80
17	367	79	368	100	51	365	100	50	367	100	80
21	392	79	396	101	51	393	100	50	393	100	80
25	411	78	417	102	51	413	101	50	409	100	80
29	430	78	435	101	51	433	101	49	429	100	80
33	438	78	444	101	51	441	101	49	439	100	80
37	450	78	460	102	51	456	101	49	452	101	80
41	461	78	471	102	51	468	102	49	462	100	79
45	470	78	477	102	51	473	101	49	470	100	79
49	473	77	483	102	51	479	101	49	474	100	79
53	476	77	491	103	51	484	102	49	476	100	79
57	480	77	487	102	51	484	101	48	481	100	77
61	485	76	487	101	50	488	101	47	485	100	77
65	486	75	487	100	49	487	101	47	482	99	77
69	487	75	497	102	49	492	101	47	489	100	76
73	483	75	490	102	49	487	101	47	483	100	75
77	476	74	493	104	48	483	101	47	479	101	73
81	477	70	495	104	48	482	101	47	479	100	71
85	483	67	490	102	47	482	100	43	481	100	69
89	478	65	479	100	46	476	100	39	471	99	66
93	459	62	469	102	42	462	101	38	458	100	61
97	455	57	468	103	34	440	97	35	446	98	55
101	446	50	454	102	31	441	99	29	435	98	48
104	436	43	448	103	26	437	100	23	417	96	44
Terminal sacrifice		42			25			23			42
Mean for weeks											
1-13	272		274	101		273	100		271	99	
17-52	432		439	101		436	101		433	100	
53-104	472		481	102		473	100		469	99	

[a] Number of animals weighed. At terminal sacrifice, number of animals alive on first day of terminal sacrifice.
[b] The number of animals weighed for this week is less than the number of animals surviving.

TABLE 6
Mean Body Weights and Survival of Female Rats in the 2-Year Drinking Water Study of Sodium Fluoride

Study Week	Control		25 ppm			100 ppm			175 ppm		
	Av.Wt. (g)	No. of Surv.[a]	Av.Wt. (g)	(%)	No. of Surv.[a]	Av.Wt. (g)	(%)	No. of Surv.[a]	Av.Wt. (g)	(%)	No. of Surv.[a]
1	105	80	105	100	50	104	99	50	105	100	81
2	125	80	125	100	50	125	100	50	124	100	81
3	141	80	141	100	50	142	100	50	141	100	81
4	153	80	153	100	50	152	100	50	153	100	81
5	165	80	165	100	50	165	100	50	166	100	81
6	173	80	174	101	50	174	101	50	173	100	81
7	180	80	180	100	50	180	100	50	180	101	81
8	187	80	187	100	50	187	100	50	187	100	81
9	191	80	191	100	50	190	100	50	189	99	81
10	194	80	194	100	50	193	100	50	194	100	81
11	195	80	196	101	50	194	99	50	195	100	81
12	198	80	198	100	50	198	100	50	196	99	81
13	198	80	200	101	50	197	100	50	196	99	81
17	208	80	210	101	50	208	100	50	207	100	81
21	220	80	219	100	50	220	100	50	219	99	81
25	227	80	230	101	50	229	101	50	227	100	81
29	236	80	238	101	50	236	100	50	235	99	81
33	237	80	240	101	50	237	100	50	236	99	81
37	239	80	243	101	50	241	101	50	241	101	81
41	256	79	258	101	50	256	100	50	256	100	81
45	264	79	268	102	50	267	101	50	262	99	81
49	269	79	273	101	50	269	100	50	264	98	80
53	277	79	283	102	50	278	100	50	273	98	80
57	284	78	290	102	50	284	100	50	279	98	80
61	294	77	296	101	50	294	100	50	288	98	79
65	297	77	302	102	49	297	100	50	292	98	79
69	301	76	305	101	49	301	100	50	299	99	79
73	306	76	310	101	49	305	100	50	302	99	79
77	316	75	320	101	49	313	99	50	310	98	78
81	323	75	326	101	49	314	97	50	316	98	76
85	327	75	327	100	47	327	100	46	322	99	74
89	328	75	327	100	46	331	101	46	324	99	73
93	323	69	321	99	43	320	99	41	320	99	65
97	323	67	318	98	42	317	98	38	321	99	65
101	333	62	334	100	37	316	95	38	321	96	64
104	336	59	338	101	31	324	96	34	325	97	54
Terminal sacrifice		59			31			34			54
Mean for weeks											
1-13	170		170	100		169	100		169	100	
17-52	240		242	101		240	100		239	99	
53-104	312		314	101		309	99		307	98	

[a] Number of animals weighed. At terminal sacrifice, number of animals alive on first day of terminal sacrifice.



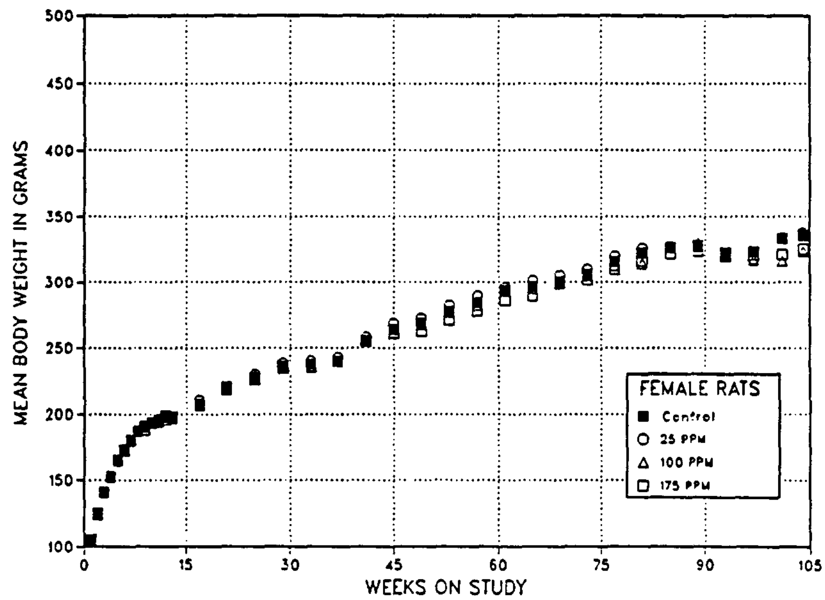


Figure 1
Growth Curves for Male and Female Rats Administered Sodium Fluoride in Drinking Water for 2 Years

groups that they were not considered related to treatment. The exceptions were abnormalities in the teeth of rats at the two highest exposure levels (Table 7).

Supplemental Studies

Hematology, clinical chemistry, urinalysis and urine concentrating ability, and fluoride concentrations in serum and urine were measured in all animals sacrificed at 27 and 66 weeks. Fluoride concentrations in bone were measured for all animals sacrificed at 27 and 66 weeks and for selected animals at termination of the studies. Results of these measurements are presented in Appendix I and in Figure 2.

There were no biologically significant differences in hematologic indices, serum concentrations of phosphorus or calcium, or alkaline phosphatase activity among dosed and control male or female rats at the 27-week or 66-week interim evaluations (Tables I7 and I8). Serum fluoride concentrations were increased over control values in females receiving drinking water containing 100 or 175 ppm sodium fluoride at 27 weeks and in all exposed males and females at 66 weeks (Table I5). These increases ranged as high as almost threefold over control values in high-dose rats. Urinalysis results did not indicate biologically significant effects related to fluoride administration with the possible exception of a small increase in calcium excretion in high-dose female rats at both time points (Tables I11 and I12). A dose-related increase was observed in the fluoride concentration of urine from male and female rats at both the 27-week and 66-week interim evaluations (Table I6). For all treated groups, dose-related fluoride concentrations in bone were significantly increased over control values for all evaluation periods. Fluoride content of bone also increased as a function of age (Table I3 and Figure 2).

TABLE 7
Tooth Abnormalities (Gross Observations) in Rats in the 2-Year Drinking Water Studies of Sodium Fluoride

Observation[a]	Control	25 ppm	100 ppm	175 ppm
Male				
Attrition[b]	0 (0%)	0 (0%)	7 (30%)	22 (50%)
Deformity[c]	1 (1%)	0 (0%)	12 (17%)	27 (27%)
Discoloration[c]	1 (1%)	2 (3%)	15 (21%)	31 (31%)
Malocclusion[c]	1 (1%)	1 (1%)	2 (3%)	13 (13%)
Mottling[b]	2 (5%)	22 (85%)	22 (96%)	44 (100%)
Female				
Attrition	0 (0%)	0 (0%)	1 (3%)	2 (4%)
Deformity	0 (0%)	0 (0%)	1 (1%)	8 (8%)
Discoloration	0 (0%0	2 (3%)	2 (3%)	8 (8%)
Malocclusion	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Mottling	0 (0%)	8 (26%)	32 (94%)	53 (98%)

[a] Discoloration designates an overall effect, while mottling indicates variegated discoloration. The terms are not mutually exclusive.
[b] The incidences for this observation are for the lower incisors of animals observed at week 104 only (males: n = 43, 26, 23, 44; females: n = 59, 31, 34, 54).
[c] The incidences for this observation include interim and terminal sacrifice animals (males and females: n = 100, 70, 70, 100).

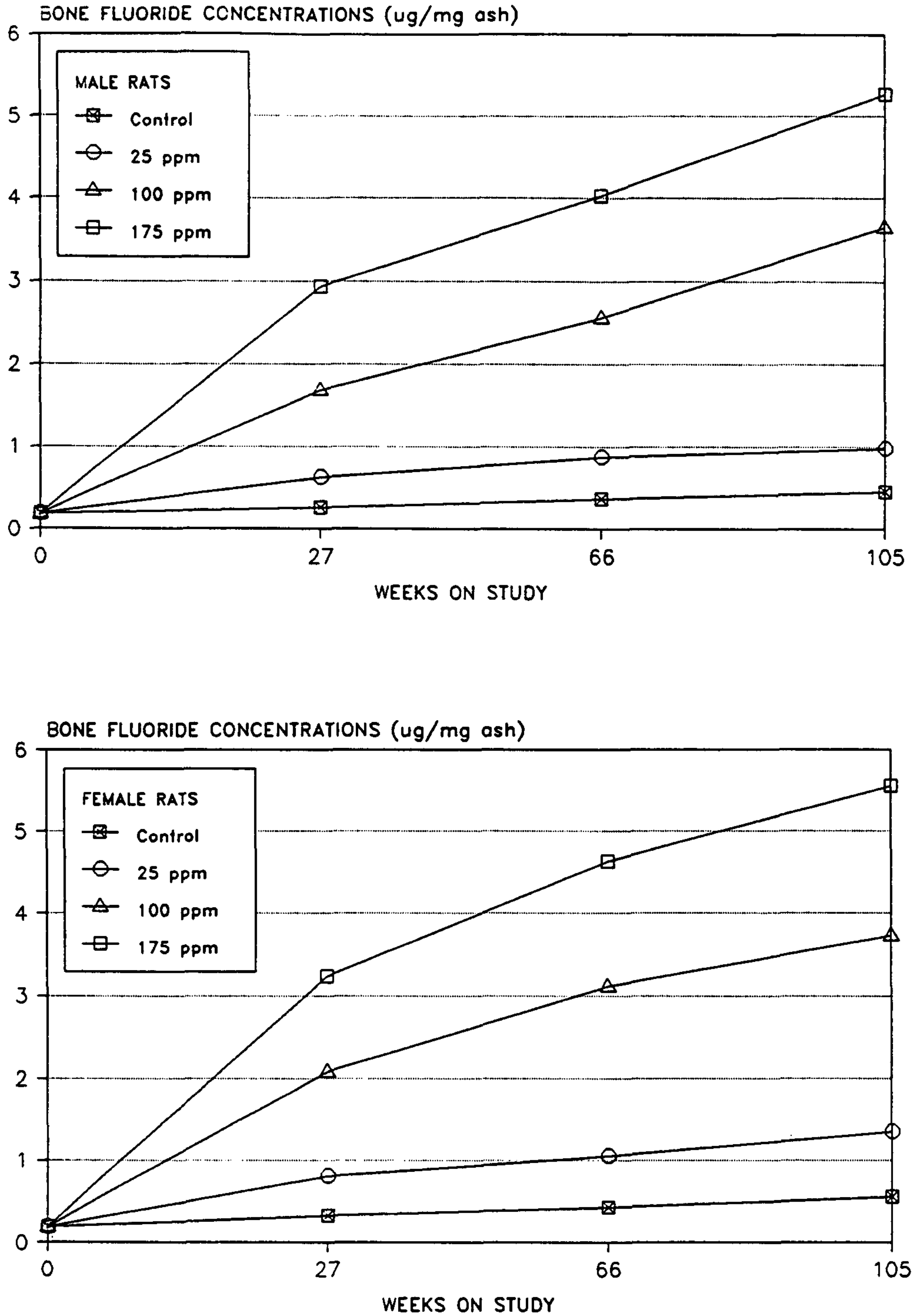


Figure 2
Bone Fluoride Content in Rats in the 2-Year Drinking Water Studies with Sodium Fluoride

Survival

Estimates of the probabilities of survival of male and female rats administered sodium fluoride in drinking water at the doses used in these studies and those of the vehicle controls are illustrated in Kaplan-Meier curves (Figure 3). Overall survival information is given in Table 8. No significant chemical-related effects on survival were observed.

Organ weights for the brain, right kidney, left kidney, and liver were recorded for rats sacrificed at 27 weeks and 66 weeks. Group mean organ weights and organ-weight-to-body-weight ratios are presented in Appendix G. There were no changes in organ weights that appeared related to sodium fluoride administration.

Pathology and Statistical Analyses of Results

Summaries of the incidence of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidence for neoplasms of interest are presented in Appendix A for male rats and Appendix B for female rats. Summaries of the incidence of neoplasms and nonneoplastic lesions in male and female rats at the interim evaluations are presented in Appendix E for the 27-week sacrifice and in Appendix F for the 66-week sacrifice. Findings of note were in bone, mesenchymal soft tissue, oral mucosa, teeth, thyroid gland, skin, and uterus.

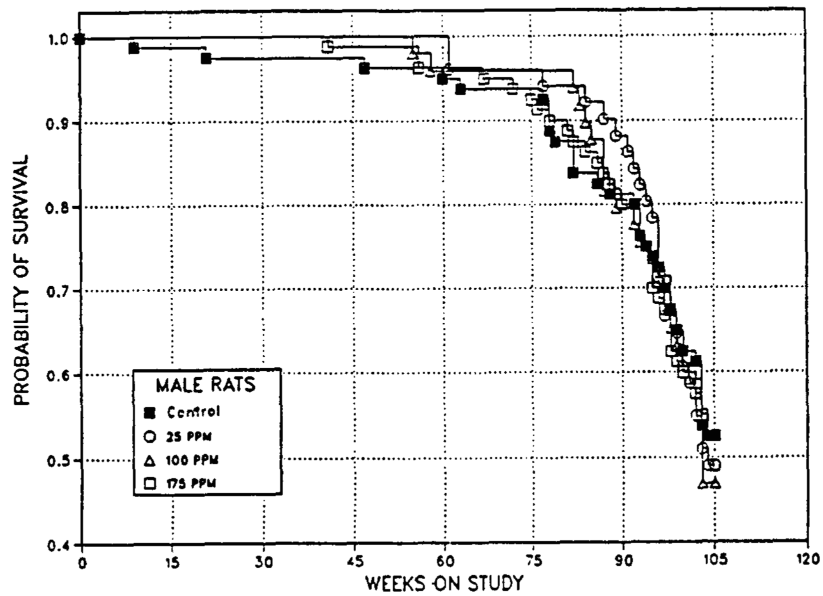
Bone: The bones examined microscopically included the proximal portions of the humerus, femur, and tibia; a thoracic vertebra; the maxilla, incisive, and nasal bones included in the sections of nose; and the mandible. All but the mandible were decalcified, routinely processed, and stained with hematoxylin and eosin; the mandible was processed and sectioned without decalcification. Lesions observed by gross examination at necropsy also were sectioned and examined microscopically.

Nonneoplastic lesions of bone occurring in control and exposed male and/or female rats included fibrous osteodystrophy and osteosclerosis. Fibrous osteodystrophy was always associated with advanced nephropathy, principally in male rats, and was considered to be due to renal secondary hyperparathyroidism. Osteosclerosis is a spontaneous bone disease of unknown cause that occurs in aging F344/N rats, primarily females. Histologically, it is similar to a congenital, hereditary disease called osteopetrosis, which occurs in some strains of rat as well as in other animals. The incidence of osteosclerosis was increased in female rats receiving 175 ppm sodium fluoride relative to untreated controls (6/80 control, 18/81 high-dose, $P=0.04$). In every rat with osteosclerosis in these studies, most of the bones examined microscopically were affected to some degree. There was an increase in the amount of trabecular bone in the diaphysis and occasionally extending into the diaphysis and/or epiphysis of the vertebrae and long bones, which varied from immature woven bone with thick osteoid seams to dense lamellar bone. The more severe lesions were detected in the radiographs of affected animals.

Osteosarcomas of the bone were observed in one male receiving 100 ppm and in three males receiving 175 ppm (Table 9). None occurred in control or low-dose male rats or in female rats. The osteosarcomas occurred with a significant dose response trend; pairwise comparison of the incidences in the dosed groups versus control were not significant.

One male rat (175 ppm, CID#0713) with a vertebral osteosarcoma exhibited posterior paralysis due to invasion of the spinal cord by the neoplasm. There were no other clinical signs attributable to the bone neoplasms. All osteosarcomas but one (175 ppm, CID#0745) were seen in the radiographs.

The osteosarcoma in the male rat that received 100 ppm (CID#0495) was a 25×20×20 mm mass surrounding the first and second coccygeal vertebrae. The peripheral margin of the neoplasm was well defined and the vertebral body was largely intact within the mass. The neoplasm consisted of an abundant osteoid matrix with interspersed single and small nests of osteoblasts within lacunae (Plate 3). The osteoblasts were more abundant at the periphery of the neoplasm where active growth was occurring. They were generally polygonal, with a large nucleus and prominent nucleolus, and were relatively uniform in size and shape. This animal had a metastatic lesion in the lungs with the same morphological appearance as the primary lesion in the coccygeal vertebra (Plate 4).



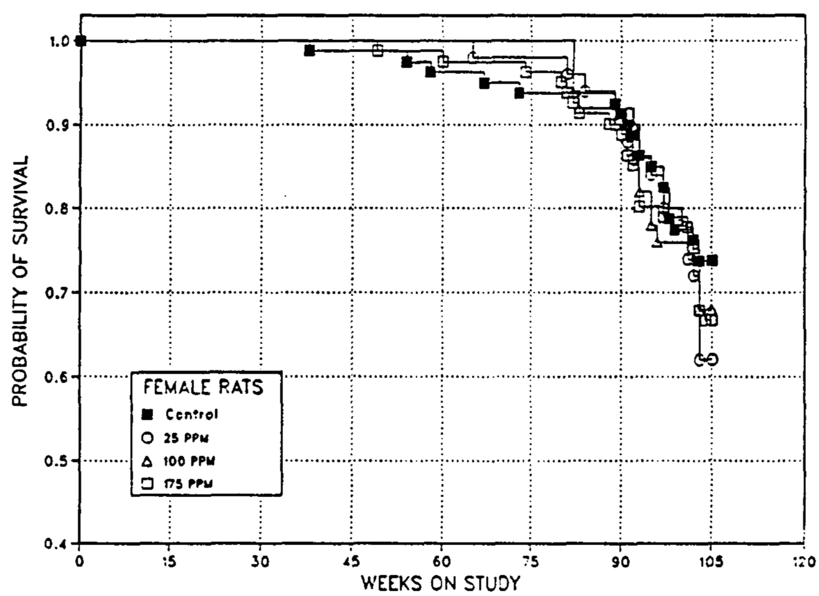


Figure 3
Kaplan-Meier Survival Curves for Male and Female Rats Administered Sodium Fluoride in Drinking Water for 2 Years

TABLE 8
Survival of Rats in the 2-Year Drinking Water Studies of Sodium Fluoride

	Control	Paired Control[a]	25 ppm	100 ppm	175 ppm
Male					
Animals initially in study	100	50	70	70	100
Missexed	1	0	0	0	0
Natural deaths	17	6	13	13	19
Moribund kills	21	12	13	13	19
Age-matched kills	0	27	0	0	0
Accidents	0	0	0	1	0
Interim kills	19	0	19	20	20
Animals surviving to study termination	42	5	25	23	42
Percent survival at end of study[b]	53	–[c]	49	47	53
Mean survival (days)[d]	668	–[c]	687	671	675
Survival P values[e]	0.973	–[c]	0.900	0.716	0.966
Female					
Animals initially in study	100	50	70	70	100
Natural deaths	10	4	11	6	10
Moribund kills	11	7	8	10	17
Age-matched kills	0	21	0	0	0
Interim kills	20	0	20	20	19
Animals surviving to study termination	59	18	31	34	54
Percent survival at end of study[b]	74	–[c]	62	68	67
Mean survival (days)[d]	697	–[c]	702	703	697
Survival P values[e]	0.634	–[c]	0.276	0.619	0.445

[a] During every study week that one or more animals from any group receiving sodium fluoride was found dead or killed in a moribund condition, one animal of the same species and sex from this group was chosen at random and killed.
[b] Kaplan-Meier determinations. Survival rates adjusted for accidental deaths and interim kills.
[c] Not determined
[d] Mean of all deaths (uncensored, censored, terminal kill)
[e] The entry under the "control" column is the trend test (Tarone, 1975) result. Subsequent entries are the results of pairwise tests (Cox, 1972).

TABLE 9
Bone Osteosarcomas in Male Rats in the 2-Year Drinking Water Study of Sodium Fluoride

	Control	25 ppm	100 ppm	175 ppm
Bone: Osteosarcoma				
Overall rates[a]	0/80 (0%)	0/51 (0%)	1/50 (2%)	3/80 (4%)[b]
Adjusted rates[c]	0.0%	0.0%	4.3%	5.3%
Terminal rates[d]	0/42 (0%)	0/25 (0%)	1/23 (4%)	1/42 (2%)
First incidence (days)	---	---	729 (T)	388
Logistic regression tests[e]	P=0.027	-[f]	P=0.380	P=0.099

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals necropsied
[b] One extraskeletal osteosarcoma occurred in a high-dose male rat (see page 53).
[c] Kaplan-Meier estimated tumor incidence at the end of the study 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 dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal.
[f] No tumors in dosed group or control group; statistical test not performed.

Of the three male rats receiving 175 ppm sodium fluoride, two had osteosarcomas involving vertebrae, and the third had an intramedullary neoplasm in the proximal portion of the humerus. The first of these male rats (CID#0775) had a 26×17×9 mm mass involving primarily the twelfth and thirteenth thoracic vertebrae. The compact bone forming the wall of the vertebral body was thin and discontinuous, apparently destroyed by neoplastic tissue extending from the medullary cavity to the dorsal and lateral aspects of the vertebra. This osteosarcoma was highly cellular and less differentiated than that observed in the male that received 100 ppm, and the neoplastic cells were present in solid sheets with occasional islands of osteoid (Plate 5). In some areas, multinucleated cells were abundant (Plate 6).

The second male rat with a vertebral osteosarcoma (CID#0713) had a 10×10×10 mm mass that appeared to involve the seventh cervical vertebra. The largest portion of the neoplasm was ventral to the vertebral body, although neoplastic tissue was present in the spinal canal and had invaded the spinal cord (Plate 7). The third high-dose male rat (CID#0745) had an osteosarcoma in the humerus that was not observed radiographically or at necropsy. It was intramedullary and located primarily on the metaphyseal side of the epiphysis. In the section of humerus examined the epiphyseal plate was intact, although large clusters of neoplastic cells were interspersed among the trabecular bone on the epiphyseal side of the growth plate. This neoplasm was also highly cellular with occasional islands of osteoid interspersed among the neoplastic cells (Plate 8).

The osteosarcomas of the bone in male rats receiving sodium fluoride are notable because of their rarity in untreated control groups from NTP studies. Osteosarcomas at any site, including extraskeletal tissues (see below), have been seen in 10/2,106 (0.5%) male untreated historical control rats. The greatest incidence observed in any one control group was 6%. Thus, the incidence rate of osteosarcoma (any site) in high-dose male rats receiving sodium fluoride is within the range of historical controls. It should be noted that the fluoride levels in the diets used in the previous studies were higher than in that used in the current studies (see the Discussion for further information).

The quality assessment pathologist confirmed the increased incidence of osteosclerosis in female rats as reported by the laboratory pathologist, and the Pathology Working Group (PWG), which reviewed selected examples of these lesions, concurred with these findings. The PWG also concurred with the diagnoses of osteosarcoma in the bone of four male rats receiving sodium fluoride.

Mesenchymal Soft Tissue: An extraskeletal osteosarcoma in the subcutis of the flank occurred in a male rat receiving 175 ppm sodium fluoride. The radiographs of this rat showed no evidence of a primary neoplasm of the bone. The neoplasm was a 45×21×21 mm mass with a large necrotic center and a more varied morphology than that of the other osteosarcomas (Plate 9). There was a mixture of cartilaginous and osteoid matrix and highly cellular areas with no intercellular matrix (Plate 10). Although this neoplasm did not arise from bone, the PWG thought that is was appropriately diagnosed as an osteosarcoma because of the cellular differentiation.

A lesion found in the subcutis of a control male rat is also notable because it consisted of collagenous connective tissue with well-defined islands of osteoid and/or woven bone. It was identified in the radiographs and was subsequently examined microscopically. The lesion was unusual and is not easily categorized in current rodent or human classification schemes. The medical and veterinary pathologists who reviewed the lesion concluded that it was not an osteoma or osteosarcoma but a benign mesenchymal growth with osseous metaplasia of uncertain histogenesis and biological potential (Plate 11).

Teeth: Alterations of the teeth associated with the administration of sodium fluoride were observed in the incisors and were more frequent in males than females (Table 10). The lesions identified were similar to those previously reported in the literature. In general the PWG concurred with the findings of the laboratory pathologist, although there was a minor difference of opinion regarding the most appropriate terminology for the lesion involving the ameloblastic epithelium. The lesion occurred primarily in the maturation and transitional zones. Although the laboratory pathologist had used the term "squamous metaplasia," the PWG thought that "degeneration" was more appropriate. Degeneration of the ameloblastic epithelium varied in severity and extent from loss of the surface columnar cells to marked reduction in cellularity (atrophy) of the surface and papillary layers with only two to three cell layers of flattened, squamous-like cells remain-

TABLE 10
Incidence of Lesions of the Tooth in Rats in the 2-Year Drinking Water Studies of Sodium Fluoride

Diagnoses	Control	Paired Control[a]	25 ppm	100 ppm	175 ppm
Male					
Tooth	(80)	(45)	(51)	(50)	(80)
Dentine, incisor, dysplasia	4 (5%)		7 (14%)	14 (28%)	30 (38%)
Incisor, odontoblast, degeneration			1 (2%)	2 (4%)	4 (5%)
Incisor, ameloblast, degeneration			1 (2%)	7 (14%)	23 (29%)
Female					
Tooth	(79)	(31)	(50)	(50)	(81)
Dentine, incisor, dysplasia		2 (6%)	8 (16%)	4 (8%)	10 (12%)
Incisor, odontoblast, degeneration					2 (2%)
Incisor, ameloblast, degeneration				1 (2%)	7 (9%)

[a] During every study week that one or more animals from any group receiving sodium fluoride was found dead or killed in a moribund condition, one special control animal of the same species and sex from this group was chosen at random, killed and necropsied.

ing (Plate 12). Since there was no evidence of proliferation of these cells and no keratin production, it was not considered analogous to squamous metaplasia as it occurs in a variety of organs in response to prolonged injury due to viral or bacterial infections or chemicals. Dentine dysplasia was characterized by variable degrees of focal flattening (atrophy) of the odontoblasts and irregularities in thickness of the dentine. In some animals there was disorganization of the dentine, with predentine-like material among the layer of odontoblasts or within the pulp and irregularities in the contour of the dentine.

Oral Mucosa (Tongue, Pharynx, Gingiva and Tooth): Squamous cell papilloma or carcinoma arising from the epithelium of the oral mucosa occurred in several dosed and control rats (Table 11). The incidence of papilloma or carcinoma combined was marginally increased in male and female rats receiving 175 ppm sodium fluoride, but it was not significantly greater than that of the control groups. Squamous cell neoplasms of the oral mucosa are relatively uncommon in F344/N rats, occurring in 14/2,106 (0.7%) historical male untreated controls and 12/2,153 (0.6%) female untreated controls. The highest incidence observed in any single control group was 4%. The squamous cell neoplasms in rats receiving sodium fluoride were not considered chemical related because a squamous cell carcinoma was observed in one control male (paired control group) and in one control female, the incidences in the dosed groups were not significantly greater than in concurrent controls and were within the range of historical controls, and there was no supporting evidence of focal hyperplasia of the oral mucosa.

Thyroid Gland: Follicular cell adenomas were observed in 1/49 mid-dose male and 3/80 high-dose male rats. Follicular cell carcinomas were observed in 1/80 control, 1/51 low-dose, and 1/80 high-dose male rats (Appendix A, Table A1). Further, a follicular cell carcinoma was seen in a high-dose male at the 66-week interim evaluation. Although there is a marginal numerical increase in follicular cell neoplasms in male rats receiving 175 ppm sodium fluoride, the incidence is not significantly greater than that in controls (Table A3). Moreover, the incidence of follicular cell neoplasms in the high-dose group is within the range of historical untreated controls (26/2,086, 1.2%, range 0%-6%) (Table A4c), and the incidence of follicular cell hyperplasia is not increased in dosed rats (Table A5). Thus, the marginal increase in follicular cell neoplasms was not considered related to administration of the chemical.

Skin: Keratoacanthomas were seen in three high-dose female rats; none occurred in lower dose groups or in controls (Appendix B, Table B1). However, other benign neoplasms arising from the stratified squamous epithelium were observed in one control female (trichoepithelioma) and one paired control female (squamous papilloma) (Table B1). The incidence of squamous cell neoplasms of the skin (keratoacanthoma, trichoepithelioma, or squamous cell papilloma combined) in high-dose female rats was not significantly greater than that in controls and was not considered related to administration of the chemical (Table B3). Keratoacanthomas also occurred in male rats, but they were not dose related (Table A3). The incidence in the high-dose group was similar to that in controls (control males, 11%; low-dose males, 4%; mid-dose males, 2%; high-dose males, 10%).

Uterus: Uterine stromal polyps were seen in 12/80 (15%) control, 4/50 (8%) low-dose, 6/50 (12%) mid-dose, and 2/81 (2%) high-dose female rats (Appendix B, Tables B1 and B3). A stromal sarcoma occurred in one high-dose female. The incidence of stromal polyp or stromal sarcoma combined in the high-dose females was significantly less than that in controls ($P=0.014$) (Table B3). However, the incidence of stromal polyps in historical untreated control groups is quite variable and ranges from 8% to 36% with a mean of 21% (Table B4c). Therefore, it is uncertain whether the decreased incidence is related to administration of the chemical.

Other lesions were incidental or part of spontaneous disease complexes of rats. There was no alteration in the incidence or severity of these lesions in the treated and control animals, and they were histopathologically typical of those commonly seen in this strain of laboratory rat.

TABLE 11
Lesions of the Oral Cavity in Rats in the 2-Year Drinking Water Studies of Sodium Fluoride

	Control	25 ppm	100 ppm	175 ppm
Male				
Tongue: Squamous Hyperplasia				
Overall rates[a]	0/80 (0%)	1/51 (2%)	0/50 (0%)	0/80 (0%)
Oral Cavity (Oral Mucosa, Tongue, or Pharynx): Squamous Papilloma				
Overall rates	0/80 (0%)	1/51 (2%)	1/50 (2%)	2/80 (3%)
Oral Mucosa: Squamous Cell Carcinoma				
Overall rates	0/80 (0%)	0/51 (0%)	1/50 (2%)	1/80 (1%)
Oral Cavity (Oral Mucosa, Tongue, or Pharynx): Squamous Papilloma or Squamous Cell Carcinoma[b]				
Overall rates	0/80 (0%)[c]	1/51 (2%)	2/50 (4%)	3/80 (4%)
Adjusted rates[d]	0.0%	4.0%	6.0%	5.9%
Terminal rates[e]	0/42 (0%)	1/25 (4%)	0/23 (0%)	1/42 (2%)
First incidence (days)	---	729 (T)	681	620
Logistic regression tests[f]	P=0.082	P=0.397	P=0.142	P=0.123
Female				
Tongue: Squamous Hyperplasia				
Overall rates	1/80 (1%)	0/50 (0%)	1/50 (2%)	1/81 (1%)
Oral Cavity (Pharynx): Squamous Papilloma				
Overall rates	0/80 (0%)	1/50 (2%)	1/50 (2%)	1/81 (1%)
Oral Mucosa: Squamous Cell Carcinoma				
Overall rates	1/80 (1%)	0/50 (0%)	0/50 (0%)	2/81 (2%)
Oral Cavity (Oral Mucosa or Pharynx): Squamous Papilloma or Squamous Cell Carcinoma[g]				
Overall rates	1/80 (1%)	1/50 (2%)	1/50 (2%)	3/81 (4%)
Adjusted rates	1.5%	3.2%	2.9%	4.5%
Terminal rates	0/59 (0%)	1/31 (3%)	1/34 (3%)	0/54 (0%)
First incidence (days)	674	729 (T)	729 (T)	628
Logistic regression tests	P=0.211	P=0.654	P=0.654	P=0.303

(T)Terminal sacrifice
[a] Incidence expressed as number of animals with lesion/total number of animals necropsied
[b] 2-year historical incidence for untreated control groups at study laboratory (mean): 1/350 (0.3%); historical incidence for untreated control groups in NTP studies (mean ± SD): 14/2106 (0.7% ± 1.3%)
[c] One male rat in the paired control group had a squamous cell carcinoma of the oral mucosa (Table A1 and A3).
[d] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal.
[g] 2-year historical incidence for untreated control groups at study laboratory (mean): 2/348 (0.6%); historical incidence for untreated control groups in NTP studies (mean ± SD): 12/2153 (0.6% ± 1.0%)

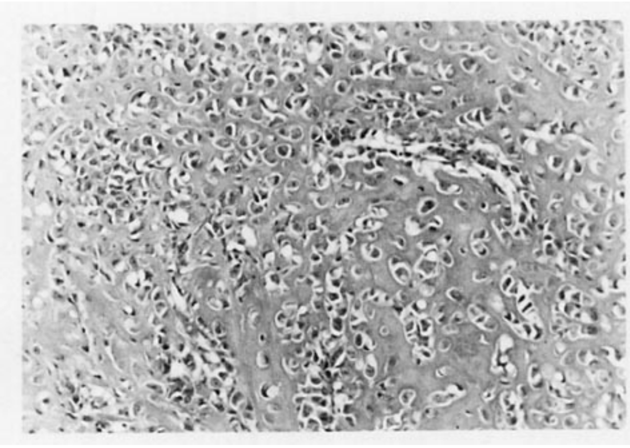


Plate 3
Vertebral osteosarcoma in mid-dose male rat CID#0495. Note the abundant osteoid matrix and osteoblasts within lacunae. H&E, 150×

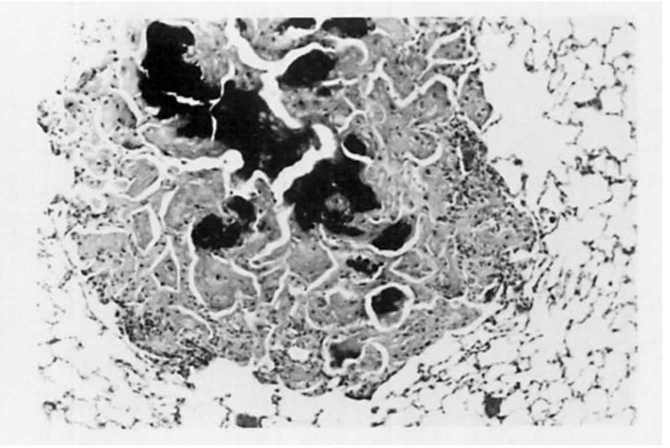


Plate 4
Metastatic osteosarcoma in the lung of mid-dose male rat CID#0495. Note the abundant osteoid similar to the primary neoplasm and dark area of mineralization in the center. H&E, 75×

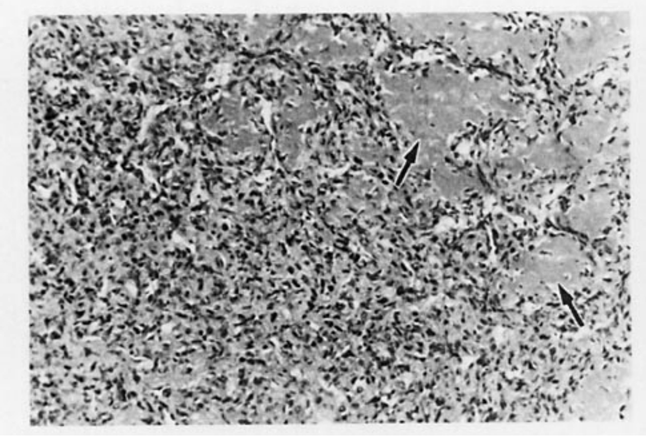


Plate 5
Vertebral osteosarcoma in high-dose male rat CID#0775. Note the cellularity in the lower left corner and clumps of osteoid (arrow). H&E, 150×

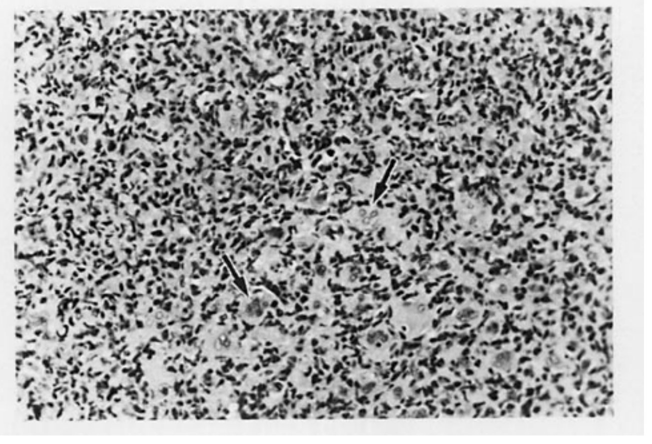


Plate 6
Osteosarcoma in high-dose male rat CID#0775 showing multinucleated giant cells (arrows) and smaller pleomorphic cells. H&E, 150×

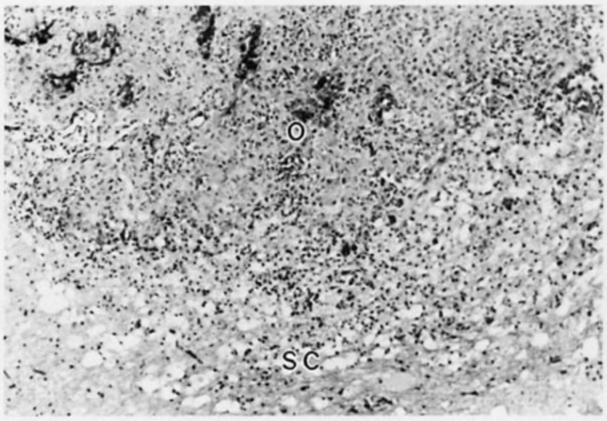


Plate 7
Spinal cord (SC) showing invasion by vertebral osteosarcoma (O) in high-dose male rat CID#0713. Note the vacuoles and degeneration of the neuropil surrounding the neoplasm. H&E, 75×

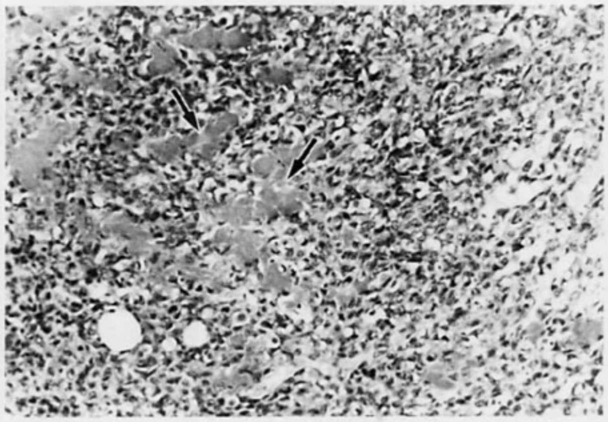


Plate 8
Intramedullary osteosarcoma of humerus of high-dose male rat CID#0745. H&E, 150×

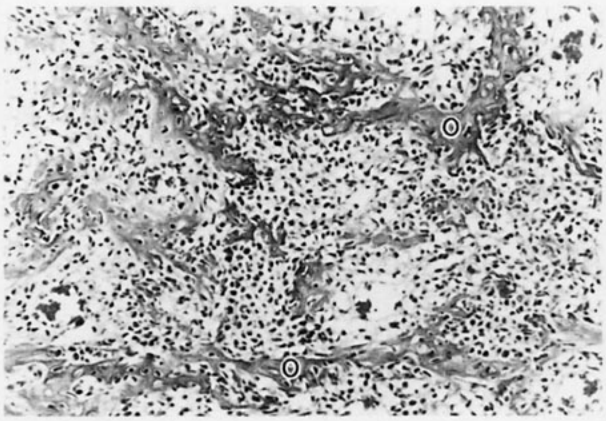


Plate 9
Subcutaneous osteosarcoma in high-dose male rat CID#0712 with delicate trabeculae of osteoid (O), which is partially mineralized, separated by highly cellular areas. H&E, 150×

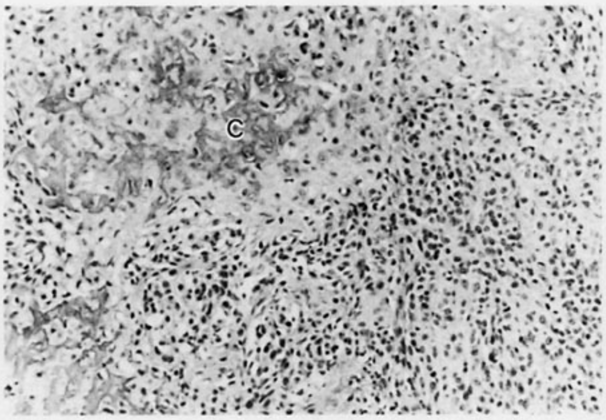


Plate 10
Another area of the subcutaneous osteosarcoma in Plate 9 showing cartilaginous differentiation (C). H&E, 150×

Plate 11
Subcutaneous lesion of uncertain classification in control male rat. Note the fibrous connective tissue with discrete islands showing osteoblast differentation, production of osteoid, and bone formation (arrows).

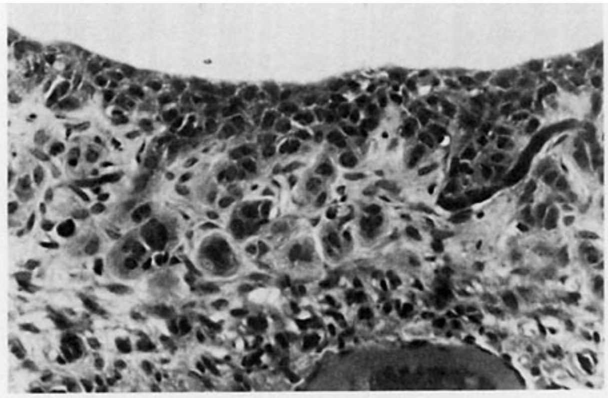


Plate 12
Ameloblastic epithelium in late maturation or early transition zone. Note the thin surface layer of flattened, squamous-like cells and the remnants of the papillary layer below.

MICE

14-Day Studies

Groups of five mice of each sex received 0, 50, 100, 200, 400, or 800 ppm sodium fluoride in deionized water *ad libitum* for 14 consecutive days. Survival and body weights are given in Table 12. All mice survived to scheduled termination, except two high-dose males that died on days 4 and 6. Among the male mice, weight changes were variable, with the high-dose group having a significant decrease in body weight. Among female mice, weight losses occurred only in the high-dose group. The two high-dose males that died began exhibiting signs of toxicity on day 4; they were noted to be thin, with stiff gait and hunched posture. Reduced water consumption was recorded for high-dose males and females. Daily water consumption averaged approximately 30% for high-dose males and 60% for high-dose females in comparison with controls.

No consistent significant gross lesions were noted in any of the surviving mice at scheduled necropsy. The tissues of these animals were not evaluated microscopically.

6-Month Studies

Groups of 8 to 12 mice of each sex were administered 0, 10, 50, 100, 200, 300, or 600 ppm sodium fluoride in deionized water *ad libitum* for 26 weeks. The study design included three control groups: one received deionized water and a semisynthetic, low fluoride diet; the second received sodium chloride-supplemented deionized water and a semisynthetic, low fluoride diet; the third received deionized water and a standard NIH-07 diet. The study design called for ten mice per sex per group; however, on the second day of dosing, one male and five female mice were found to have been missexed, and they were placed with the group of the correct sex at the same dose level.

Survival and body weight data are summarized in Table 13. All but one early death occurred in the high-dose groups: four high-dose males died during weeks 13 and 14; one male mouse in the second highest dose group died during week 19; nine high-dose females died during weeks 8 to 18. All other mice survived to scheduled termination. Body weight gain was depressed in the three highest dose groups for both sexes.

Among the 13 high-dose animals that died before scheduled sacrifice, six were killed because they were moribund. Signs of toxicity (thin appearance, hunched posture, weakness) were observed in only two of these before they became moribund. Mice exposed to the four highest doses of sodium fluoride had chalky white teeth; the lower incisors were more affected than upper incisors, and some teeth in mice in the two highest dose groups were chipped. No other signs of toxicity were observed in any of the animals that died early or that survived to the end of the studies.

Average weekly feed consumption was within 20% of control values for all groups, except high-dose males which consumed only 77% of that consumed by controls. Average weekly water consumption was within approximately 20% of control values for all dosed groups.

At termination of the studies, the fluoride content of bone, plasma, and urine was determined from samples collected from all surviving mice from all groups (except the control group given sodium chloride-supplemented deionized drinking water and a semisynthetic, low fluoride diet). Results are presented in Appendix I (Table I2).

The fluoride content of bone and urine was increased in a dose-related fashion with increasing fluoride concentrations in the drinking water. The fluoride concentration in plasma appeared to increase with the dose of fluoride, but the necessity of pooling samples to obtain sufficient material for analysis prevented performance of meaningful statistical analyses of these data. The fluoride content of urine and bone for control mice fed the standard NIH-07 diet was greater than the values obtained for mice given the semisynthetic diet and drinking water containing 10 ppm sodium fluoride.

A number of histological alterations were identified in the kidney, liver, testes, and/or myocardium of mice dying early or sacrificed while moribund (Table 14). The acute nephrosis in three male and two female mice was characterized by extensive multifocal degeneration and necrosis of the tubular epithelium. The proximal convoluted tubules in the cortex and straight portions of the nephron in the

TABLE 12
Survival and Mean Body Weights of Mice in the 14-Day Drinking Water Studies of Sodium Fluoride

Dose (ppm)	Survival[a]	Mean Body Weights (g) Initial[b]	Final	Change[c]	Final Weight Relative to Controls (%)
Male					
0	5/5	27.8 ± 0.7	31.4 ± 0.2	3.6 ± 0.7	100
50	5/5	26.0 ± 0.8	23.6 ± 1.0**	−2.4 ± 0.7*	75
100	5/5	28.4 ± 0.2	25.6 ± 0.5*	−2.8 ± 0.5*	82
200	5/5	26.6 ± 0.7	30.2 ± 0.8	3.6 ± 0.2	96
400	5/5	26.4 ± 0.7	28.0 ± 0.9	1.6 ± 0.9	89
800	3/5[d]	25.2 ± 0.7*	20.0 ± 2.5**	−6.0 ± 2.1*	64
Female					
0	5/5	21.6 ± 0.4	23.0 ± 0.6	1.4 ± 0.2	100
50	5/5	21.6 ± 0.4	22.8 ± 0.7	1.2 ± 0.6	99
100	5/5	21.8 ± 0.6	23.0 ± 0.6	1.2 ± 0.2	100
200	5/5	21.0 ± 0.3	23.0 ± 0.5	2.0 ± 0.3	100
400	5/5	21.2 ± 0.2	21.6 ± 0.4	0.4 ± 0.4	94
800	5/5	21.6 ± 0.2	19.6 ± 0.5**	−2.0 ± 0.3**	85

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Number surviving/number initially on study
[b] Initial group mean body weight given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Mean body weight change of survivors given as mean ± standard error
[d] Day of death: 4,6

TABLE 13
Survival and Mean Body Weights of Mice in the 6-Month Drinking Water Studies of Sodium Fluoride

Dose (ppm)	Survival[a]	Mean Body Weights (g) Initial[b]	Final	Change[c]	Final Weight Relative to Controls (%)
Male					
Control[d]	9/9	16.9 ± 0.4	40.2 ± 1.0	23.3 ± 1.1	100
Control[e]	10/10	18.6 ± 0.4*	41.6 ± 0.6	23.0 ± 0.7	103
Control[f]	11/11	17.8 ± 0.4	39.2 ± 1.0	21.4 ± 1.0	97
10	9/9	17.3 ± 0.5	43.1 ± 1.5	25.8 ± 1.8	107
50	10/10	18.0 ± 0.6	41.1 ± 1.1	23.1 ± 1.3	102
100	10/10	19.2 ± 0.8	41.5 ± 1.1	22.3 ± 1.3	103
200	10/10	17.9 ± 0.7	36.5 ± 1.2	18.6 ± 1.4*	91
300	7/8[g]	18.8 ± 0.7	38.1 ± 1.1	19.0 ± 1.4*	95
600	5/9[h]	17.4 ± 0.4	32.0 ± 1.6**	14.8 ± 1.9**	80
Female					
Control[d]	11/11	16.9 ± 0.6	30.2 ± 1.4	13.3 ± 1.6	100
Control[e]	10/10	18.6 ± 0.4	31.5 ± 1.0	12.9 ± 1.1	104
Control[f]	9/9	16.6 ± 0.2	28.7 ± 0.9	12.1 ± 0.8	95
10	11/11	17.1 ± 0.4	29.6 ± 1.1	12.5 ± 1.1	98
50	10/10	16.4 ± 0.3	32.2 ± 1.1	15.8 ± 1.2	107
100	10/10	17.2 ± 0.4	30.6 ± 1.5	13.4 ± 1.4	101
200	10/10	17.2 ± 0.4	25.3 ± 0.6**	8.1 ± 0.7*	84
300	12/12	16.9 ± 0.3	26.2 ± 0.8*	9.3 ± 0.7*	87
600	2/11[i]	16.6 ± 0.4	24.5 ± 1.5	9.0 ± 1.0	81

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test.
** $P \leq 0.01$
a Number surviving/number initially on study
b Initial group mean body weight given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
c Mean body weight change of survivors given as mean ± standard error
d Control group receiving semisynthetic, low fluoride diet and deionized water
e Control group receiving semisynthetic, low fluoride diet and sodium chloride-supplemented deionized water
f Control group receiving standard NIH-07 diet and deionized water
g Week of death: 19
h Week of death: 13,14,14,14
i Week of death: 8,8,9,10,15,15,16,16,18

Table 14
Histopathologic Alterations in Mice Dying Before Scheduled Sacrifice in the 6-Month Drinking Water Studies of Sodium Fluoride[a]

Organs and Diagnoses	300 ppm	600 ppm
Male		
Animals initially in study	8	9
Early deaths	1	4
Kidney		
Nephrosis, multifocal	1	2
Liver		
Megalocytosis, multifocal	1	4
Syncytial alteration, multifocal	1	4
Myocardium		
Mineralization, multifocal	1	4
Testis		
Necrosis	1	3
Tubule, degeneration, multifocal		2
Tubule, multinucleated giant cells, multifocal	1	1
Female		
Animals initially in study	12	11
Early deaths	0	9
Kidney		
Nephrosis, multifocal		2
Liver		
Megalocytosis, multifocal		7
Syncytial alteration, multifocal		7
Myocardium		
Degeneration, multifocal		2
Mineralization, multifocal		4

[a] Early deaths occurred only in the 300 ppm and 600 ppm dose groups; these lesions were not observed in mice in these groups that survived to the end of the study.

outer medulla were affected. Nephrosis was likely the principal cause of death in these mice. Multifocal myocardial degeneration was seen in two high-dose female mice, and scattered focal accumulations of mineral were seen in the myocardium of several others. The changes in the liver consisted of widely scattered, individual, enlarged cells with multiple nuclei (megalocytosis and syncytial alteration). Generally, only a few affected cells were observed in the field of view at 200× magnification. Degeneration and/or necrosis of the germinal epithelium in the seminiferous tubules, noted in dosed males, often occurs in debilitated mice or those dying from other toxic lesions and was not considered a direct compound-related effect.

Compound-related effects were observed in the femur and, to a lesser extent, in the tibia of nearly all male and female mice receiving 100 to 600 ppm sodium fluoride and 5/10 males receiving 50 ppm (Table 15). In control mice the circumferential lamellae of the cortical bone were relatively uniform in thickness and the cement lines were regularly spaced. In mice receiving 600 ppm some lamellae appeared thicker and more irregular with cement lines that were less prominent and smooth in contour. The osteoid seams lining some osteons (haversian canals) of the cortical bone were increased in thickness (Plates 13 and 14). These changes were not uniform or diffuse. In mice receiving 50 or 100 ppm only occasional prominent osteoid seams were evident. The spectrum of changes are indicative of altered rates of bone deposition and remodeling.

Paraffin-embedded sagittal sections of the upper incisors and incisive bone were unsatisfactory for critical examination of the teeth. Therefore, the lower incisors were embedded in glycol methacrylate, sectioned, and stained with hematoxylin and eosin. The results of this evaluation are shown in Table 15. The lesions were generally more extensive in the mice receiving 300 or 600 ppm than in mice receiving lower doses. The enamel organ from the affected mice that were examined had focal or multifocal irregularity of the layer of ameloblasts, with projections and folds that sometimes surrounded isolated islands of enamel. In some mice, there was loss of the surface columnar cells and variable loss of cells from the stratum intermedium. The remaining cells were reduced in size and disorganized. These changes collectively were diagnosed as dysplasia by the study pathologist.

Dose Selection Rationale: The primary factor considered in the selection of the sodium fluoride drinking water concentrations for the first 2-year studies in mice was the reduction in weight gain in all groups of mice that received sodium fluoride at concentrations of 200 ppm or higher in the 6-month studies. In addition, 1/20 mice given 300 ppm died with nephrosis. Therefore, the concentrations selected for the first 2-year studies were 0, 10, 30, and 100 ppm. Upon completion of the first 2-year studies in mice (Appendix M), it was determined that the animals could tolerate a higher concentration. Therefore, drinking water concentrations selected for the second 2-year studies in mice were 0, 25, 100, and 175 ppm.

2-Year Studies

Groups of 100 mice of each sex received 0 or 175 ppm sodium fluoride and groups of 70 mice of each sex received 25 or 100 ppm sodium fluoride in deionized water *ad libitum* for up to 103 weeks. Interim sacrifices of ten animals per sex per group occurred at 24 weeks and 66 weeks. An additional group of 50 animals of each sex received deionized water and provided paired (age-matched) controls for early deaths of mice given sodium fluoride.

Body Weights

Group mean body weights and mean body weights relative to control values are presented by week on study in Tables 16 and 17. Growth curves, plotting mean body weights against week on test, are shown in Figure 4. No notable chemical-related effectswere observed; however, the maximum mean body weights achieved (51.4 g for control males; 57.4 g for control females) were markedly higher than the average peak body weights achieved by historical controls (42.5 g for males and 41.7 g for females; see Haseman *et al.*, 1985).

TABLE 15
Incidence of Lesions of Tooth and Bone in Mice in the 6-Month Studies of Sodium Fluoride

Organs and Diagnoses	Control[a]	Control[b]	Control[c]	50 ppm	100 ppm	200 ppm	300 ppm	600 ppm
Male								
Incisor tooth, enamel organ[d]	(2)	(2)	(2)	(4)	(5)	(5)	(5)	(1)
Degeneration[e]	0	0	0	0	1	0	5	1
Femur, cortex	(9)	(10)	(11)	(10)	(10)	(10)	(8)	(9)
Increased osteoid[f]	0	0	0	3	9	7	7	9
Tibia, cortex	(9)	(10)	(11)	(10)	(10)	(10)	(8)	(9)
Increased osteoid	0	0	0	5	9	7	6	4
Female								
Incisor tooth, enamel organ	(1)	(2)	(2)	(4)	(5)	(5)	(3)	(2)
Degeneration[e]	0	1	0	0	0	1	1	2
Femur, cortex	(11)	(10)	(9)	(10)	(10)	(10)	(12)	(11)
Increased osteoid[f]	0	0	0	0	8	6	12	11
Tibia, cortex	(11)	(10)	(9)	(10)	(10)	(10)	(12)	(11)
Increased osteoid	0	0	0	0	8	7	11	6

a Control group received semisynthetic, low-fluoride diet and deionized water.
b Control group received semisynthetic, low-fluoride diet and sodium chloride-supplemented deionized water.
c Control group received standard NIH-07 diet and deionized water.
d The number in parentheses is the number of animals examined microscopically. More than one lesion may occur within the same organ.
e The study pathologist used the term "dysplasia" for this lesion.
f The study pathologist used the term "hypomineralization" for this lesion.

Plate 13
Cortex of femur from a control male mouse. The circumferential lamellae are separated by well-defined cement lines which have a smooth and even contour. Note the remnant of cartilage (arrow). H&E, 150×

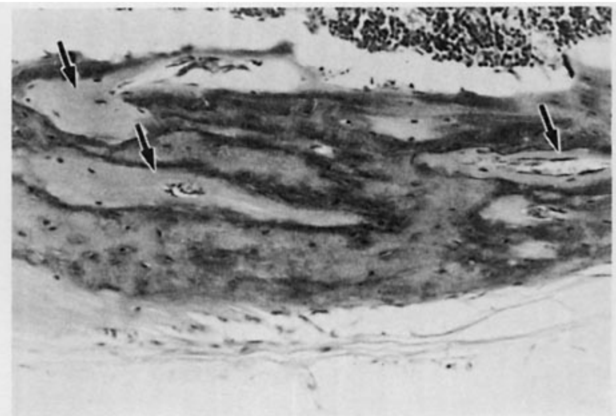


Plate 14
Cortex of femur from a male mouse receiving 600 ppm sodium fluoride for six months. The lamellae are thicker and the cement lines are not as distinct as those in the control. Note the thick osteoid seams surrounding several of the vessels (arrows). H&E, 150×

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

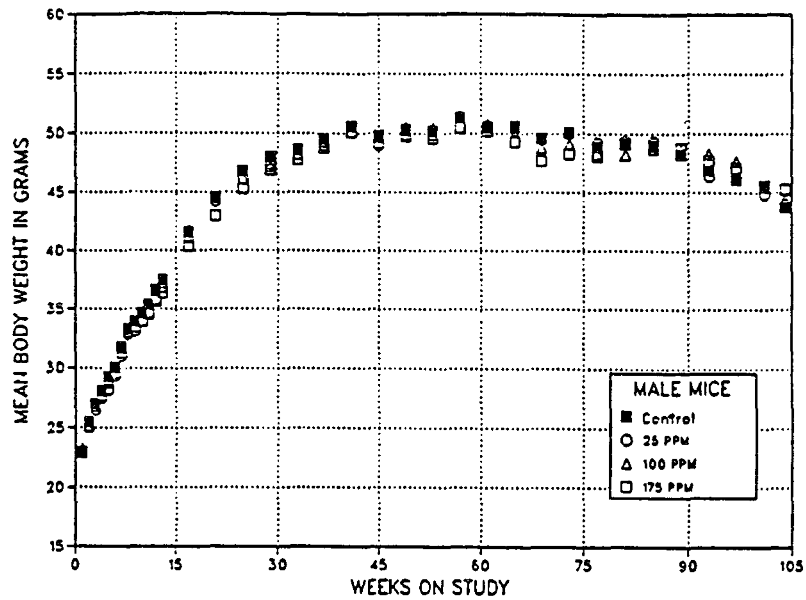
Study Week	Control Av.Wt. (g)	Control No. of Surv.[a]	25 ppm Av.Wt. (g)	25 ppm (%)	25 ppm No. of Surv.[a]	100 ppm Av.Wt. (g)	100 ppm (%)	100 ppm No. of Surv.[a]	175 ppm Av.Wt. (g)	175 ppm (%)	175 ppm No. of Surv.[a]
1	23.1	79	22.7	98.3	50	23.4	101.3	51	22.8	98.7	80
2	25.6	78[b]	24.7	96.5	49[b]	25.0	97.7	51	25.2	98.4	79[b]
3	27.1	79	26.2	96.7	50	27.0	99.6	50	26.6	98.2	80
4	28.2	79	27.1	96.1	49[b]	28.1	99.6	49[b]	27.6	97.9	80
5	29.4	79	27.9	94.9	50	28.9	98.3	50	28.7	97.6	80
6	30.1	79	29.1	96.7	50	30.4	101.0	50	29.4	97.7	80
7	31.8	79	30.8	96.9	50	31.9	100.3	49[b]	31.1	97.8	80
8	33.5	79	32.4	96.7	49[b]	33.5	100.0	50	32.9	98.2	80
9	34.1	79	32.7	95.9	50	34.2	100.3	50	33.4	97.9	79[b]
10	34.8	79	33.5	96.3	50	34.9	100.3	50	33.7	96.8	79[b]
11	35.4	79	34.3	96.9	50	35.7	100.8	50	34.4	97.2	80
12	36.8	79	35.4	96.2	50	36.9	100.3	50	35.5	96.5	80
13	37.7	79	36.4	96.6	50	37.8	100.3	50	36.2	96.0	80
17	41.6	79	40.6	97.6	50	41.9	100.7	50	40.1	96.4	80
21	44.6	79	43.9	98.4	50	44.5	99.8	50	42.8	96.0	80
25	46.8	79	45.8	97.9	50	46.1	98.5	50	45.0	96.2	80
29	48.1	79	47.3	98.3	50	47.3	98.3	50	46.6	96.9	80
33	48.6	79	48.0	98.8	49	48.2	99.2	50	47.6	97.9	80
37	49.6	79	48.7	98.2	49	49.5	99.8	49	48.6	98.0	80
41	50.7	79	49.9	98.4	49	50.9	100.4	49	49.8	98.2	79
45	49.9	79	48.7	97.6	49	49.9	100.0	49	49.0	98.2	79
49	50.3	79	49.7	98.8	49	50.8	101.0	49	49.5	98.4	79
53	50.3	79	49.7	98.8	49	50.7	100.8	49	49.5	98.4	79
57	51.4	79	51.2	99.6	49	51.4	100.0	49	50.4	98.1	78
61	50.5	78	50.5	100.0	49	50.8	100.6	49	50.1	99.2	78
65	50.7	78	50.1	98.8	49	50.4	99.4	49	49.3	97.2	78
69	49.6	78	49.6	100.0	49	48.8	98.4	49	47.7	96.2	78
73	50.1	77	50.0	99.8	49	49.1	98.0	48	48.3	96.4	77
77	48.9	77	49.2	100.6	49	48.3	98.8	47	48.1	98.4	75
81	49.2	77	49.4	100.4	48	48.2	98.0	47	49.1	99.8	75
85	49.0	74	49.3	100.6	48	48.7	99.4	45	48.9	99.8	75
89	48.2	74	48.8	101.2	47	48.7	101.0	43	48.8	101.2	73
93	46.9	70	46.4	98.9	45	48.3	103.0	41	47.7	101.7	72
97	46.1	68	46.1	100.0	43	47.7	103.5	39	47.1	102.2	72
101	45.5	62	44.9	98.7	42	45.6	100.2	38	45.6	100.2	69
104	43.8	58	44.0	100.5	40	44.5	101.6	37	45.3	103.4	65
Terminal sacrifice		58			39			37			65
Mean for weeks											
1-13	31.4		30.3	96.5		31.4	100.0		30.6	97.6	
17-52	47.8		47.0	98.2		47.7	99.7		46.6	97.4	
53-104	48.6		48.5	99.9		48.7	100.2		48.3	99.4	

[a] Number of animals weighed. At terminal sacrifice, number of animals surviving on first day of terminal sacrifice.
[b] The number of animals weighed for this week is less than the number of animals surviving.

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

Study Week	Control		25 ppm			100 ppm			175 ppm		
	Av.Wt. (g)	No. of Surv.[a]	Av.Wt. (g)	(%)	No. of Surv.[a]	Av.Wt. (g)	(%)	No. of Surv.[a]	Av.Wt. (g)	(%)	No. of Surv.[a]
1	19.5	80	19.1	97.9	52	19.0	97.4	50	19.2	98.5	80
2	20.7	77[b]	20.2	97.6	51[b]	20.2	97.6	49[b]	20.5	99.0	78[b]
3	22.1	80	22.3	100.9	52	22.2	100.5	50	22.4	101.4	80
4	23.2	80	23.2	100.0	52	22.8	98.3	50	23.0	99.1	80
5	23.8	80	23.7	99.6	52	23.3	97.9	50	23.4	98.3	80
6	24.4	80	24.4	100.0	52	23.9	98.0	50	24.3	99.6	80
7	25.9	80	25.8	99.6	52	25.4	98.1	50	25.7	99.2	80
8	26.7	79[b]	26.6	99.6	51[b]	25.9	97.0	50	26.5	99.3	80
9	27.5	80	27.2	98.9	52	26.6	96.7	50	27.2	98.9	79[b]
10	29.0	80	28.4	97.9	52	28.1	96.9	50	28.5	98.3	80
11	29.7	80	28.8	97.0	52	29.0	97.6	50	29.2	98.3	80
12	30.3	79[b]	29.7	98.0	51[b]	29.6	97.7	49[b]	29.5	97.4	78[b]
13	31.7	80	31.2	98.4	52	31.0	97.8	50	30.7	96.8	80
17	36.0	80	34.9	96.9	52	34.5	95.8	50	34.7	96.4	80
21	39.6	80	38.4	97.0	52	38.3	96.7	50	38.0	96.0	79
25	42.5	80	42.2	99.3	52	41.4	97.4	50	40.6	95.5	79
29	44.2	80	44.0	99.5	51	43.4	98.2	50	42.3	95.7	78
33	45.3	80	45.8	101.1	51	44.9	99.1	50	43.9	96.9	78
37	48.2	80	47.9	99.4	51	47.0	97.5	50	46.4	96.3	77
41	49.5	80	49.7	100.4	51	48.6	98.2	50	48.5	98.0	76
45	50.4	80	50.1	99.4	51	49.2	97.6	50	48.8	96.8	74
49	52.9	80	52.8	99.8	51	52.6	99.4	49	51.1	96.6	74
53	54.0	79	54.0	100.0	51	53.1	98.3	49	52.9	98.0	72
57	55.2	79	55.6	100.7	51	54.9	99.5	48	54.8	99.3	72
61	55.6	78	56.3	101.3	50	55.3	99.5	47	55.2	99.3	72
65	56.1	78	56.2	100.2	50	55.1	98.2	47	55.0	98.0	71
69	55.5	78	56.0	100.9	50	54.8	98.7	46	54.2	97.7	70
73	55.7	77	55.7	100.0	50	54.4	97.7	46	54.1	97.1	69
77	55.5	75	55.6	100.2	48	54.5	98.2	45	53.7	96.8	69
81	56.8	74	56.3	99.1	48	55.6	97.9	44	54.9	96.7	69
85	57.4	72	57.3	99.8	46	55.7	97.0	43	55.7	97.0	64
89	54.4	69	53.6	98.5	45	53.0	97.4	41	53.6	98.5	61
93	53.2	66	51.6	97.0	43	52.0	97.7	40	52.3	98.3	60
97	54.7	61	51.9	94.9	40	52.3	95.6	38	51.0	93.2	59
101	52.7	59	51.5	97.7	38	51.1	97.0	36	49.2	93.4	56
104	50.6	53	49.3	97.4	38	49.7	98.2	34	48.4	95.7	52
Terminal sacrifice		53			38			34			52
Mean for weeks											
1-13	25.7		25.4	98.9		25.2	97.8		25.4	98.8	
17-52	45.4		45.1	99.2		44.4	97.8		43.8	96.5	
53-104	54.8		54.4	99.1		53.7	97.9		53.2	97.1	

[a] Number of animals weighed. At terminal sacrifice, number of animals surviving on first day of terminal sacrifice.
[b] The number of animals weighed for this week is less than the number of animals surviving.



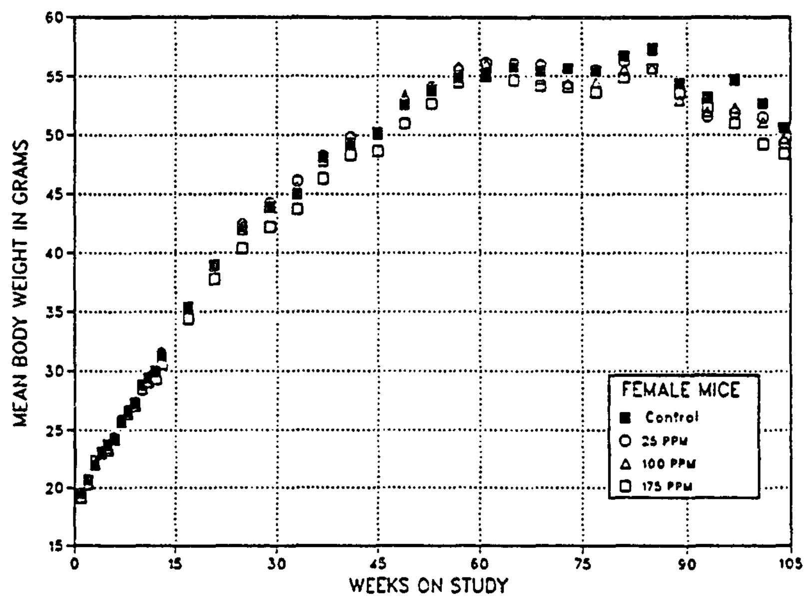


Figure 4
Growth Curves for Male and Female Mice Administered Sodium Fluoride in Drinking Water for 2 Years

Feed, Water, and Compound Consumption

Average daily feed consumption for control and treated groups ranged from 4.9 to 5.2 g for males and 5.4 to 5.8 g for females (data on file at NIEHS). Administration of sodium fluoride in drinking water at the concentrations used in these studies had no effect on feed consumption.

Deionized drinking water was the vehicle for administering sodium fluoride to mice. Average daily water consumption for control and treated groups ranged from 4.1 to 4.2 g for males and 4.4 to 4.6 g for females (Appendix L, Tables L3 and L4). Administration of sodium fluoride in drinking water at the concentrations used in these studies had no effect on water consumption. Estimated daily ingestion of the chemical throughout the studies is presented in Appendix L (Tables L3 and L4). When averaged over the 2-year studies, the daily amounts of sodium fluoride ingested were 2.4 mg/kg for low-dose males, 9.6 mg/kg for mid-dose males, 16.7 mg/kg for high-dose males, 2.8 mg/kg for low-dose females, 11.3 mg/kg for mid-dose females, and 18.8 mg/kg for high-dose females.

Clinical Signs

While numerous clinical signs were recorded over the course of these studies, most occurred with such low frequency or with such similarity across dosed and control groups that they were not considered related to treatment. The exception was white discoloration of the teeth at the higher exposure levels (Table 18). This abnormality occurred earlier in the high-dose groups (day 74), later in mice receiving lower concentrations (from day 81 to 200), and much later in control animals (day 508).

TABLE 18
Tooth Abnormalities (Gross Observations) in Mice in the 2-Year Drinking Water Studies of Sodium Fluoride

Observation[a]	Control	25 ppm	100 ppm	175 ppm
Male				
Attrition[b]	11 (19%)	12 (31%)	9 (24%)	18 (28%)
Discoloration[c]	27 (27%)	27 (39%)	56 (80%)	100 (100%)
Mottling[b]	16 (26%)	25 (64%)	32 (86%)	62 (95%)
Female				
Attrition[b]	0 (0%)	0 (0%)	0 (0%)	4 (8%)
Discoloration[c]	19 (19%)	30 (43%)	59 (84%)	99 (100%)
Mottling[b]	8 (15%)	17 (45%)	32 (94%)	51 (98%)

[a] Discoloration designates an overall effect, while mottling indicates variegated discoloration. The terms are not mutually exclusive.
[b] The incidences for this observation are for the lower incisors of animals observed at week 104 only (males: n = 58, 40, 37, 65; females: 53, 38, 34, 52).
[c] The incidences for this observation include interim and terminal sacrifice animals (males: n = 99, 70, 70, 100; females: 100, 70, 70, 99).

Supplemental Studies

Hematology and clinical chemistry data were collected for all animals sacrificed at the 24-week and 66-week interim sacrifices. Bone fluoride concentrations were measured for all animals sacrificed at 24 weeks and 66 weeks and for selected animals at the termination of the studies. Results of these studies are presented in Appendix I and in Figure 5.

There were no biologically significant differences in hematologic parameters or in serum concentrations of calcium or phosphorous in dosed versus control male or female mice at the 24-week or 66-week interim evaluations (Tables I9 and I10). Serum alkaline phosphatase activity was increased mildly at 24 weeks and moderately at 66 weeks in high-dose female mice (Tables I9 and I10). For all treated groups, fluoride concentrations in bone were dose and age related, and were significantly increased over control values for all evaluation periods (Table I4 and Figure 5).

Survival

Estimates of the probabilities of survival of male and female mice administered sodium fluoride in drinking water at the doses used in these studies and those of the vehicle controls are illustrated in Kaplan-Meier curves (Figure 6). Overall survival information is given in Table 19. No significant chemical-related effects on survival were observed.

Organ weights for the brain, right kidney, left kidney, and liver were recorded for mice sacrificed at 24 weeks and 66 weeks. Group mean organ weights and organ-weight-to-body-weight ratios are presented in Appendix G. No changes in organ weights were observed that were attributed to sodium fluoride administration.

Pathology and Statistical Analyses of Results

Summaries of the incidence of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidence for the neoplasms identified by the Pathology Working Group are presented in Appendix C for male mice and Appendix D for female mice. Summaries of the incidence of neoplasms and nonneoplastic lesions in male and female mice at the interim evaluations are presented in Appendix E for the 24-week sacrifice and in Appendix F for the 66-week sacrifice. Findings of note were in the hematopoietic system, harderian gland, lung, pars distalis of the pituitary gland, and liver.

Hematopoietic System: The incidence of malignant lymphoma (all types) and malignant lymphoma and histiocytic sarcoma combined were marginally increased in female mice receiving 175 ppm sodium fluoride (Table 20). Histiocytic sarcoma is a term used synonymously with malignant lymphoma, histiocytic type, in previous NTP studies. The precise origin of this neoplasm is uncertain, but both terms suggest a histiocytic origin. Although the incidence in the high-dose group was increased relative to controls, malignant lymphoma has occurred with a variable incidence rate in NTP historical controls. Moreover, the incidence in the high-dose group is similar to the mean rate and well within the range of historical untreated controls at the study laboratory (145/419, 34.6%, range 18%-48%) and all NTP laboratories combined (639/2209, 31.4%, range 10%-74%). Therefore, the marginal increase in malignant lymphomas in mice was not considered related to sodium fluoride.

Liver: The incidences of hepatocellular neoplasms in all groups of dosed and control male and female mice were higher than those of historical controls in previous NTP studies (Table 21, Appendixes C4, D4b). Five liver neoplasms in dosed male mice and four in dosed female mice were diagnosed by the laboratory pathologist as hepatocholangiocarcinoma. Although one of these and one other lesion identified as an hepatocholangiocarcinoma in a paired control female (Table 21) clearly demonstrated areas of biliary differentiation, the others contained well-defined populations of cells which more closely resembled embryonal liver cells than biliary cells. The PWG thought that the latter neoplasms were more appropriately diagnosed as hepatoblastoma. In both types of neoplasms the biliary or embryonal cell populations represent phenotypic variants within a primary liver neoplasm that is otherwise characteristic of a hepatocellular carcinoma. Malignant neoplasms commonly contain a heterogenous population of cells, some of which may be relatively undifferentiated and therefore resemble stem cells or which demonstrate divergent differentiation.

Although hepatocellular neoplasms with the embryonal cell type (i.e. hepatoblastomas) occur rarely (historical control incidences of 0/2197 in males and 1/2202 in females) and occurred more frequently in mice receiving sodium fluoride, the overall incidences of primary hepatocellular neoplasms in males were similar or somewhat decreased among dosed groups compared to controls. Thus, the slight numerical increase in hepatoblastomas was not considered biologically significant.

Negative Trends: Among male mice, there was a dose-related decrease in harderian gland adenomas (7/79; 2/50; 0/51; 1/80); the incidence in the control group was nearly threefold higher than is typically seen in historical control groups (3.2%) (Haseman *et al.*, 1984). In female mice, a negative dose-related trend was seen in adenomas of the pituitary gland (pars distalis, 25/80; 7/51; 8/50; 13/79). Neither of these decreases was considered to be related to chemical administration.

Teeth: Dentine dysplasia occurred in both dosed and control groups of male and female mice (Appendixes C5 and D5). The incidence of this lesion was significantly greater in high-dose than in control male mice (62/79; 44/50; 43/51; 73/80; P=0.016).

Other lesions were incidental or part of spontaneous disease complexes of mice. There was no alteration in the incidence or severity of these lesions in the treated versus control animals, and they were histopathologically typical of those commonly seen in this strain of laboratory mouse.

GENETIC TOXICOLOGY

Tabular results of all assays are presented in Appendix H. Sodium fluoride did not induce gene mutations in *Salmonella typhimurium* when studied with a preincubation protocol at doses of 100 to 10,000 μg/plate in strains TA98, TA100, TA1535, and TA1537; all strains were tested with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Haworth *et al.*, 1983).

Sodium fluoride was studied at two laboratories for induction of trifluorothymidine resistance in mouse L5178Y lymphoma cells. In the first laboratory, sodium fluoride was positive both with and without Aroclor 1254-induced male Fischer 344 rat liver S9; the effective doses, with and without S9, ranged from 300 to 600 μg/mL (Caspary *et al.*, 1987). In the second laboratory, sodium fluoride was tested without S9 only, and test results were positive in the first trial at 62.5, 125, and 1,000 μg/mL and in the second trial at 800 and 900 μg/mL. The mutant colonies obtained after sodium fluoride treatment of L5178Y cells were primarily small colonies, suggesting that chromosomal abnormalities may be involved.

Sodium fluoride was studied for the induction of cytogenetic effects in Chinese hamster ovary (CHO) cells in two laboratories with different results. Sister chromatid exchanges (SCE) were induced in one laboratory at doses of 66.7 and 75 μg/mL without S9 and at doses greater than 1,200 μg/mL with S9. In all but one case, the positive results were seen following delayed harvest to allow cells, the division time of which was inhibited by the higher doses of sodium fluoride, to progress to the second metaphase division to the point where the cells could be scored. The laboratory reporting negative SCE results did not employ extended harvest times and was able to test up to only 50 μg/mL sodium fluoride without S9 and 500 μg/mL with S9.

In the tests for the induction of chromosomal aberrations (Abs), positive results were reported in one laboratory at doses of 400 μg/mL sodium fluoride and greater without S9. The second laboratory reported negative results without S9, but the highest dose tested was 200 μg/mL. Neither laboratory showed a reproducible increase in Abs in the presence of S9.

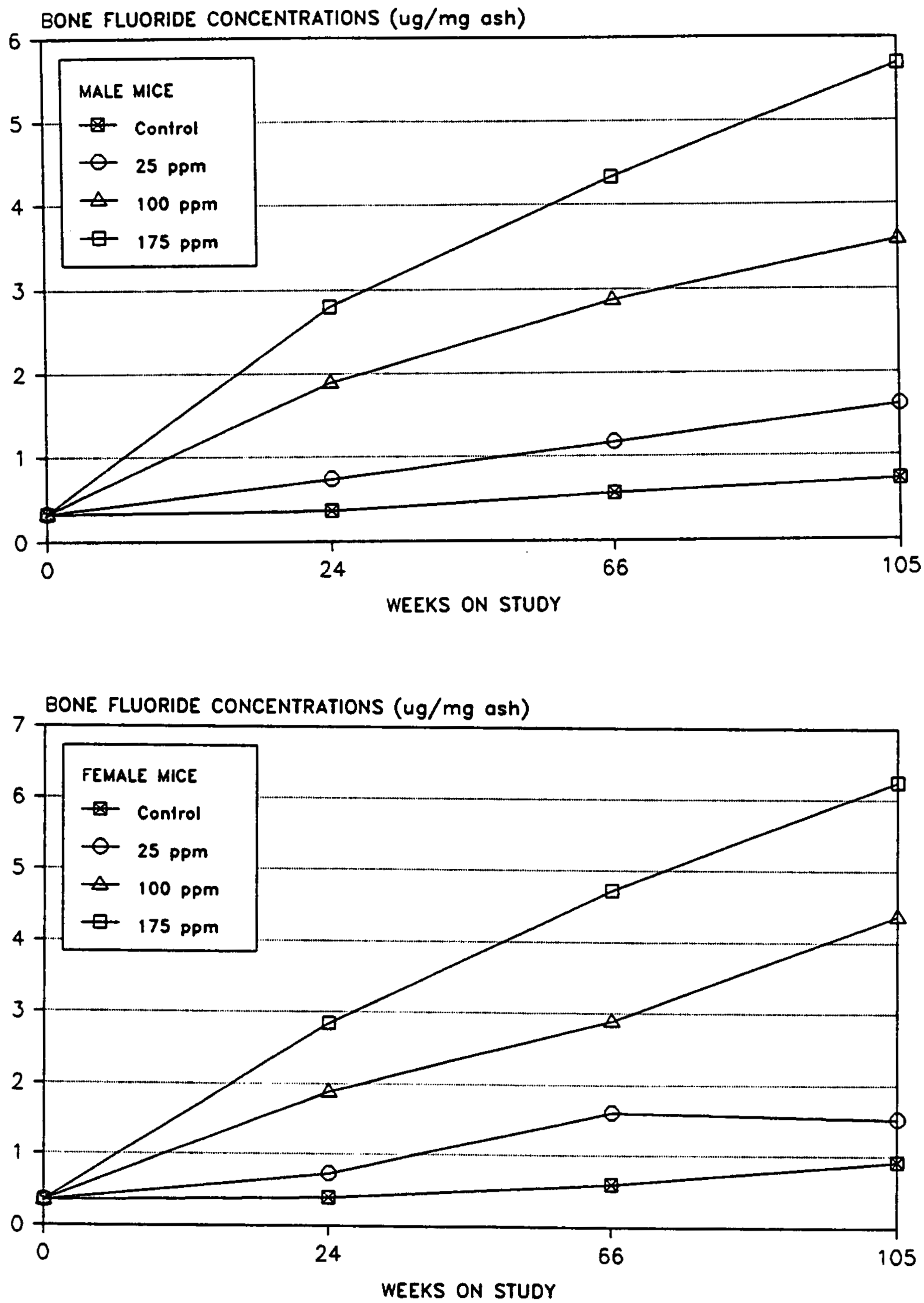
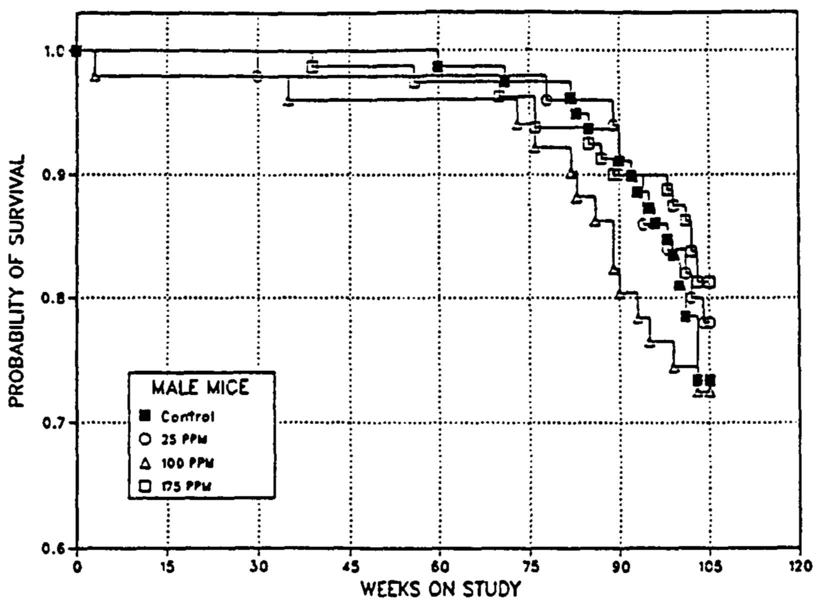


Figure 5
Bone Fluoride Content in Mice in the 2-Year Drinking Water Studies with Sodium Fluoride



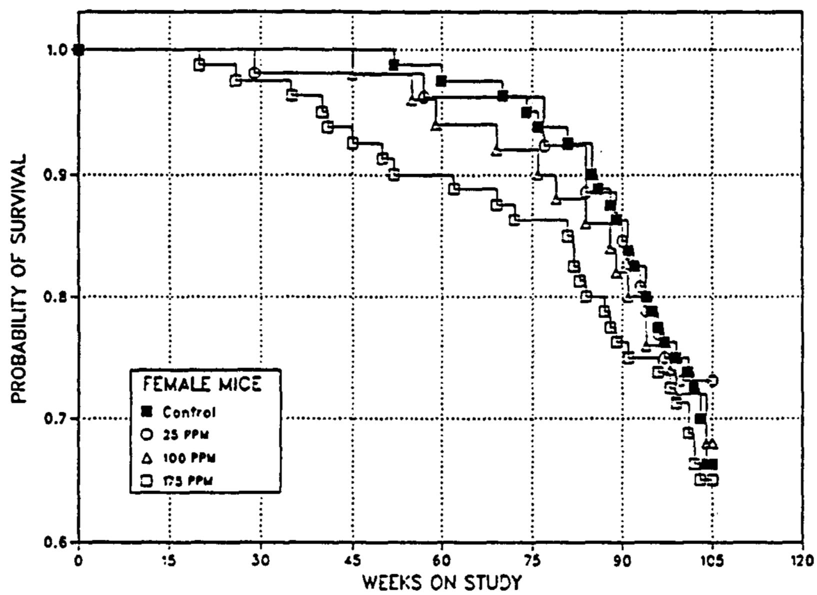


Figure 6
Kaplan-Meier Survival Curves for Male and Female Mice Administered Sodium Fluoride in Drinking Water for 2 Years

TABLE 19
Survival of Mice in the 2-Year Drinking Water Studies of Sodium Fluoride

	Control	Paired Control[a]	25 ppm	100 ppm	175 ppm
Male					
Animals initially in study	99	50	70	70	100
Natural deaths	16	3	8	6	11
Moribund kills	5	9	3	8	4
Age-matched kills	0	20	0	0	0
Interim kills	20	0	20	19	20
Animals surviving to study termination	58[b]	18	39	37	65
Percent survival at end of study[c]	73	–[d]	78	73	81
Mean survival (days)[e]	707	–[d]	704	678	705
Survival P values[f]	0.437N	–[d]	0.717N	0.892	0.341N
Female					
Animals initially in study	100	50	70	70	99
Natural deaths	13	7	5	7	16
Moribund kills	14	6	9	9	12
Age-matched kills	0	29	0	0	0
Interim kills	20	0	18	20	19
Animals surviving to study termination	53	8	38	34[b]	52[g]
Percent survival at end of study[c]	66	–[d]	73	68	65
Mean survival (days)[e]	693	–[d]	688	681	655
Survival P values[f]	0.506	–[d]	0.607N	1.000N	0.754

[a] During every study week that one or more animals from any group receiving sodium fluoride was found dead or killed in a moribund condition, one animal of the same species and sex from this group was chosen at random, killed, and necropsied.
[b] Two of these animals were found dead after the start of the terminal sacrifice period.
[c] Kaplan-Meier determinations. Survival rates adjusted for interim kills.
[d] Not determined
[e] Mean of all deaths (uncensored, censored, terminal kill)
[f] The entry under the "control" column is the trend test (Tarone, 1975) result. Subsequent entries are the results of pairwise tests (Cox, 1972). Negative trends are indicated by N.
[g] One of these animals was found dead after the start of the terminal sacrifice period.

TABLE 20
Malignant Lymphomas and Histiocytic Sarcomas in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride

	Control	25 ppm	100 ppm	175 ppm
Malignant Lymphoma (Lymphocytic)				
Overall rates[a]	2/80 (3%)	0/52 (0%)	1/50 (2%)	5/80 (6%)
Malignant Lymphoma (Mixed)				
Overall rates	4/80 (5%)	5/52 (10%)	7/50 (14%)	8/80 (10%)
Malignant Lymphoma (Undifferentiated Cell Type)				
Overall rates	5/80 (6%)	0/52 (0%)	3/50 (6%)	6/80 (8%)
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)[b]				
Overall rates	11/80 (14%)	5/52 (10%)	11/50 (22%)	19/80 (24%)
Adjusted rates[c]	19.3%	12.4%	30.0%	32.6%
Terminal rates[d]	8/53 (15%)	4/38 (11%)	9/34 (26%)	14/52 (27%)
First incidence (days)	652	587	379	241
Life table tests[e]	P=0.012	P=0.282N	P=0.181	P=0.069
Logistic regression tests[e]	P=0.010	P=0.333N	P=0.145	P=0.051
All Organs: Histiocytic Sarcoma				
Overall rates	5/80 (6%)	3/52 (6%)	2/50 (4%)	5/80 (6%)
Adjusted rates	7.9%	7.2%	4.9%	8.0%
Terminal rates	2/53 (4%)	2/38 (5%)	0/34 (0%)	1/52 (2%)
First incidence (days)	562	584	587	584
Life table tests	P=0.515	P=0.577N	P=0.452N	P=0.577
Logistic regression tests	P=0.481N	P=0.590N	P=0.405N	P=0.580N
All Organs: Malignant Lymphoma or Histiocytic Sarcoma				
Overall rates	16/80 (20%)	8/52 (15%)	13/50 (26%)	24/80 (30%)
Adjusted rates	26.2%	19.3%	33.4%	38.4%
Terminal rates	10/53 (19%)	6/38 (16%)	9/34 (26%)	15/52 (29%)
First incidence (days)	562	584	379	241
Life table tests	P=0.022	P=0.282N	P=0.301	P=0.089
Logistic regression tests	P=0.023	P=0.335N	P=0.267	P=0.077

[a] Number of tumor-bearing animals/number of animals necropsied
[b] 2-year historical incidence for untreated control groups at study laboratory (mean): 145/419 (34.6%); historical incidence for untreated control groups in NTP studies (mean ± SD): 693/2209 (31.4% ± 14.0%)
[c] Kaplan-Meier estimated tumor incidence at the end of the study 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 dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

TABLE 21
Hepatocellular Neoplasms in Male and Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride

	Control	25 ppm	100 ppm	175 ppm
Male				
Hepatocellular Adenoma[a]				
Overall rates[b]	50/79 (63%)	34/50 (68%)	30/51 (59%)	53/80 (66%)
Hepatocellular Carcinoma[c]				
Overall rates	25/79 (32%)	15/50 (30%)	13/51 (25%)	15/80 (19%)
Hepatoblastoma				
Overall rates	0/79 (0%)	1/50 (2%)	1/51 (2%)	3/80 (4%)
Hepatocellular Neoplasms (Adenoma, Carcinoma, Hepatoblastoma)				
Overall rates	62/79 (78%)	39/50 (78%)	37/51 (73%)	61/80 (76%)
Adjusted rates[d]	86.0%	82.9%	84.0%	82.4%
Terminal rates[e]	48/58 (83%)	31/39 (79%)	30/37 (81%)	52/65 (80%)
First incidence (days)	420	619	579	529
Logistic regression tests[f]	P=0.410N	P=0.581N	P=0.496N	P=0.470N
Female				
Hepatocellular Adenoma[g]				
Overall rates	49/80 (61%)	28/52 (54%)	23/50 (46%)	34/80 (43%)
Hepatocellular Carcinoma[h]				
Overall rates	14/80 (18%)	11/52 (21%)	8/50 (16%)	12/80 (15%)
Hepatoblastoma				
Overall rates	0/80 (0%)	1/52 (2%)	0/50 (0%)	2/80 (3%)
Hepatocholangiocarcinoma				
Overall rates	0/80 (0%)[i]	0/52 (0%)	0/50 (0%)	1/80 (1%)
Hepatocellular Neoplasms (Adenoma, Carcinoma, Hepatoblastoma, Hepatocholangiocarcinoma)				
Overall rates	55/80 (69%)	33/52 (63%)	26/50 (52%)	43/80 (54%)
Adjusted rates	84.4%	78.5%	64.8%	72.6%
Terminal rates	43/53 (81%)	29/38 (76%)	20/34 (59%)	36/52 (69%)
First incidence (days)	358	587	527	361
Logistic regression tests	P=0.077N	P=0.339N	P=0.056N	P=0.116N

TABLE 21
Hepatocellular Neoplasms in Male and Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

[a] 2-year historical incidence for untreated control groups at study laboratory (mean): 70/414 (16.9%); historical incidence for untreated control groups in NTP studies (mean ± SD): 323/2197 (14.7% ± 7.9%)
[b] Incidence expressed as number of animals with lesion/total number of animals necropsied
[c] 2-year historical incidence for untreated control groups at study laboratory (mean): 72/414 (17.4%); historical incidence for untreated control groups in NTP studies (mean ± SD): 358/2197 (16.3% ± 6.9%)
[d] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal.
[g] 2-year historical incidence for untreated control groups at study laboratory (mean): 23/417 (5.5%); historical incidence for untreated control groups in NTP studies (mean ± SD): 131/2202 (5.9% ± 3.7%)
[h] 2-year historical incidence for untreated control groups at study laboratory (mean): 11/417 (2.6%); historical incidence for untreated control groups in NTP studies (mean ± SD): 78/2202 (3.5% ± 2.4%)
[i] A hepatocholangiocarcinoma occurred in 1/42 paired control female mice.

DISCUSSION

Sodium fluoride administered in drinking water was evaluated for toxicity and carcinogenicity in F344/N rats and B6C3F$_1$ mice in 14-day, 6-month, and 2-year studies. Two types of diet were used in these studies; both contained less fluoride than is typically found in laboratory rodent diets. The diet used in the 14-day and 6-month studies was semisynthetic and contained less than 2.1 ppm fluoride in the 6-month studies. The diet used in the 2-year studies was the NIH-07 diet, formulated with selected lots of fish meal and calcium diphosphate containing less than the usual amounts of fluoride such that the average fluoride content was 7.9 ppm. Estimates of the fraction of dietary fluoride that was available from the NIH-07 diet ranged from 38% to 64% during the studies (Appendix I). This is somewhat higher than the estimate of 37% for the bioavailability of fluoride in bone meal ingested by humans (Largent, 1960).

Two-year studies in rats and mice were also conducted with the same low fluoride, semisynthetic diet that was used in the 6-month studies. However, nutritional deficiencies were discovered in the low fluoride, semisynthetic diet during the conduct of the studies, and these first 2-year studies were considered inadequate for the assessment of the toxicity and carcinogenicity of sodium fluoride. These first 2-year studies are discussed in Appendix M.

Toxicity Studies

In the 14-day studies, all male and female rats and several male mice given water containing 800 ppm died (concentrations are expressed as sodium fluoride; fluoride ion is about 45% of the sodium salt on a weight basis); 1/5 female rats given 400 ppm also died. No gross lesions were observed at necropsy; tissues were not examined microscopically.

In the 6-month studies in mice, 4/9 males and 9/11 females receiving 600 ppm sodium fluoride and 1/8 males receiving 300 ppm died. No rats given water containing as much as 300 ppm sodium fluoride died. Male and female rats given 300 ppm and mice given 200 to 600 ppm gained notably less weight than did controls. Weight gains of control rats and mice maintained on the low fluoride, semisynthetic diet were greater than those of control animals fed the NIH-07 diet, suggesting that the diet was sufficient to support growth at normal rates.

The fluoride content of urine and bone increased with the concentration of sodium fluoride in the drinking water in both sexes of rats and mice. Bone fluoride concentrations were as high as 14.8 μg/mg (14,800 ppm) of ashed bone in male mice receiving 600 ppm sodium fluoride in the water. The bone fluoride content found in mice was somewhat greater than that found in rats given comparable sodium fluoride concentrations in the water. This may be partly due to a greater water intake on a body weight basis by mice than by rats, resulting in higher exposures. Plasma fluoride concentrations in dosed rats appeared clearly elevated over that of controls only in the groups receiving water containing 300 ppm sodium fluoride. The plasma fluoride levels of mice showed a better dose relationship and appeared increased in groups receiving water containing 50 ppm of sodium fluoride or higher concentrations.

Clinical signs attributed to sodium fluoride administration were limited to changes in the appearance of the teeth in rats given water containing 300 ppm and in mice given water containing 100 to 600 ppm; the teeth had a chalky white appearance instead of the dull yellow color seen in normal rats and mice. The teeth of affected rats also showed unusual wear patterns. Increased wear of molars of rats of the Sabra strain following ingestion of fluoridated drinking water (25 ppm) for 40 days was reported by Markitziu *et al.* (1985).

Histopathologic findings for rats and mice are consistent with previously recognized toxic effects of sodium fluoride in laboratory rodents. Rats receiving 100 or 300 ppm sodium fluoride in the drinking water for 6 months had slight hyperplasia of the mucosal epithelium of the glandular stomach with individual cell necrosis and hyperplasia of the stratified epithelium of the forestomach near the limiting ridge. These lesions are consistent with low-grade cytotoxicity and increased cell turnover, perhaps due to the formation of hydrogen fluoride at the low pH in the gut (IPCS, 1984). However, the lesions in the gastric mucosa occurred only in rats, despite the fact that mice were given up to twice the concentration given to rats. Hemorrhagic gastroenteritis has been reported in acute oral fluoride toxicity in humans, and epithelial cell degeneration and other changes in the duodenal mucosa of rabbits receiving 10 mg/kg sodium fluoride per day for 24 months have been described (Susheela and Das, 1988).

Mice that died during the 6-month studies had microscopic lesions in the kidney, myocardium, liver, and/or testis. The acute nephrosis observed in the kidneys was considered a likely cause of death. These findings were similar to the kidney injury attributed to the administration of sodium fluoride in rats of the Rochester strain (Taylor *et al.*, 1961). However, the F344 rats in the current 6-month studies did not develop kidney lesions, perhaps due to strain differences. The myocardial degeneration and accumulation of mineral in degenerate myofibers are also indicative of cytotoxicity. Whether the lesions in the germinal epithelium of the testis were due to a direct effect of fluoride on the cells or secondary to debilitation is unknown, but they are commonly seen in mice dying from any one of a variety of unrelated causes.

The lesions of the incisor teeth were similar in rats and mice in these 6-month studies and were consistent with the findings of others (Yaeger, 1966; Walton and Eisenmann, 1974). These changes were observed in the incisor teeth, which are continuously growing and erupting and thus retain a functionally active enamel ("odontogenic") organ. Unlike the incisor teeth, the molars of rodents do not continuously grow and the enamel organ regresses. Fluoride seems to exert its primary effects on the secretory and maturation stages of the ameloblasts, resulting in an increased organic content and decreased mineral content of the dental enamel (Denbesten *et al.*, 1985; Nordlund *et al.*, 1986).

Lesions were observed in the femur and tibia of mice receiving sodium fluoride for 6 months in the current studies, but not in rats. However, more sensitive morphometric techniques might have demonstrated changes in the bones of rats. The lesions observed in mice are consistent with the findings of others and are indicative of altered rates of bone deposition and remodeling. The effects of fluoride on the bone have been studied in a variety of species of varying ages. Baylink *et al.* (1970) previously demonstrated increases in periosteal matrix and bone formation, an inhibition of mineralization at the periosteum, and an increase in endosteal bone resorption in young Sprague-Dawley rats receiving as little as 100 to 125 ppm fluoride in the drinking water for periods as short as 2 weeks. In contrast, Marie and Hott (1986) demonstrated rapid stimulation of bone formation without detectable change in resorption in C57BL/6J mice receiving 4 mg/L sodium fluoride in the drinking water for 4 weeks.

Dose Selection for the 2-Year Studies

The sodium fluoride drinking water concentrations selected for the first 2-year studies using the low fluoride, semisynthetic diet were 0, 10, 30, and 100 ppm for both sexes of rats and mice. Higher concentrations were not chosen based on the decreased body weight gain of rats receiving 300 ppm and of mice receiving 200 to 600 ppm in the 6-month studies, and because of the severity of gastric lesions seen in rats at the 300 ppm dose level. Histopathologic examinations were performed on all early death animals and on a portion of the animals that survived to the end of the first 2-year studies (with the low fluoride, semisynthetic diet) to assess the cumulative toxic effects of sodium fluoride at these concentrations. The results of this evaluation revealed no significant toxic effects that could be attributed to sodium fluoride administration, suggesting that higher doses could be tolerated by both sexes of rats and mice. Therefore, concentrations selected for the second 2-year studies were 0, 25, 100, and 175 ppm sodium fluoride (equivalent to 0, 11, 45, and 79 ppm fluoride ion). Because of the nutrition problems encountered with the use of the semisynthetic diet during the first 2-year studies, the second set of studies were performed with the low fluoride NIH-07 diet. The NIH-07 diet is customarily used in NTP studies.

In-Life Observations in the 2-Year Studies

During the 2-year studies using the low fluoride NIH-07 diet, survival and weight gains of all dosed and control rats and mice were similar. The peak weights achieved by rats were similar to those typically observed in other NTP studies, but the weights of dosed and control mice were greater than historical control average weights. No specific reason for this increased weight gain in mice was determined, but this is one of the first studies completed in which mice were housed singly rather than in groups and factors associated with this change may be involved in the higher weight gains. Food and water consumption did not differ between dosed and control rats or mice. The average daily dose of sodium fluoride consumed by the dosed animals ranged from 1.3 to 8.6 mg/kg for male rats; 1.3 to 9.5 mg/kg for female rats; 2.4 to 16.7 mg/kg for male mice; and 2.8 to 18.8 mg/kg for female mice. Actual doses achieved throughout the studies varied from these average figures because of normal changes in the pattern of water consumption as a function of animal age and body weight (Appendix L). The highest doses were achieved early in the study when body (and skeletal) growth is at its peak. The average amount of fluoride ion, rather than sodium fluoride, consumed through the water by the dosed animals ranged from 0.6 to 8.5 mg/kg per day. The estimated total fluoride intake from feed and from dosed water for dosed and control animals is given in Table 22. Also given in Table 22 are estimates of the average fluoride intake (primarily from the feed) by historical control groups of animals that have been maintained on the standard NIH-07 diet, which has not been closely monitored or controlled for fluoride content. By comparison, estimates of the total daily fluoride intake by human adults living in areas served by nonfluoridated water supplies range from 0.4 to 0.9 mg (6 to 13 μg/kg per day), and from about 1 to 5 mg (15 to 70 μg/kg per day) in areas with fluoridated water (IPCS, 1984). Doses of sodium fluoride given therapeutically for osteoporosis range from 50 to 100 mg/day (0.3 to 0.6 mg fluoride/kg per day) (Farley *et al.*, 1987).

The teeth of both rats and mice were visibly affected by exposure to sodium fluoride during the 2-year studies. Rats, primarily males, showed dose-related increased incidences of whitish discoloration and deformity leading to malocclusion. Approximately 50% of high-dose male rats showed attrition of the lower incisors at the end of the studies, and dosed male and female mice had increased incidences of mottling relative to the incidence in controls. In mice, the whitish discoloration occurred to a much greater extent than in rats, but there was little evidence of increased attrition, deformity, or malocclusion. Dosed animals were otherwise similar to controls in behavior, general health, and appearance.

TABLE 22
Estimated Total Daily Fluoride Intake from Diet and Water in the Sodium Fluoride Drinking Water Studies and in Previous NTP Studies in F344/N Rats and B6C3F$_1$ Mice

Dose (ppm)	0 ppm	25 ppm	100 ppm	175 ppm	Previous Studies
Male Rats	0.2[a]	0.8	2.5	4.1	0.9
Female Rats	0.2	0.8	2.7	4.5	1.0
Male Mice	0.6	1.7	4.9	8.1	2.5
Female Mice	0.6	1.9	5.7	9.1	2.8

[a] Units of mg fluoride/kg body weight per day. Fluoride (F) intake for control animals is from the diet; values for other groups represent F in the diet and water, assuming 60% of dietary F and 100% of water F is bioavailable. Values for previous studies do not include minor contribution from fluoridated tap water.

Hematology, Clinical Chemistry, and Tissue Fluoride Analyses in the 2-Year Studies

Hematology, clinical chemistry (calcium, phosphorus, alkaline phosphatase), and fluoride analyses of bone, serum (rats only), and urine (rats only) were conducted at 24 weeks for mice or 27 weeks for rats and at 66 weeks for both species. Bone fluoride concentrations were also determined at the end of the 2-year studies. There were no biologically significant changes in hematologic measures or in serum levels of calcium or phosphorus in rats or in mice. Serum alkaline phosphatase activity was elevated at both 24 and 66 weeks in female mice given 175 ppm. The reason for this is not clear, but it could indicate increased activity of osteoblasts (Farley *et al.*, 1987). However, there was no gross or microscopic evidence of increased bone formation in the female mice in this dose group.

The concentration of fluoride in both the serum and the urine of rats increased with the concentration of sodium fluoride in the drinking water. Serum fluoride concentrations of high-dose rats were 2- to 3-fold greater than those of control animals. These concentrations were within the range of values of the fluoride concentrations determined for the plasma of rats in the 6-month studies and are in general agreement with previously published values for rat plasma obtained by this method (Singer and Ophaug, 1977). Plasma fluoride concentrations in humans have been reported to be about 0.01 μg/mL and vary with the fluoride concentration of the drinking water (IPCS, 1984). If the serum fluoride concentrations for rats are directly comparable to plasma levels for humans, then the fluoride concentrations for rats in the present studies range from 5- to 7-fold higher in control animals to 10- to 20-fold higher in the high-dose animals at the times measured during the studies. However, the current studies used a procedure for fluoride determination that employed sample decomposition. Guy (1979) has reported that methods involving sample decomposition generally give estimates of fluoride content that are higher than methods using non-decomposed samples, and may overestimate the actual concentration of ionic fluoride.

Fluoride concentrations of bone showed expected dose- and age-related increases that were similar in both sexes of rats and mice. The maximum concentration of fluoride in bone ash of high-dose rats and mice at the end of the 2-year studies ranged from 5.3 to 6.2 μg/mg ash (5,300 to 5,200 ppm). This represents an approximate 17-fold increase in mice and a 29-fold increase in rats over the prestudy bone fluoride levels measured in 6-week old animals, and an approximate 7- to 8-fold increase in mice and 10- to 12-fold increase in rats over the fluoride levels accumulated in the bones of control animals during the 2-year studies. Bone fluoride levels similar to those determined in the high-dose animals have been reported in human bone samples taken from people who had lived for at least 10 years in an area with an average fluoride content of 4 ppm in drinking water (Zipkin *et al.*, 1958) and from patients who had taken 50 to 66 mg of sodium fluoride daily for 5 to 6 years in the treatment of osteoporosis (Boivin *et al.*, 1988).

Neoplastic and Nonneoplastic Lesions in the 2-Year Studies

Lesions observed in the incisor teeth of rats receiving sodium fluoride for 2 years included dysplasia (malformation) of the dentine layer, degeneration of ameloblasts, and, less frequently, degeneration of odontoblasts. The degenerative changes in the ameloblasts were similar to, but less severe than, those observed in the 6-month studies. The teeth of mice apparently were less affected by sodium fluoride than were those of rats. However, dysplasia or malformation of the dentine layer occurs with increasing frequency in untreated control mice as they age. Thus, the effects of sodium fluoride may be less discernible in mice.

There was an increased incidence and severity of osteosclerosis observed in high-dose female rats, but not in dosed male rats or in mice. This change occurred during the last 9 months of the 2-year studies because no increases were observed in animals examined at 27 or 66 weeks. Osteosclerosis is characterized by an increase in trabecular bone in the metaphysis of long bones and the vertebrae and occurs spontaneously, particularly in aging female rats. The increased incidence and severity of this lesion are consistent with the demonstrated stimulatory effects of fluoride on osteoblasts and osteoid production, although an effect on bone resorption cannot be ruled out. The stimulatory effects of fluoride on bone production form the basis for the use of fluoride in treating osteoporosis in humans (Farley *et al.*, 1987).

Lesions of the femur and tibia similar to those identified in the 6-month studies were not observed in the 2-year studies in mice. The reason for this is not known, but may be related to the levels of sodium fluoride administered and changes in the rates of bone remodeling as the animals age. Exostoses or other bone changes typically associated with severe skeletal fluorosis were not found in rats or mice.

Osteosarcomas of the bone were observed in 3/80 (4%) high-dose and in 1/50 (2%) mid-dose male rats. An additional osteosarcoma, which was determined to be of subcutaneous origin, was observed in a fourth high-dose male rat. No osteosarcomas were seen in controls or in male rats receiving 25 ppm. The neoplasms were clearly malignant (one metastasized to the lung) and there was complete agreement concerning the diagnoses at both the Quality Assessment and the Pathology Working Group stages of histopathology review. Table 23 summarizes the location, method of first observation, and the time during the sodium fluoride studies at which the osteosarcomas were observed.

Many scientific and technical factors enter into the determination of whether there is an association between sodium fluoride exposure and the occurrence of osteosarcomas in male rats. A number of factors support such an association and others suggest that there may be no association. To fully consider these, it is necessary to review certain aspects of the design of the studies and the nature of the NTP historical database for osteosarcomas.

The procedures for the examination of bones and teeth used in these studies differed from those used in the studies that compose the NTP historical database. When animals in the dosed or control groups died or were killed in the sodium fluoride studies, whole body radiographs were taken and a complete gross necropsy was conducted. Sections of bone from the tibia, femur, humerus, thoracic vertebra, maxilla, incisive bones, nasal bones, and the mandible were routinely examined microscopically in addition to any bone lesions observed on gross or radiographic examination. In a typical NTP study, sections of bone from the maxilla, rib, or the femur are routinely taken in addition to any gross bone lesions. Radiographs are not routinely taken.

Osteosarcomas (in bone or extraskeletal) are not commonly observed in control male rats in NTP studies. The historical incidence in control male rats from dosed feed or water studies is 10/2,106 (0.47%) and in male controls from studies by all routes of administration, including gavage and inhalation, the rate is 37/6,131 (0.60%) (includes 5 tumors diagnosed as osteoma). Of these 37 tumors occurring in control male rats, one was found in an animal killed at approximately 40 weeks, 25 occurred in animals dying between

TABLE 23
Osteosarcomas in Male Rats in the Sodium Fluoride Studies

Site	Dose (ppm)	Method of First Observation[a]	Time
Vertebra	100	gross exam	end of study (104 weeks)
Vertebra	175	gross exam	55 weeks
Vertebra	175	gross exam	96 weeks
Humerus	175	microscopy	end of study
Subcutis	175	gross exam	end of study

[a] All neoplasms observed at gross necropsy were also visible on the radiographs.

weeks 70 and the end of the 2-year experiments, and the other 11 were observed in animals killed at 2 years. About 20% of the osteosarcomas occurred in the vertebra, 20% in the skull, and about 10% were found in the rib. The remainder were observed at various sites in the long bones, pelvis, subcutaneous tissue, and lung. All but one of these tumors were observed upon gross examination of the animal, and of these, two were found in the subcutis. The other tumor was observed microscopically in the lung. Thus, the majority of osteosarcomas and osteomas found in control animals occurred in bone and were observed grossly during the latter part of the 2-year studies.

The number of studies with 0, 1, 2, or 3 osteosarcomas in control male rats in the 122 studies that compose the historical control database (6,131 male rats) fits a Poisson distribution centered on a historical incidence of 0.5%. As many as 3 osteosarcomas in a group of 50 control male rats (6%) was observed on one occasion, in agreement with the frequency expected based upon the Poisson distribution.

An important consideration that limits the usefulness of the historical control database in the interpretation of the current studies is that the diet used in all other NTP studies has not been closely controlled or monitored for fluoride content. Fluoride concentrations in typical batches of the NIH-07 diet range between 28 and 47 ppm (Rao and Knapka, 1987). Assuming a maximum bioavailability of 60%, the historical database animals actually constitute a group receiving sufficient fluoride to place them between the low- and mid-concentration groups in the current 2-year studies (Table 22). The fact that this fluoride is available for absorption from the standard diet is supported by the levels of fluoride found in the bones of animals maintained on this diet in the 6-month studies (Appendix I). If fluoride is in fact influencing the "spontaneous" or background incidence of osteosarcomas in male rats, comparisons of the incidences observed in the current studies with those in the historical database may be misleading. This forces an even greater reliance on the within-study comparisons, i.e. the incidences in the dosed groups compared with the concurrent control, in the interpretation of the results of the sodium fluoride studies.

The four osteosarcomas of bone (one in the mid-dose and three in the high-dose groups) in the current studies occurred with a statistically significant dose-response trend by the logistic regression test ($P=0.027$); the pairwise comparison of the incidence in the high-dose group versus that in controls was not statistically significant ($P=0.099$). The statistical significance of the trend test is increased ($P=0.010$) when the subcutaneous osteosarcoma in the fourth high-dose rat is included in the incidence, but the pairwise comparison remains not significant ($P=0.057$). The incidence of bone osteosarcomas of 3/80 and the incidence of all osteosarcomas of 4/80 in the high-dose male rats are both significantly greater than the rate of 0.6% for osteosarcomas and osteomas at all sites in control male rats in the historical database. Note that one of the tumors in the current studies was observed microscopically and was not visible on the radiograph. It is likely that the actual occurrence of microscopic osteosarcomas is underrepresented in the historical database and possibly in the current studies because few sections of bone are taken for routine microscopic analysis.

The analyses of osteosarcomas are considered both with and without the subcutaneous tumor because it may not be appropriate biologically to combine these for statistical comparison with the controls. Chemical carcinogens typically produce site-specific increases in tumor incidences (Haseman *et al.*, 1986); thus tumors are usually combined for analysis on the basis of the tissue of origin and not simply because they may have the same histologic diagnosis. Osteosarcomas of bone contain neoplastic osteoblasts which presumably are responsible for the abnormal deposition of osteoid and collagen in osteosarcomas (Spjut *et al.*, 1971). Osteosarcomas that originate in bone may metastasize to soft tissues. On the other hand, sarcomas of soft tissues may occasionally produce osteoid and develop into an osteosarcoma (Carter, 1973). Careful examination of the radiograph of the male rat with the subcutaneous osteosarcoma did not reveal a potential site of origin within bone for this tumor; thus it is unlikely that the subcutaneous neoplasm represents a metastatic bone tumor.

The distinction concerning the site of origin is also important because, if fluoride were to exert a neoplastic effect, it is reasonable to expect that this might be expressed in a tissue that accumulates fluoride. This would include bone, and, therefore, there is biological plausibility for an association between sodium fluoride administration and the development of bone osteosarcomas. However, fluoride does not accumulate in soft tissues such as the subcutis (Smith *et al.*, 1960), making it perhaps less likely that this tumor developed as a consequence of sodium fluoride administration.

Fluoride was found to accumulate in the bone of female rats and male and female mice to a similar extent as in male rats. There were no osteosarcomas observed in female rats, yet high-dose female rats had the clearest evidence of fluoride-induced osteosclerosis, suggesting that a stimulatory or mitogenic effect of fluoride on osteoblasts (Farley *et al.*, 1983; Marie and Hott, 1986) was occurring in female rats. Male and female mice had no microscopic evidence of osteosclerosis of bone. A total of three osteosarcomas and one osteoma were found in male and female mice in the present studies. An osteosarcoma occurred in one low-dose male mouse killed for evaluation at 66 weeks, in one low-dose female mouse, and one osteosarcoma and one osteoma occurred among the female mice in the control group. None of the female rats or male or female mice in the mid- or high-dose groups had an osteosarcoma.

The lack of supporting evidence in female rats and male and female mice for the apparent association between sodium fluoride administration and osteosarcoma production in male rats may, however, have only limited significance. While only one chemical previously studied by the NTP has been associated with osteosarcoma formation (Acronycine in Sprague-Dawley rats, NCI, 1978), the tumor response in this earlier study was clearly shown in male and not in female rats. The study in mice was judged inadequate for evaluation. On the other hand, Litvinov and Soloviev (1973), in a review of tumors of the bone in rats, stated that the sex of the animal does not play a role in the tumor response to chemical inducing agents. Their review of the literature indicates that most experimentally induced bone tumors in rats have been found in the long bones following administration of radioactive isotopes of bone-seeking elements such as phosphorus-32, calcium-45, or strontium-90, skeletal irradiation, or intraosseous administration of chemical carcinogens. A review of more recent literature has not added significant information concerning the potential for a sex-linked response of bone tumor formation in animals. However, osteosarcomas in humans occur more frequently in males than in females (NCI, 1989).

No studies were found in the literature which have directly assessed the genotoxic potential of sodium fluoride to osteoblasts. However, sodium fluoride was found positive in assays for gene mutation induction in mammalian cells *in vitro* and in *Drosophila*. It is positive in some plant and animal systems for the induction of chromosomal aberrations, and it is positive in *in vitro* assays for morphologic transformation of Syrian hamster ovary cells. While the mechanisms for these effects are not understood, the data suggest that sodium fluoride has the capability, probably through an indirect mechanism, for genotoxic activity.

To summarize these considerations, a small number of osteosarcomas occurred in mid- and high-dose male rats. These neoplasms occurred with a significant dose response trend, but at a rate within the upper range of incidences previously seen in control male rats in NTP studies. Three of the tumors arose in the vertebra, a site not commonly associated with chemically induced osteosarcomas. Bone is known to accumulate fluoride, and fluoride has been shown to be genotoxic to some mammalian cells in culture. No osteosarcomas were seen in female rats, and several osteosarcomas seen in mice occurred with an incidence that did not suggest a relationship with sodium fluoride exposure. Taken together, the current findings are inconclusive, but are weakly supportive of an association between sodium fluoride administration and the occurrence of osteosarcomas in male rats.

A second potential target site for sodium fluoride when given in drinking water is the upper digestive tract and oral cavity. Squamous cell neoplasms of the oral mucosa (tongue, palate, or gingiva) occurred with marginally increased incidences in dosed male and female rats over the rates in controls. The increased incidences of these neoplasms were not statistically significant when compared with the incidences in concurrent controls; however, the incidences in the high-dose groups were significantly higher than the incidences observed in historical control animals (0.7% male rats; 0.6% female rats).

As with lesions of the bone, a direct comparison with the historical rates for oral cavity neoplasms is not completely accurate because of the increased attention given to the oral cavity and teeth in the sodium fluoride studies compared to previous NTP studies. Rates for oral cavity neoplasms similar to those observed in high-dose male and female rats in the sodium fluoride studies (4%) have been observed twice for males and once for females in the historical control database of 42 dosed feed or water studies. Neoplasms of the oral cavity were observed in control male and female rats in the current studies; one was observed in an age-matched control male rat and one occurred in a control female rat in the main study.

An argument could be made for combining the male and female rat studies for analysis of oral cavity neoplasms because a marginal increase occurred in both groups. An analysis for significance of the combined P values for the logistic regression trend tests for male and female rats resulted in a nonsignificant P value of 0.065.

In contrast to osteosarcomas, for which there are no recognized benign or preneoplastic counterparts (Litvinov and Soloviev, 1973), squamous cell hyperplasias of the oral cavity are considered preneoplastic precursor lesions of squamous cell neoplasms of the oral cavity (Brown and Hardisty, 1990). Squamous cell hyperplasia occurred in no more than one animal in any of the dosed or control groups in the current studies. Thus, based on the absence of statistical significance versus the concurrent controls, the occurrence of these tumors in control animals, and the lack of a dose-related increase in nonneoplastic precursor lesions, it is concluded that there is insufficient evidence to relate tumors of the oral cavity with administration of sodium fluoride to male or female rats. Glattre and Wiese (1979) reported an association between a decrease in human mortality due to oral cavity neoplasia and increasing fluoride content in water over the range of 0 to 0.5 ppm.

Follicular cell neoplasms of the thyroid gland appeared with a marginally increased incidence in high-dose male rats compared with controls. This increase is not statistically significant compared with controls unless control animals from both interim groups (27 and 66 weeks) and the age-matched controls are pooled with the main study control group. If this is done, the logistic regression P value for the trend is 0.027. Thyroid follicular cell neoplasms typically occur with an incidence of 1.2% in historical control animals. Incidences of 6% have previously been observed in untreated control groups and incidences as high as 10% have occurred in control groups for gavage studies. The incidence of these neoplasms in the high-dose groups was 5/90 (5.5%; includes 10 animals from the 66-week interim sacrifice, one of which had a thyroid follicular cell carcinoma). Three of these tumors were adenomas. The incidence of carcinomas did not differ across the dosed groups and the incidence of follicular cell hyperplasia was not increased. No increase in the incidence of these tumors occurred in female rats. Based on these considerations, follicular cell neoplasms of the thyroid are not considered related to sodium fluoride administration.

In mice, the only neoplasm that appeared to be possibly related to sodium fluoride administration was lymphoma in females. However, lymphoma is a common neoplasm in mice, occurring with rates varying from 10% to 74% in historical controls. In the current studies, the incidences in control and in low-dose female mice (14% and 10%) were less than the lowest incidence observed in the 9 studies composing the historical database at the study laboratory. The incidence of 24% in high-dose female mice (or 30% when considering the combination of all lymphomas and histiocytic sarcomas) is similar to the average historical control incidence of 31% in female mice. There was no increase in the incidence of lymphomas in male mice. For these reasons, it is considered unlikely that sodium fluoride administration affected the incidence of this neoplasm in female mice.

One other finding in the sodium fluoride studies deserves mention. The incidence of liver neoplasms in all groups of dosed and control male and female mice was higher than has typically been seen in NTP studies (Appendixes C4 and D4b). A review of pathology information from NTP studies which began about the same time as the sodium fluoride studies, but which have not yet been completely evaluated and reported, has revealed a sharp increase in liver neoplasms, especially in females. The reasons for this trend toward increasing liver neoplasms in control mice have not been determined, but it is worth noting that the weights of all groups of male and female mice in the sodium fluoride studies were quite high compared to the weights attained by previous control groups. A possible relationship between body weight and the incidence of liver neoplasms in $B6C3F_1$ mice has been discussed by Rao *et al.* (1987).

In these 2-year studies, toxic effects of the concentrations of sodium fluoride employed were noted in the teeth and bones of rats and several osteosarcomas occurred in dosed males. Higher sodium fluoride concentrations in drinking water may have been tolerated by the rats, but it is difficult to predict the concentration above which effects on dentition would become so severe as to interfere with the animals' ability to eat. The effects of these sodium fluoride concentrations in mice were limited to discoloration of teeth and a marginal increase in dentine dysplasia in males. Based on these findings, it would appear that mice could have tolerated somewhat higher sodium fluoride concentrations in the drinking water.

Conclusions

Under the conditions of these 2-year dosed water studies, there was *equivocal evidence of carcinogenic activity** of sodium fluoride in male F344/N rats, based on the occurrence of a small number of osteosarcomas in dosed animals. "Equivocal evidence" is a category for uncertain findings defined as studies that are interpreted as showing a marginal increase of neoplasms that may be related to chemical administration. There was *no evidence of carcinogenic activity* in female F344/N rats receiving sodium fluoride at concentrations of 25, 100, or 175 ppm (11, 45, or 79 ppm fluoride) in drinking water for 2 years. There was *no evidence of carcinogenic activity* of sodium fluoride in male or female mice receiving sodium fluoride at concentrations of 25, 100, or 175 ppm in drinking water for 2 years.

Dosed rats had lesions typical of fluorosis of the teeth and female rats receiving drinking water containing 175 ppm sodium fluoride had increased osteosclerosis of long bones.

*Explanation of Levels of Carcinogenic Activity is on page 8. A summary of peer review comments and the public discussion on this technical report appear on page 10.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR DRINKING WATER STUDIES OF SODIUM FLUORIDE

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

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Disposition Summary					
Animals initially in study	100	50	70	70	100
Early deaths					
Moribund sacrifice	21	12	13	13	19
Natural death	17	6	13	13	19
Survivors					
Terminal sacrifice	42	5	25	23	42
Paired control		27			
Animals examined microscopically	80	45	51	50	80
Alimentary System					
Intestine large, colon	(79)	(45)	(51)	(50)	(80)
Adenocarcinoma	1 (1%)				
Intestine small, ileum	(79)	(45)	(51)	(50)	(79)
Adenocarcinoma		1 (2%)			
Intestine small, jejunum	(80)	(45)	(51)	(50)	(80)
Adenocarcinoma					1 (1%)
Leiomyoma					1 (1%)
Liver	(80)	(45)	(51)	(50)	(80)
Fibrosarcoma, metastatic, skin				1 (2%)	
Hepatocellular adenoma	1 (1%)		1 (2%)	1 (2%)	1 (1%)
Histiocytic sarcoma, multiple					1 (1%)
Mesentery	(13)	(6)	(9)	(5)	(16)
Histiocytic sarcoma				1 (20%)	
Liposarcoma			1 (11%)		
Oral mucosa		(1)		(1)	(2)
Buccal, papilloma squamous					1 (50%)
Buccal, squamous cell carcinoma		1 (100%)			
Gingival, squamous cell carcinoma				1 (100%)	1 (50%)
Pancreas	(79)	(45)	(50)	(50)	(79)
Histiocytic sarcoma, metastatic, mesentery				1 (2%)	
Acinus, adenoma			1 (2%)		
Pharynx				(1)	(1)
Palate, papilloma squamous				1 (100%)	1 (100%)
Salivary glands	(80)	(45)	(50)	(50)	(80)
Carcinoma		1 (2%)			
Hemangiosarcoma, metastatic, skin		1 (2%)			
Stomach, forestomach	(79)	(45)	(51)	(50)	(80)
Basal cell adenoma	1 (1%)				
Papilloma squamous				1 (2%)	
Stomach, glandular	(79)	(45)	(51)	(49)	(80)
Tongue			(2)		
Papilloma squamous			1 (50%)		
Tooth	(80)	(45)	(51)	(50)	(80)
Gingiva, molar, lower, squamous cell carcinoma, metastatic	1 (1%)				
Peridontal tissue, squamous cell carcinoma, metastatic					1 (1%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Cardiovascular System					
Heart	(80)	(45)	(51)	(50)	(80)
Hemangiosarcoma					1 (1%)
Endocardium, ventricle left, schwannoma benign	1 (1%)				
Endocrine System					
Adrenal gland, cortex	(80)	(45)	(51)	(50)	(80)
Adenoma	1 (1%)			1 (2%)	1 (1%)
Adrenal gland, medulla	(80)	(45)	(51)	(50)	(80)
Pheochromocytoma malignant	2 (3%)			1 (2%)	
Pheochromocytoma complex	1 (1%)				
Pheochromocytoma benign	19 (24%)	6 (13%)	12 (24%)	7 (14%)	22 (28%)
Bilateral, pheochromocytoma benign	5 (6%)	2 (4%)	8 (16%)	7 (14%)	8 (10%)
Islets, pancreatic	(79)	(45)	(49)	(50)	(80)
Adenoma	2 (3%)	1 (2%)		3 (6%)	4 (5%)
Carcinoma	1 (1%)		1 (2%)	1 (2%)	1 (1%)
Parathyroid gland	(77)	(43)	(51)	(49)	(77)
Adenoma	4 (5%)		1 (2%)	1 (2%)	1 (1%)
Carcinoma, metastatic, thyroid gland					1 (1%)
Pituitary gland	(80)	(44)	(50)	(49)	(80)
Pars distalis, adenoma	15 (19%)	3 (7%)	9 (18%)	9 (18%)	13 (16%)
Pars distalis, carcinoma				1 (2%)	
Pars intermedia, carcinoma			1 (2%)		
Thyroid gland	(80)	(45)	(51)	(50)	(80)
Bilateral, c-cell, adenoma		1 (2%)	1 (2%)	1 (2%)	2 (3%)
Bilateral, c-cell, carcinoma			1 (2%)		
C-cell, adenoma	14 (18%)	6 (13%)	9 (18%)	8 (16%)	10 (13%)
C-cell, carcinoma	1 (1%)				4 (5%)
Follicular cell, adenoma				1 (2%)	3 (4%)
Follicular cell, carcinoma	1 (1%)		1 (2%)		1 (1%)
General Body System					
Tissue NOS			(1)	(1)	(1)
Chordoma			1 (100%)		
Fibrosarcoma				1 (100%)	
Genital System					
Epididymis	(80)	(45)	(51)	(50)	(80)
Preputial gland	(80)	(45)	(51)	(47)	(80)
Adenoma	7 (9%)	2 (4%)	4 (8%)	3 (7%)	4 (5%)
Carcinoma	1 (1%)	1 (2%)	3 (6%)	1 (2%)	4 (5%)
Prostate	(79)	(45)	(50)	(49)	(80)
Seminal vesicle	(78)	(45)	(51)	(49)	(77)
Testes	(80)	(45)	(51)	(50)	(80)
Bilateral, interstitial cell, adenoma	57 (71%)	21 (47%)	38 (75%)	37 (76%)	62 (78%)
Interstitial cell, adenoma	13 (16%)	14 (31%)	8 (16%)	9 (18%)	11 (14%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Hematopoietic System					
Bone marrow	(79)	(45)	(51)	(50)	(80)
Carcinoma, metastatic, thyroid gland			1 (2%)		
Lymph node	(79)	(45)	(51)	(50)	(80)
Axillary, carcinoma, metastatic, thyroid gland			1 (2%)		
Deep cervical, carcinoma, metastatic, thyroid gland					1 (1%)
Mediastinal, carcinoma, metastatic, thyroid gland			1 (2%)		
Mediastinal, histiocytic sarcoma, metastatic, spleen			1 (2%)		
Lymph node, mandibular	(79)	(45)	(50)	(50)	(80)
Carcinoma, metastatic, thyroid gland			1 (2%)		
Hemangiosarcoma, metastatic, skin		1 (2%)			
Histiocytic sarcoma, metastatic, spleen			1 (2%)		
Lymph node, mesenteric	(79)	(45)	(50)	(49)	(76)
Histiocytic sarcoma, metastatic, spleen			1 (2%)		
Spleen	(79)	(45)	(51)	(50)	(80)
Fibrosarcoma	1 (1%)			1 (2%)	
Fibrous histiocytoma		1 (2%)			
Hemangioma					1 (1%)
Histiocytic sarcoma			3 (6%)		
Thymus	(69)	(43)	(48)	(42)	(76)
Thymoma malignant		1 (2%)			1 (1%)
Integumentary System					
Mammary gland	(75)	(43)	(48)	(47)	(72)
Fibroadenoma	6 (8%)		1 (2%)		2 (3%)
Skin	(80)	(45)	(51)	(50)	(80)
Basal cell adenoma	1 (1%)				
Basal cell carcinoma				1 (2%)	
Keratoacanthoma	8 (10%)	1 (2%)	2 (4%)	1 (2%)	8 (10%)
Keratoacanthoma, multiple	1 (1%)	1 (2%)			
Papilloma			1 (2%)		2 (3%)
Papilloma squamous	1 (1%)		2 (4%)	1 (2%)	2 (3%)
Trichoepithelioma				1 (2%)	
Sebaceous gland, adenoma		1 (2%)			
Subcutaneous tissue, fibroma			2 (4%)	3 (6%)	4 (5%)
Subcutaneous tissue, fibrosarcoma	1 (1%)			1 (2%)	
Subcutaneous tissue, hemangiosarcoma		1 (2%)			
Subcutaneous tissue, lipoma	1 (1%)				
Subcutaneous tissue, neurofibroma			1 (2%)	1 (2%)	
Subcutaneous tissue, neurofibrosarcoma			1 (2%)		
Subcutaneous tissue, neurofibrosarcoma, multiple			1 (2%)		
Subcutaneous tissue, osteosarcoma					1 (1%)
Subcutaneous tissue, osteosarcoma, metastatic, bone					1 (1%)
Subcutaneous tissue, schwannoma malignant		1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Musculoskeletal System					
Bone	(80)	(45)	(51)	(50)	(80)
Humerus, osteosarcoma					1 (1%)
Vertebra, osteosarcoma					2 (3%)
Vertebra, coccygeal, osteosarcoma				1 (2%)	
Skeletal muscle	(1)	(1)		(1)	(1)
Diaphragm, histiocytic sarcoma, metastatic, mesentery				1 (100%)	
Diaphragm, thymoma malignant, metastatic, thymus					1 (100%)
Nervous System					
Brain	(80)	(45)	(51)	(50)	(80)
Granular cell tumor malignant			1 (2%)		
Meninges, carcinoma, metastatic, Zymbal's gland					1 (1%)
Spinal cord	(1)	(2)			(2)
Astrocytoma malignant	1 (100%)				
Osteosarcoma, metastatic, bone					1 (50%)
Respiratory System					
Lung	(80)	(45)	(51)	(50)	(80)
Alveolar/bronchiolar adenoma			1 (2%)		
Carcinoma, metastatic, prostate				1 (2%)	
Carcinoma, metastatic, thyroid gland	1 (1%)		1 (2%)		
Carcinoma, metastatic, Zymbal's gland					1 (1%)
Fibrosarcoma, metastatic, ear				1 (2%)	
Osteosarcoma, metastatic, multiple, bone				1 (2%)	
Thymoma malignant, metastatic, thymus		1 (2%)			
Mediastinum, histiocytic sarcoma, metastatic, mesentery				1 (2%)	
Mediastinum, thymoma malignant, metastatic, thymus					1 (1%)
Nose	(80)	(45)	(51)	(50)	(80)
Mucosa, papilloma squamous					1 (1%)
Mucosa, squamous cell carcinoma					1 (1%)
Special Senses System					
Ear	(3)	(1)		(1)	
Pinna, fibrosarcoma				1 (100%)	
Pinna, neurofibrosarcoma	1 (33%)	1 (100%)			
Pinna, squamous cell carcinoma	1 (33%)				
Zymbal's gland	(3)	(1)	(2)	(1)	(3)
Carcinoma	3 (100%)	1 (100%)	1 (50%)	1 (100%)	2 (67%)
Bilateral, carcinoma					1 (33%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Urinary System					
Kidney	(79)	(45)	(51)	(50)	(80)
Liposarcoma					1 (1%)
Cortex, myxoma				1 (2%)	
Renal tubule, adenoma					1 (1%)
Urinary bladder	(79)	(44)	(51)	(48)	(80)
Systemic Lesions					
Multiple organs[a]	(80)	(45)	(51)	(50)	(80)
Histiocytic sarcoma			3 (6%)	1 (2%)	1 (1%)
Leukemia monocytic	1 (1%)				
Leukemia mononuclear	54 (68%)	14 (31%)	23 (45%)	18 (36%)	47 (59%)
Mesothelioma benign	1 (1%)				2 (3%)
Mesothelioma malignant		3 (7%)	1 (2%)	1 (2%)	
Tumor Summary					
Total animals with primary neoplasms[b]	76	38	51	48	80
Total primary neoplasms	230	86	143	130	239
Total animals with benign neoplasms	74	35	49	47	76
Total benign neoplasms	159	59	103	98	169
Total animals with malignant neoplasms	58	22	31	26	62
Total malignant neoplasms	71	27	40	32	71
Total animals with secondary neoplasms[c]	2	3	2	5	7
Total secondary neoplasms	2	7	8	7	9

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control

Number of Days on Study	059	145	325	417	441	533	543	543	543	549	570	570	571	599	613	644	645	646	648	656	665	669	676	677
Carcass ID Number	025	161	114	013	145	181	024	142	201	195	162	174	103	132	124	115	125	173	154	053	153	054	101	164
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																								
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								
Mesentery						+	+								+		+			+	+			+
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																								
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gingiva, molar, lower, squamous cell carcinoma, metastatic																						X		
Cardiovascular System																								
Blood vessel																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocardium, ventricle left, schwannoma benign																								
Endocrine System																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																								
Pheochromocytoma complex																								
Pheochromocytoma benign																			X					X
Bilateral, pheochromocytoma benign																								
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X							
Carcinoma																								

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	684	686	690	692	694	697	712	716	718	718	718	719	719	726	729	729	729	729	729	729	729	729	729	729	730
Carcass ID Number	194	072	144	102	202	021	034	175	011	061	004	134	143	093	012	022	042	073	081	091	094	111	172	191	014
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery	+	+									+				+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gingiva, molar, lower, squamous cell carcinoma, metastatic																									
Cardiovascular System																									
Blood vessel														+											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocardium, ventricle left, schwannoma benign																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma complex						X																			
Pheochromocytoma benign	X							X		X			X	X		X									X
Bilateral, pheochromocytoma benign		X																				X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Carcinoma																					X				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	3	3
	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Carcass ID Number	1	2	3	3	4	4	6	6	6	6	7	8	8	0	1	1	2	2	3	3	4	5	5	5	6
	5	3	2	5	1	4	2	3	4	5	4	2	4	5	2	3	2	3	1	3	1	1	2	5	3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma								X																	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma	X																								
Mesentery															+								+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma										X															
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gingiva, molar, lower, squamous cell carcinoma, metastatic																									
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocardium, ventricle left, schwannoma benign																					X				
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																X					X				
Pheochromocytoma complex																									
Pheochromocytoma benign			X	X		X	X	X				X				X					X				X
Bilateral, pheochromocytoma benign		X							X		X														
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 6 5	1 7 1	1 8 2	1 8 3	1 8 5	2 0 3	**Total Tissues/ Tumors**
Alimentary System							
Esophagus	+	+	+	+	+	+	80
Intestine large	+	+	+	+	+	+	79
Intestine large, cecum	+	+	+	+	+	+	79
Intestine large, colon	+	+	+	+	+	+	79
Adenocarcinoma							1
Intestine large, rectum	+	+	+	+	+	+	79
Intestine small	+	+	+	+	+	+	80
Intestine small, duodenum	+	+	+	+	+	+	80
Intestine small, ileum	+	+	+	+	+	+	79
Intestine small, jejunum	+	+	+	+	+	+	80
Liver	+	+	+	+	+	+	80
Hepatocellular adenoma							1
Mesentery							13
Pancreas	+	+	+	+	+	+	79
Salivary glands	+	+	+	+	+	+	80
Stomach	+	+	+	+	+	+	79
Stomach, forestomach	+	+	+	+	+	+	79
Basal cell adenoma							1
Stomach, glandular	+	+	+	+	+	+	79
Tooth	+	+	+	+	+	+	80
Gingiva, molar, lower, squamous cell carcinoma, metastatic							1
Cardiovascular System							
Blood vessel							1
Heart	+	+	+	+	+	+	80
Endocardium, ventricle left, schwannoma benign							1
Endocrine System							
Adrenal gland	+	+	+	+	+	+	80
Adrenal gland, cortex	+	+	+	+	+	+	80
Adenoma	X						1
Adrenal gland, medulla	+	+	+	+	+	+	80
Pheochromocytoma malignant							2
Pheochromocytoma complex							1
Pheochromocytoma benign	X						19
Bilateral, pheochromocytoma benign							5
Islets, pancreatic	+	+	+	+	+	+	79
Adenoma							2
Carcinoma							1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	0	1	3	4	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6
Number of Days on Study	5	4	2	1	4	3	4	4	4	4	7	7	7	9	1	4	4	4	4	5	6	6	7	7
	9	5	5	7	1	3	3	3	3	9	0	0	1	9	3	4	5	6	8	6	5	9	6	7
	0	1	1	0	1	1	0	1	2	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1
Carcass ID Number	2	6	1	1	4	8	2	4	0	9	6	7	0	3	2	1	2	7	5	5	5	5	0	6
	5	1	4	3	5	1	4	2	1	5	2	4	3	2	4	5	5	3	4	3	3	4	1	4
Endocrine System (continued)																								
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Adenoma																								
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X						X														X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X				X					X		
C-cell, carcinoma																								
Follicular cell, carcinoma																								
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis	+																							
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X		X
Carcinoma																			X					
Prostate	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma									X		X			X	X	X	X		X	X	X	X		
Interstitial cell, adenoma							X	X				X						X					X	
Hematopoietic System																								
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																								
Thymus	A	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+
Integumentary System																								
Mammary gland	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																								
Keratoacanthoma										X							X							X
Keratoacanthoma, multiple																								
Papilloma squamous																								
Subcutaneous tissue, fibrosarcoma																		X						
Subcutaneous tissue, lipoma																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	684	686	690	692	694	697	712	716	718	718	718	719	719	726	729	729	729	729	729	729	729	729	729	729	730
Carcass ID Number	194	072	144	102	022	121	034	175	011	061	104	134	143	093	012	022	042	073	081	091	094	011	172	191	014
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X			X									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X		X									X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma								X	X												X				X
C-cell, carcinoma													X												
Follicular cell, carcinoma							X																		
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X				X					X			X	
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	X	X	X			X	X	X	X			X	X	X	X	X	X	X		X	X	X	X	X	X
Interstitial cell, adenoma					X					X	X								X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Thymus	+	+	+	M	+	+	M	M	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma							X				X					X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma																				X					
Keratoacanthoma, multiple																									
Papilloma squamous																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, lipoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	3	3
	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1
Carcass ID Number	1	2	3	3	4	4	6	6	6	6	7	8	8	0	1	1	2	2	3	3	4	5	5	5	6
	5	3	2	5	1	4	2	3	4	5	4	2	4	5	2	3	2	3	1	3	1	1	2	5	3
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X					X														
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X		X				X						X			X	X			X	X		X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma		X							X		X	X		X											
C-cell, carcinoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X	X		X
Interstitial cell, adenoma																		X	X	X				X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma									X																
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma							X															X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																		X							
Keratoacanthoma		X		X							X													X	
Keratoacanthoma, multiple												X													
Papilloma squamous																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, lipoma				X																					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 6 5	1 7 1	1 8 2	1 8 3	1 8 5	2 0 3	**Total Tissues/ Tumors**
Endocrine System (continued)							
Parathyroid gland	+	+	+	+	M	+	77
Adenoma							4
Pituitary gland	+	+	+	+	+	+	80
Pars distalis, adenoma							15
Thyroid gland	+	+	+	+	+	+	80
C-cell, adenoma				X		X	14
C-cell, carcinoma							1
Follicular cell, carcinoma							1
General Body System							
None							
Genital System							
Epididymis	+	+	+	+	+	+	80
Penis							1
Preputial gland	+	+	+	+	+	+	80
Adenoma							7
Carcinoma							1
Prostate	+	+	+	+	+	+	79
Seminal vesicle	+	+	+	+	+	+	78
Testes	+	+	+	+	+	+	80
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	57
Interstitial cell, adenoma							13
Hematopoietic System							
Bone marrow	+	+	+	+	+	+	79
Lymph node	+	+	+	+	+	+	79
Lymph node, mandibular	+	+	+	+	+	+	79
Lymph node, mesenteric	+	+	+	+	+	+	79
Spleen	+	+	+	+	+	+	79
Fibrosarcoma							1
Thymus	+	+	+	+	+	+	69
Integumentary System							
Mammary gland	+	+	+	+	+	+	75
Fibroadenoma					X		6
Skin	+	+	+	+	+	+	80
Basal cell adenoma							1
Keratoacanthoma							8
Keratoacanthoma, multiple							1
Papilloma squamous		X					1
Subcutaneous tissue, fibrosarcoma							1
Subcutaneous tissue, lipoma							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	0	1	3	4	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6
Number of Days on Study	5	4	2	1	4	3	4	4	4	4	7	7	7	9	1	4	4	4	4	5	6	6	7	7
	9	5	5	7	1	3	3	3	3	9	0	0	1	9	3	4	5	6	8	6	5	9	6	7
	0	1	1	0	1	1	0	1	2	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1
Carcass ID Number	2	6	1	1	4	8	2	4	0	9	6	7	0	3	2	1	2	7	5	5	5	5	0	6
	5	1	4	3	5	1	4	2	1	5	2	4	3	2	4	5	5	3	4	3	3	4	1	4
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																					
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+																					
Spinal cord			+																					
Astrocytoma malignant			X																					
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear																								
Pinna, neurofibrosarcoma																								
Pinna, squamous cell carcinoma																								
Eye												+	+											
Harderian gland																								
Lacrimal gland																								
Zymbal's gland																+						+		
Carcinoma																X						X		
Urinary System																								
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monocytic																								
Leukemia mononuclear			X			X	X	X	X			X	X	X	X	X	X		X	X	X	X	X	X
Mesothelioma benign																								

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	8	8	9	9	9	9	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	3
	4	6	0	2	4	7	2	6	8	8	8	9	9	6	9	9	9	9	9	9	9	9	9	9	0
	1	0	1	1	2	1	0	1	0	0	1	1	1	0	0	0	0	0	0	0	0	1	1	1	0
Carcass ID Number	9	7	4	0	0	2	3	7	1	6	0	3	4	9	1	2	4	7	8	9	9	1	7	9	1
	4	2	4	2	2	1	4	5	1	1	4	4	3	3	2	2	2	3	1	1	4	1	2	1	4
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									
Astrocytoma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Pinna, neurofibrosarcoma																									
Pinna, squamous cell carcinoma																									
Eye		+							+					+	+	+		+				+	+	+	+
Harderian gland																					+				
Lacrimal gland											M														
Zymbal's gland										+															
Carcinoma										X															
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monocytic											X														
Leukemia mononuclear	X	X	X			X	X	X	X		X	X	X				X	X		X	X		X	X	X
Mesothelioma benign																									X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	3	3
	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Carcass ID Number	1	2	3	3	4	4	6	6	6	6	7	8	8	0	1	1	2	2	3	3	4	5	5	5	6
	5	3	2	5	1	4	2	3	4	5	4	2	4	5	2	3	2	3	1	3	1	1	2	5	3
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									
Astrocytoma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear							+														+				
Pinna, neurofibrosarcoma							X																		
Pinna, squamous cell carcinoma																					X				
Eye	+	+								+	+						+	+							+
Harderian gland																									
Lacrimal gland																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monocytic																									
Leukemia mononuclear		X	X		X				X		X	X	X	X		X		X	X	X	X	X			X
Mesothelioma benign																									

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	733	733	733	733	733	733	
Carcass ID Number	165	171	182	183	185	203	**Total Tissues/ Tumors**
Musculoskeletal System							
Bone	+	+	+	+	+	+	80
Skeletal muscle							1
Nervous System							
Brain	+	+	+	+	+	+	80
Peripheral nerve							1
Spinal cord							1
Astrocytoma malignant							1
Respiratory System							
Lung	+	+	+	+	+	+	80
Carcinoma, metastatic, thyroid gland							1
Nose	+	+	+	+	+	+	80
Trachea	+	+	+	+	+	+	79
Special Senses System							
Ear					+		3
Pinna, neurofibrosarcoma							1
Pinna, squamous cell carcinoma							1
Eye	+	+				+	22
Harderian gland							1
Lacrimal gland							
Zymbal's gland							3
Carcinoma							3
Urinary System							
Kidney	+	+	+	+	+	+	79
Urinary bladder	+	+	+	+	+	+	79
Systemic Lesions							
Multiple organs	+	+	+	+	+	+	80
Leukemia monocytic							1
Leukemia mononuclear	X		X	X	X	X	54
Mesothelioma benign							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control

Number of Days on Study	180	282	317	382	388	389	404	414	422	441	464	501	522	526	533	537	537	544	555	561	570	575	584	591	602
Carcass ID Number	233	293	271	294	252	301	221	273	263	285	211	303	264	302	251	232	295	222	231	241	281	262	235	225	253
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+	+																						+
Oral mucosa																									
Buccal, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Hemangiosarcoma, metastatic, skin																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																X									
Bilateral, pheochromocytoma benign																						X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

Number of Days on Study	6 0 7	6 1 3	6 1 4	6 2 0	6 2 7	6 3 4	6 4 1	6 4 4	6 4 5	6 5 5	6 6 0	6 7 0	6 7 7	6 8 0	6 9 1	6 9 5	7 0 5	7 1 0	7 1 6	7 2 6	
Carcass ID Number	2 8 3	2 6 1	2 8 4	2 1 4	2 3 4	2 7 2	3 0 4	2 9 2	2 7 4	2 4 5	2 7 5	2 2 4	2 1 2	2 5 5	3 0 5	2 8 2	2 9 1	2 4 4	2 2 3	2 1 3	**Total Tissues/ Tumors**
Alimentary System																					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenocarcinoma																X					45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Mesentery			+											+			+				6
Oral mucosa						+															1
Buccal, squamous cell carcinoma						X															1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma												X									1
Hemangiosarcoma, metastatic, skin																			X		1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Cardiovascular System																					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Endocrine System																					
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pheochromocytoma benign		X						X				X	X		X						6
Bilateral, pheochromocytoma benign					X																2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma					X																1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

Number of Days on Study	1 8 0	2 8 2	3 1 7	3 8 2	3 8 8	3 8 9	4 0 4	4 1 4	4 2 2	4 4 1	4 6 4	5 0 1	5 2 2	5 2 6	5 3 3	5 3 7	5 3 7	5 4 4	5 5 5	5 6 1	5 7 0	5 7 5	5 8 4	5 9 1	6 0 2
Carcass ID Number	2 3 3	2 9 3	2 7 1	2 9 4	2 5 2	3 0 1	2 2 1	2 7 3	2 6 3	2 8 5	2 1 1	3 0 3	2 6 4	3 0 2	2 5 1	2 3 2	2 9 5	2 2 2	2 3 1	2 4 1	2 8 1	2 6 2	2 3 5	2 2 5	2 5 3
Endocrine System (continued)																									
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																			X					X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, c-cell, adenoma																									
C-cell, adenoma																									
General Body System																									
None																									
Genital System																									
Ductus deferens																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																	X								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																		X		X	X		X		X
Interstitial cell, adenoma								X		X		X	X		X	X	X		X			X		X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, mesothelioma malignant, metastatic, mesentery			X																						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, skin																									
Mesothelioma malignant, metastatic, mesentery			X																						
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery			X																						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																									
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant								X																	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

Number of Days on Study	6 0 7	6 1 3	6 1 4	6 2 0	6 2 7	6 3 4	6 4 1	6 4 4	6 4 5	6 5 5	6 6 0	6 7 0	6 7 7	6 8 0	6 9 1	6 9 5	7 0 5	7 1 0	7 1 6	7 2 6	
Carcass ID Number	2 8 3	2 6 1	2 8 4	2 1 4	2 3 4	2 7 2	3 0 4	2 9 2	2 7 4	2 4 5	2 7 5	2 2 4	2 1 2	2 5 5	3 0 5	2 8 2	2 9 1	2 4 4	2 2 3	2 1 3	**Total Tissues/ Tumors**
Endocrine System (continued)																					
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pars distalis, adenoma														X							3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Bilateral, c-cell, adenoma													X								1
C-cell, adenoma	X			X						X		X				X				X	6
General Body System																					
None																					
Genital System																					
Ductus deferens												+									1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma			X	X																	2
Carcinoma																					1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Bilateral, interstitial cell, adenoma	X	X	X	X		X	X	X	X	X			X	X	X	X	X	X	X		21
Interstitial cell, adenoma					X						X	X								X	14
Hematopoietic System																					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Mediastinal, mesothelioma malignant, metastatic, mesentery																					1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Hemangiosarcoma, metastatic, skin																			X		1
Mesothelioma malignant, metastatic, mesentery																					1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Mesothelioma malignant, metastatic, mesentery																					1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Fibrous histiocytoma																		X			1
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Thymoma malignant																					1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

	1	2	3	3	3	3	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5	6
Number of Days on Study	8	8	1	8	8	8	0	1	2	4	6	0	2	2	3	3	3	4	5	6	7	7	8	9	0
	0	2	7	2	8	9	4	4	2	1	4	1	2	6	3	7	7	4	5	1	0	5	4	1	2
	2	2	2	2	2	3	2	2	2	2	2	3	2	3	2	2	2	2	2	2	2	2	2	2	2
Carcass ID Number	3	9	7	9	5	0	2	7	6	8	1	0	6	0	5	3	9	2	3	4	8	6	3	2	5
	3	3	1	4	2	1	1	3	3	5	1	3	4	2	1	2	5	2	1	1	1	2	5	5	3
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Keratoacanthoma, multiple																								X	
Sebaceous gland, adenoma																X									
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, schwannoma malignant	X																								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord						+																			
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant, metastatic, thymus								X																	
Mediastinum, mesothelioma malignant, metastatic, mesentery			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Pinna, neurofibrosarcoma																									
Eye																								+	
Harderian gland																									
Zymbal's gland															+										
Carcinoma															X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X									X	X									
Mesothelioma malignant			X																			X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

Number of Days on Study	607	613	614	620	627	634	641	644	645	655	660	670	677	680	691	695	705	710	716	726	
Carcass ID Number	283	261	284	214	234	272	304	292	274	245	275	224	212	255	305	282	291	244	233	213	**Total Tissues/ Tumors**
Integumentary System																					
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Keratoacanthoma																X					1
Keratoacanthoma, multiple																					1
Sebaceous gland, adenoma																					1
Subcutaneous tissue, hemangiosarcoma																			X		1
Subcutaneous tissue, schwannoma malignant																					1
Musculoskeletal System																					
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Skeletal muscle																					1
Nervous System																					
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Peripheral nerve									+												1
Spinal cord									+												2
Respiratory System																					
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thymoma malignant, metastatic, thymus																					1
Mediastinum, mesothelioma malignant, metastatic, mesentery																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Special Senses System																					
Ear																		+			1
Pinna, neurofibrosarcoma																		X			1
Eye												+							+		3
Harderian gland														+		+					2
Zymbal's gland																					1
Carcinoma																					1
Urinary System																					
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Systemic Lesions																					
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear	X	X	X	X	X				X			X		X		X	X			X	14
Mesothelioma malignant			X																		3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm

Number of Days on Study	422	424	533	584	607	623	634	638	647	654	663	668	669	670	671	673	676	691	697	699	706	710	711	717	718	727
Carcass ID Number	402	414	385	365	362	425	445	375	352	323	334	322	373	351	374	434	353	384	403	441	394	371	343	415	381	442
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma									X																	
Mesentery										+							+	+							+	
Liposarcoma										X																
Pancreas	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																										
Papilloma squamous																										
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign			X						X					X	X									X		
Bilateral, pheochromocytoma benign																X	X		X						X	X
Islets, pancreatic	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Pituitary gland	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X					X					X					X			X		X
Pars intermedia, carcinoma																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, c-cell, adenoma																				X						
Bilateral, c-cell, carcinoma		X																								
C-cell, adenoma													X								X			X		
Follicular cell, carcinoma																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	9	9	9	9	9	9	9	9	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3	
	3	3	3	3	3	3	3	4	4	3	3	3	3	4	3	3	3	3	3	3	4	4	4	4	4	**Total**
Carcass ID Number	1	2	3	4	5	5	9	2	4	1	2	2	3	4	3	4	4	6	8	9	0	1	3	3	3	**Tissues/**
	3	1	2	5	4	5	1	1	3	4	4	5	1	4	5	1	2	3	3	3	1	2	1	2	5	**Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular adenoma																										1
Mesentery					+										+		+							+	+	9
Liposarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma																		X								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tongue					+																		+			2
Papilloma squamous																							X			1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign		X					X							X	X				X		X				X	12
Bilateral, pheochromocytoma benign											X						X						X			8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma													X													1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																X										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X								X										X					9
Pars intermedia, carcinoma					X																					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, c-cell, adenoma																										1
Bilateral, c-cell, carcinoma																										1
C-cell, adenoma	X						X	X			X				X					X						9
Follicular cell, carcinoma																	X									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

	4	4	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7
Number of Days on Study	2	2	3	8	0	2	3	3	4	5	6	6	6	7	7	7	7	9	9	9	0	1	1	1	1	2
	2	4	3	4	7	3	4	8	7	4	3	8	9	0	1	3	6	1	7	9	6	0	1	7	8	7
	4	4	3	3	3	4	4	3	3	3	3	3	3	3	3	4	3	3	4	4	3	3	3	4	3	4
Carcass ID Number	0	1	8	6	6	2	4	7	5	2	3	2	7	5	7	3	5	8	0	4	9	7	4	1	8	4
	2	4	5	5	2	5	5	5	2	3	4	2	3	1	4	4	3	4	3	1	4	1	3	5	1	2
General Body System																										
Tissue NOS							+																			
Chordoma							X																			
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X										
Carcinoma								X	X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X						X	X			X	X	X	X	X	X	X	X		X		X	X	
Interstitial cell, adenoma				X	X		X	X			X	X											X			
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland		X																								
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, carcinoma, metastatic, thyroid gland		X																								
Mediastinal, carcinoma, metastatic, thyroid gland		X																								
Mediastinal, histiocytic sarcoma, metastatic, spleen																					X					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland		X																								
Histiocytic sarcoma, metastatic, spleen																					X					
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, spleen																					X					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				X	
Thymus	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	9	9	9	9	9	9	9	9	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3	
Carcass ID Number	3	3	3	3	3	3	3	4	4	3	3	3	3	4	3	3	3	3	3	3	4	4	4	4	4	**Total**
	1	2	3	4	5	5	9	2	4	1	2	2	3	4	3	4	4	6	8	9	0	1	3	3	3	**Tissues/**
	3	1	2	5	4	5	1	1	3	4	4	5	1	4	5	1	2	3	3	3	1	2	1	2	5	**Tumors**
General Body System																										
Tissue NOS																										1
Chordoma																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma			X				X													X						4
Carcinoma																							X			3
Prostate	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	38
Interstitial cell, adenoma																	X									8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, metastatic, thyroid gland																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Axillary, carcinoma, metastatic, thyroid gland																										1
Mediastinal, carcinoma, metastatic, thyroid gland																										1
Mediastinal, histiocytic sarcoma, metastatic, spleen																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Histiocytic sarcoma, metastatic, spleen																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, spleen																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma													X													3
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Number of Days on Study	422	424	533	584	607	623	634	638	647	654	663	668	669	670	671	673	676	691	697	699	706	710	711	717	718	727
Carcass ID Number	402	414	385	365	362	425	445	375	352	323	334	322	373	351	374	434	353	384	403	441	394	371	343	415	381	442
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																										
Papilloma																		X								
Papilloma squamous																										
Subcutaneous tissue, fibroma				X																						
Subcutaneous tissue, neurofibroma																										
Subcutaneous tissue, neurofibrosarcoma																				X						
Subcutaneous tissue, neurofibrosarcoma, multiple																						X				
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor malignant													X													
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Carcinoma, metastatic, thyroid gland		X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye																				+	+					
Zymbal's gland																					+					
Carcinoma																					X					
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				X	
Leukemia mononuclear	X		X	X	X		X	X	X			X		X	X			X	X					X		X
Mesothelioma malignant																									X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	9	9	9	9	9	9	9	9	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3	
Carcass ID Number	3	3	3	3	3	3	3	4	4	3	3	3	3	4	3	3	3	3	3	3	4	4	4	4	4	**Total**
	1	2	3	4	5	5	9	2	4	1	2	2	3	4	3	4	4	6	8	9	0	1	3	3	3	**Tissues/**
	3	1	2	5	4	5	1	1	3	4	4	5	1	4	5	1	2	3	3	3	1	2	1	2	5	**Tumors**
Integumentary System																										
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma										X																1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Keratoacanthoma										X		X														2
Papilloma																										1
Papilloma squamous														X	X											2
Subcutaneous tissue, fibroma													X													2
Subcutaneous tissue, neurofibroma	X																									1
Subcutaneous tissue, neurofibrosarcoma																										1
Subcutaneous tissue, neurofibrosarcoma, multiple																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Granular cell tumor malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma						X																				1
Carcinoma, metastatic, thyroid gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																										
Eye	+										+	+									+	+				7
Zymbal's gland															+											2
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma													X													3
Leukemia mononuclear				X	X	X	X				X		X				X				X	X				23
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm

Number of Days on Study	1	3	4	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7
	8	8	0	7	7	8	9	0	0	0	1	4	4	6	6	8	8	8	9	9	0	1	1	1	1
	5	2	4	0	5	3	1	3	7	7	9	2	8	0	8	1	1	4	3	8	2	5	5	6	7
Carcass ID Number	4	4	5	4	5	4	4	5	5	5	4	5	4	5	4	4	5	5	4	5	5	4	4	5	5
	9	7	5	8	3	9	6	2	7	7	7	2	7	6	6	6	8	5	6	2	1	5	7	4	6
	3	3	5	1	4	2	2	5	1	2	1	2	4	5	5	1	3	4	4	4	3	3	2	5	4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin													X												
Hepatocellular adenoma																									
Mesentery				+	+				+										+				+		
Histiocytic sarcoma																							X		
Oral mucosa																+									
Gingival, squamous cell carcinoma																X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, mesentery																							X		
Pharynx																				+					
Palate, papilloma squamous																				X					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous				X																					
Stomach, glandular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																							X		
Bilateral, pheochromocytoma benign											X							X		X	X				X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																					X				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	1	1	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	
	8	8	9	9	9	9	9	9	9	9	9	9	0	0	0	0	1	1	1	2	2	2	3	3	3	
	5	5	4	4	4	4	5	5	5	5	5	5	4	4	5	5	5	5	5	5	5	5	5	5	5	**Total**
Carcass ID Number	0	1	5	9	9	9	3	4	4	5	6	8	8	8	0	4	4	5	6	6	7	7	8	8	8	**Tissues/**
	5	4	5	1	4	5	5	3	4	3	3	5	2	4	3	1	2	2	1	2	3	4	1	2	4	**Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Hepatocellular adenoma																								X		1
Mesentery																										5
Histiocytic sarcoma																										1
Oral mucosa																										1
Gingival, squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, mesentery																										1
Pharynx																										1
Palate, papilloma squamous																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																							X			1
Pheochromocytoma benign		X			X				X			X		X						X						7
Bilateral, pheochromocytoma benign				X																		X				7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X						X																X	3
Carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

Number of Days on Study	1 8 5	3 8 2	4 0 4	5 7 0	5 7 5	5 8 3	5 9 1	6 0 3	6 0 7	6 0 7	6 1 9	6 4 2	6 4 8	6 6 0	6 6 8	6 8 1	6 8 1	6 8 4	6 9 3	6 9 8	7 0 2	7 1 5	7 1 5	7 1 6	7 1 7
Carcass ID Number	4 9 3	4 7 3	5 5 5	4 8 1	5 3 4	4 9 2	4 6 2	5 2 5	5 7 1	5 7 2	4 7 1	5 2 2	4 7 4	5 6 5	4 6 5	4 6 1	5 8 3	5 5 4	4 6 4	5 2 4	5 1 3	4 5 3	4 7 2	5 4 5	5 6 4
Endocrine System (continued)																									
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X									X	X												
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, c-cell, adenoma																									
C-cell, adenoma										X			X	X	X									X	X
Follicular cell, adenoma																									
General Body System																									
Tissue NOS																	+								
Fibrosarcoma																	X								
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma								X					X												
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																							X		
Thymus	+	+	+	M	M	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma																									
Papilloma squamous																									
Trichoepithelioma																									
Subcutaneous tissue, fibroma															X									X	X
Subcutaneous tissue, fibrosarcoma													X												
Subcutaneous tissue, neurofibroma																									

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

Number of Days on Study	718	718	729	729	729	729	729	729	729	729	729	729	730	730	730	730	731	731	731	732	732	732	733	733	733	
Carcass ID Number	505	514	455	491	494	495	553	543	544	553	563	585	482	484	503	541	542	552	561	562	573	574	581	582	584	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma					X																					1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Pars distalis, adenoma	X	X		X		X										X									X	9
Pars distalis, carcinoma						X																				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, c-cell, adenoma										X																1
C-cell, adenoma							X							X												8
Follicular cell, adenoma																									X	1
General Body System																										
Tissue NOS																										1
Fibrosarcoma																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma			X																							3
Carcinoma	X																									1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	37
Interstitial cell, adenoma	X							X																		9
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	42
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																					X					1
Keratoacanthoma																X										1
Papilloma squamous									X																	1
Trichoepithelioma																								X		1
Subcutaneous tissue, fibroma																										3
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, neurofibroma		X																								1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

Number of Days on Study	185	382	404	570	575	583	591	603	607	607	619	642	648	660	668	681	681	684	693	698	702	715	715	716	717
Carcass ID Number	493	473	555	481	534	492	462	525	571	572	471	522	474	565	465	461	583	554	464	524	513	453	472	545	564
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, coccygeal, osteosarcoma																									
Skeletal muscle																							+		
Diaphragm, histiocytic sarcoma, metastatic, mesentery																							X		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, prostate																									
Fibrosarcoma, metastatic, ear										X															
Osteosarcoma, metastatic, multiple, bone																									
Mediastinum, histiocytic sarcoma, metastatic, mesentery																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear										+															
Pinna, fibrosarcoma										X															
Eye													+						+						+
Zymbal's gland													+												
Carcinoma													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortex, myxoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Leukemia mononuclear				X	X	X	X		X	X					X			X	X	X	X			X	
Mesothelioma malignant				X																					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

Number of Days on Study	718	718	729	729	729	729	729	729	729	729	729	729	730	730	730	730	731	731	731	732	732	732	733	733	733	
Carcass ID Number	505	514	455	491	494	495	535	543	544	553	563	585	482	484	503	541	542	552	561	562	573	574	581	582	584	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, coccygeal, osteosarcoma						X																				1
Skeletal muscle																										1
Diaphragm, histiocytic sarcoma, metastatic, mesentery																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, prostate	X																									1
Fibrosarcoma, metastatic, ear																										1
Osteosarcoma, metastatic, multiple, bone						X																				1
Mediastinum, histiocytic sarcoma, metastatic, mesentery																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Pinna, fibrosarcoma																										1
Eye		+	+							+	+			+	+		+	+	+	+		+				14
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortex, myxoma												X														1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear			X	X					X	X			X				X									18
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm

Number of Days on Study	2	3	3	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	8	8	8	6	0	2	2	4	6	7	8	0	0	1	2	2	4	4	4	5	5	6	6	6	7
	2	8	9	4	1	2	6	4	1	0	7	2	7	4	0	8	5	6	6	5	9	1	1	4	1
Carcass ID Number	7	7	7	6	6	7	6	7	6	6	6	6	6	7	6	5	6	6	7	7	6	6	6	7	7
	7	1	5	0	7	2	5	4	3	1	0	9	5	3	9	9	6	1	8	6	8	2	5	4	7
	1	3	1	2	4	5	5	3	3	5	1	2	4	5	1	3	3	4	2	4	5	2	2	1	5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Leiomyoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Histiocytic sarcoma, multiple														X											
Mesentery		+											+			+				+					
Oral mucosa															+										
Buccal, papilloma squamous																									
Gingival, squamous cell carcinoma															X										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																									
Palate, papilloma squamous																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peridontal tissue, squamous cell carcinoma, metastatic																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma	X																								
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																		X							
Bilateral, pheochromocytoma benign																	X		X				X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Carcinoma																									

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	678	681	681	683	683	687	695	710	711	718	718	726	726	729	729	729	729	729	729	729	729	729	729	730	730
Carcass ID Number	641	705	742	711	765	612	744	684	651	761	763	672	673	632	634	644	653	681	694	703	712	724	783	592	594
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																	X								
Leiomyoma								X																	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																				X					
Histiocytic sarcoma, multiple																									
Mesentery					+										+						+		+		
Oral mucosa									+																
Buccal, papilloma squamous									X																
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																+									
Palate, papilloma squamous																X									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peridontal tissue, squamous cell carcinoma, metastatic				X																					
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign		X		X				X	X							X				X	X	X		X	X
Bilateral, pheochromocytoma benign											X	X					X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma							X																		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	3	3	3
	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
Carcass ID Number	0	0	1	1	2	2	3	3	4	4	4	6	8	8	0	0	1	2	2	2	3	3	3	4	5
	4	5	1	3	1	4	1	5	2	3	5	2	2	3	1	4	4	1	2	3	2	3	4	5	2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Leiomyoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Histiocytic sarcoma, multiple																									
Mesentery													+	+	+					+		+		+	+
Oral mucosa																									
Buccal, papilloma squamous																									
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																									
Palate, papilloma squamous																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peridontal tissue, squamous cell carcinoma, metastatic																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X																				
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign	X	X	X				X		X					X		X			X	X			X		
Bilateral, pheochromocytoma benign												X													X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X			X									X
Carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	7 5 3	7 5 5	7 6 2	7 7 4	7 8 1	**Total Tissues/ Tumors**
Alimentary System						
Esophagus	+	+	+	+	+	80
Intestine large	+	+	+	+	+	80
Intestine large, cecum	+	+	+	+	+	80
Intestine large, colon	+	+	+	+	+	80
Intestine large, rectum	+	+	+	+	+	80
Intestine small	+	+	+	+	+	80
Intestine small, duodenum	+	+	+	+	+	80
Intestine small, ileum	+	+	+	+	+	79
Intestine small, jejunum	+	+	+	+	+	80
Adenocarcinoma						1
Leiomyoma						1
Liver	+	+	+	+	+	80
Hepatocellular adenoma						1
Histiocytic sarcoma, multiple						1
Mesentery		+				16
Oral mucosa						2
Buccal, papilloma squamous						1
Gingival, squamous cell carcinoma						1
Pancreas	+	+	+	+	+	79
Pharynx						1
Palate, papilloma squamous						1
Salivary glands	+	+	+	+	+	80
Stomach	+	+	+	+	+	80
Stomach, forestomach	+	+	+	+	+	80
Stomach, glandular	+	+	+	+	+	80
Tooth	+	+	+	+	+	80
Peridontal tissue, squamous cell carcinoma, metastatic						1
Cardiovascular System						
Heart	+	+	+	+	+	80
Hemangiosarcoma						1
Endocrine System						
Adrenal gland	+	+	+	+	+	80
Adrenal gland, cortex	+	+	+	+	+	80
Adenoma						1
Adrenal gland, medulla	+	+	+	+	+	80
Pheochromocytoma benign				X		22
Bilateral, pheochromocytoma benign						8
Islets, pancreatic	+	+	+	+	+	80
Adenoma						4
Carcinoma						1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	282	388	389	464	501	522	526	544	561	570	587	602	607	614	620	628	645	646	646	655	659	661	661	664	671
Carcass ID Number	771	713	751	602	674	725	655	743	633	615	601	692	654	735	691	593	663	614	782	764	685	622	652	741	775
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma, metastatic, thyroid gland																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X							X			X				X							X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, c-cell, adenoma																		X							
C-cell, adenoma									X		X														X
C-cell, carcinoma																									
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
Tissue NOS															+										
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma													X					X							
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X						X	X	X		X	X	X	X	X		X	X		X	
Interstitial cell, adenoma							X	X	X	X				X						X			X		
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, carcinoma, metastatic, thyroid gland																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																				X					
Thymus	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant						X																			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	678	681	681	683	683	687	695	710	711	718	718	726	726	729	729	729	729	729	729	729	729	729	729	730	730
Carcass ID Number	641	705	742	711	765	612	744	684	651	761	763	672	673	632	634	644	653	681	694	703	712	724	783	592	594
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Adenoma													X												
Carcinoma, metastatic, thyroid gland								X																	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X	X			X															X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, c-cell, adenoma																								X	
C-cell, adenoma							X				X				X					X	X				
C-cell, carcinoma								X																	
Follicular cell, adenoma															X				X						
Follicular cell, carcinoma																									
General Body System																									
Tissue NOS																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X					X										
Carcinoma																								X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+
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	X	X
Interstitial cell, adenoma					X	X																			
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, carcinoma, metastatic, thyroid gland																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant																									

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	3	3	3
	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
Carcass ID Number	0	0	1	1	2	2	3	3	4	4	4	6	8	8	0	0	1	2	2	2	3	3	3	4	5
	4	5	1	3	1	4	1	5	2	3	5	2	2	3	1	4	4	1	2	3	2	3	4	5	2
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M
Adenoma																									
Carcinoma, metastatic, thyroid gland																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X						X				X												X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, c-cell, adenoma																									
C-cell, adenoma													X												X
C-cell, carcinoma					X		X														X				
Follicular cell, adenoma																X									
Follicular cell, carcinoma																									
General Body System																									
Tissue NOS																									
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	X	X	
Interstitial cell, adenoma																									X
Hematopoietic System																									
Blood					+																				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, carcinoma, metastatic, thyroid gland							X																		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant																									

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	7 5 3	7 5 5	7 6 2	7 7 4	7 8 1	**Total Tissues/ Tumors**
Endocrine System (continued)						
Parathyroid gland	+	+	+	+	+	77
Adenoma						1
Carcinoma, metastatic, thyroid gland						1
Pituitary gland	+	+	+	+	+	80
Pars distalis, adenoma						13
Thyroid gland	+	+	+	+	+	80
Bilateral, c-cell, adenoma						2
C-cell, adenoma						10
C-cell, carcinoma						4
Follicular cell, adenoma						3
Follicular cell, carcinoma					X	1
General Body System						
Tissue NOS						1
Genital System						
Epididymis	+	+	+	+	+	80
Preputial gland	+	+	+	+	+	80
Adenoma				X		4
Carcinoma						4
Prostate	+	+	+	+	+	80
Seminal vesicle	+	+	+	+	+	77
Testes	+	+	+	+	+	80
Bilateral, interstitial cell, adenoma		X	X	X	X	62
Interstitial cell, adenoma	X					11
Hematopoietic System						
Blood						1
Bone marrow	+	+	+	+	+	80
Lymph node	+	+	+	+	+	80
Deep cervical, carcinoma, metastatic, thyroid gland						1
Lymph node, mandibular	+	+	+	+	+	80
Lymph node, mesenteric	+	+	+	+	+	76
Spleen	+	+	+	+	+	80
Hemangioma						1
Thymus	+	+	+	+	+	76
Thymoma malignant						1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	282	388	389	464	501	522	526	544	561	570	587	602	607	614	620	628	645	646	646	655	659	661	661	664	671
Carcass ID Number	771	713	751	602	674	725	655	743	633	615	601	692	654	735	691	593	663	614	782	764	685	622	652	741	775
Integumentary System																									
Mammary gland	M	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	M	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																						X			
Papilloma																									
Papilloma squamous																									
Subcutaneous tissue, fibroma											X														
Subcutaneous tissue, osteosarcoma																									
Subcutaneous tissue, osteosarcoma, metastatic, bone																									X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Humerus, osteosarcoma																									
Vertebra, osteosarcoma		X																							X
Skeletal muscle						+																			
Diaphragm, thymoma malignant, metastatic, thymus						X																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, carcinoma, metastatic, Zymbal's gland																									
Peripheral nerve																									
Spinal cord		+																							
Osteosarcoma, metastatic, bone		X																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland																									
Mediastinum, thymoma malignant, metastatic, thymus						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucosa, papilloma squamous																									
Mucosa, squamous cell carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland																									
Zymbal's gland										+	+														
Carcinoma										X															
Bilateral, carcinoma											X														

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	678	681	681	683	683	687	695	710	711	718	718	726	726	729	729	729	729	729	729	729	729	729	729	730	730
Carcass ID Number	641	705	742	711	765	612	744	684	651	761	763	672	673	632	634	644	653	681	694	703	712	724	783	592	594
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma										X															
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma				X		X																X			
Papilloma								X																	
Papilloma squamous																									
Subcutaneous tissue, fibroma	X														X								X		
Subcutaneous tissue, osteosarcoma																					X				
Subcutaneous tissue, osteosarcoma, metastatic, bone																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Humerus, osteosarcoma																									
Vertebra, osteosarcoma																									
Skeletal muscle																									
Diaphragm, thymoma malignant, metastatic, thymus																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, carcinoma, metastatic, Zymbal's gland			X																						
Peripheral nerve		+																							
Spinal cord		+																							
Osteosarcoma, metastatic, bone																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland			X																						
Mediastinum, thymoma malignant, metastatic, thymus																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucosa, papilloma squamous																X									
Mucosa, squamous cell carcinoma				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye			+						+		+		+				+			+					
Harderian gland																			+						
Zymbal's gland			+																						
Carcinoma			X																						
Bilateral, carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	733	733	733
Carcass ID Number	604	605	611	613	621	624	631	635	642	643	645	662	682	683	701	704	714	721	722	723	732	733	734	745	752
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																		X	X					X	
Papilloma				X																					
Papilloma squamous													X				X								
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, osteosarcoma																									
Subcutaneous tissue, osteosarcoma, metastatic, bone																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Humerus, osteosarcoma																								X	
Vertebra, osteosarcoma																									
Skeletal muscle																									
Diaphragm, thymoma malignant, metastatic, thymus																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, carcinoma, metastatic, Zymbal's gland																									
Peripheral nerve																									
Spinal cord																									
Osteosarcoma, metastatic, bone																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland																									
Mediastinum, thymoma malignant, metastatic, thymus																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucosa, papilloma squamous																									
Mucosa, squamous cell carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+				+			+	+						+	+					+				+
Harderian gland																									
Zymbal's gland																									
Carcinoma																									
Bilateral, carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	7 5 3	7 5 5	7 6 2	7 7 4	7 8 1	**Total Tissues/ Tumors**
Integumentary System						
Mammary gland	+	+	+	+	+	72
Fibroadenoma				X		2
Skin	+	+	+	+	+	80
Keratoacanthoma					X	8
Papilloma						2
Papilloma squamous						2
Subcutaneous tissue, fibroma						4
Subcutaneous tissue, osteosarcoma						1
Subcutaneous tissue, osteosarcoma, metastatic, bone						1
Musculoskeletal System						
Bone	+	+	+	+	+	80
Humerus, osteosarcoma						1
Vertebra, osteosarcoma						2
Skeletal muscle						1
Diaphragm, thymoma malignant, metastatic, thymus						1
Nervous System						
Brain	+	+	+	+	+	80
Meninges, carcinoma, metastatic, Zymbal's gland						1
Peripheral nerve						1
Spinal cord						2
Osteosarcoma, metastatic, bone						1
Respiratory System						
Lung	+	+	+	+	+	80
Carcinoma, metastatic, Zymbal's gland						1
Mediastinum, thymoma malignant, metastatic, thymus						1
Nose	+	+	+	+	+	80
Mucosa, papilloma squamous						1
Mucosa, squamous cell carcinoma						1
Trachea	+	+	+	+	+	80
Special Senses System						
Eye		+		+		16
Harderian gland						1
Zymbal's gland						3
Carcinoma						2
Bilateral, carcinoma						1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	2	3	3	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Number of Days on Study	8	8	8	6	0	2	2	4	6	7	8	0	0	1	2	2	4	4	4	5	5	6	6	6	7
	2	8	9	4	1	2	6	4	1	0	7	2	7	4	0	8	5	6	6	5	9	1	1	4	1
	7	7	7	6	6	7	6	7	6	6	6	6	6	7	6	5	6	6	7	7	6	6	6	7	7
Carcass ID Number	7	1	5	0	7	2	5	4	3	1	0	9	5	3	9	9	6	1	8	6	8	2	5	4	7
	1	3	1	2	4	5	5	3	3	5	1	2	4	5	1	3	3	4	2	4	5	2	2	1	5
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma																					X				
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X		X	X	X			X	X	X	X	X	X	X		X		X	X	X	
Mesothelioma benign											X														

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	678	681	681	683	683	687	695	710	711	718	718	726	726	729	729	729	729	729	729	729	729	729	729	730	730
Carcass ID Number	641	705	742	711	765	612	744	684	651	761	763	672	673	632	634	644	653	681	694	703	712	724	783	592	594
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma																									
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X	X	X	X	X		X	X	X				X	X		X		X	X		X
Mesothelioma benign																X									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	733	733	733
Carcass ID Number	604	605	611	613	621	624	631	635	642	643	645	662	682	683	701	704	714	721	722	723	732	733	734	745	752
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma																									
Renal tubule, adenoma																		X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X								X	X		X	X	X		X	X		X		X	X	X		
Mesothelioma benign																									

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	7 5 3	7 5 5	7 6 2	7 7 4	7 8 1	**Total Tissues/ Tumors**
Urinary System						
Kidney	+	+	+	+	+	80
Liposarcoma						1
Renal tubule, adenoma						1
Urinary bladder	+	+	+	+	+	80
Systemic Lesions						
Multiple organs	+	+	+	+	+	80
Leukemia mononuclear		X	X	X	X	47
Mesothelioma benign						2

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

	Control	25 ppm	100 ppm	175 ppm
Adrenal Gland (Medulla): Pheochromocytoma Benign				
Overall rates[a]	24/80 (30%)	20/51 (39%)	14/50 (28%)	30/80 (38%)
Adjusted rates[b]	47.1%	55.5%	45.2%	56.7%
Terminal rates[c]	16/42 (38%)	10/25 (40%)	7/23 (30%)	20/42 (48%)
First incidence (days)	648	533	619	645
Life table tests[d]	P=0.306	P=0.149	P=0.515	P=0.197
Logistic regression tests[d]	P=0.263	P=0.214	P=0.525N	P=0.167
Cochran-Armitage test[d]	P=0.311			
Fisher exact test[d]		P=0.184	P=0.484N	P=0.202
Adrenal Gland (Medulla): Pheochromocytoma (Benign, Complex, and Malignant)				
Overall rates	25/80 (31%)	20/51 (39%)	15/50 (30%)	30/80 (38%)
Adjusted rates	48.2%	55.5%	48.6%	56.7%
Terminal rates	16/42 (38%)	10/25 (40%)	8/23 (35%)	20/42 (48%)
First incidence (days)	648	533	619	645
Life table tests	P=0.339	P=0.187	P=0.475	P=0.246
Logistic regression tests	P=0.297	P=0.264	P=0.564N	P=0.217
Cochran-Armitage test	P=0.347			
Fisher exact test		P=0.227	P=0.520N	P=0.253
Bone: Osteosarcoma				
Overall rates	0/80 (0%)	0/51 (0%)	1/50 (2%)	3/80 (4%)
Adjusted rates	0.0%	0.0%	4.3%	5.3%
Terminal rates	0/42 (0%)	0/25 (0%)	1/23 (4%)	1/42 (2%)
First incidence (days)	---	---	729 (T)	388
Life table tests	P=0.030	-[e]	P=0.380	P=0.124
Logistic regression tests	P=0.027	-	P=0.380	P=0.099
Cochran-Armitage test	P=0.029			
Fisher exact test		-	P=0.385	P=0.123
Bone: Osteosarcoma[f]				
Overall rates	0/144 (0%)	0/70 (0%)	1/70 (1%)	3/100 (3%)
Adjusted rates	0.0%	0.0%	4.3%	5.2%
Interim sacrifice 1[g]	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Interim sacrifice 2[g]	0/9 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)
Terminal rates	0/42 (0%)	0/25 (0%)	1/23 (4%)	1/42 (2%)
First incidence (days)	---	---	729 (T)	388
Life table tests	P=0.025	-	P=0.380	P=0.095
Logistic regression tests	P=0.016	-	P=0.380	P=0.067
Cochran-Armitage test	P=0.015			
Fisher exact test		-	P=0.327	P=0.068
Mammary Gland: Fibroadenoma				
Overall rates	6/80 (8%)	1/51 (2%)	0/50 (0%)	2/80 (3%)
Adjusted rates	13.2%	4.0%	0.0%	4.5%
Terminal rates	4/42 (10%)	1/25 (4%)	0/23 (0%)	1/42 (2%)
First incidence (days)	712	729 (T)	---	718
Life table tests	P=0.098N	P=0.193N	P=0.079N	P=0.147N
Logistic regression tests	P=0.098N	P=0.171N	P=0.067N	P=0.145N
Cochran-Armitage test	P=0.093N			
Fisher exact test		P=0.166N	P=0.050N	P=0.138N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
Oral Cavity (Oral Mucosa, Tongue, or Pharynx): Squamous Papilloma				
Overall rates	0/80 (0%)	1/51 (2%)	1/50 (2%)	2/80 (3%)
Adjusted rates	0.0%	4.0%	3.2%	4.5%
Terminal rates	0/42 (0%)	1/25 (4%)	0/23 (0%)	1/42 (2%)
First incidence (days)	---	729 (T)	698	711
Life table tests	P=0.191	P=0.397	P=0.405	P=0.233
Logistic regression tests	P=0.185	P=0.397	P=0.405	P=0.233
Cochran-Armitage test	P=0.192			
Fisher exact test		P=0.389	P=0.385	P=0.248
Oral Cavity (Oral Mucosa, Tongue, or Pharynx): Squamous Papilloma or Squamous Cell Carcinoma				
Overall rates	0/80 (0%)	1/51 (2%)	2/50 (4%)	3/80 (4%)
Adjusted rates	0.0%	4.0%	6.0%	5.9%
Terminal rates	0/42 (0%)	1/25 (4%)	0/23 (0%)	1/42 (2%)
First incidence (days)	---	729 (T)	681	620
Life table tests	P=0.083	P=0.397	P=0.143	P=0.121
Logistic regression tests	P=0.082	P=0.397	P=0.142	P=0.123
Cochran-Armitage test	P=0.083			
Fisher exact test		P=0.389	P=0.146	P=0.123
Oral Cavity (Oral Mucosa, Tongue, or Pharynx): Squamous Papilloma or Squamous Cell Carcinoma[f]				
Overall rates	1/144 (0%)	1/70 (1%)	2/70 (3%)	3/100 (3%)
Adjusted rates	1.2%	4.0%	6.0%	5.9%
Interim sacrifice 1	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Interim sacrifice 2	0/9 (0%)	0/9 (0%)	0/10 (0%)	0/10 (0%)
Terminal rates	0/42 (0%)	1/25 (4%)	0/23 (0%)	1/42 (2%)
First incidence (days)	634	729 (T)	681	620
Life table tests	P=0.165	P=0.634	P=0.294	P=0.262
Logistic regression tests	P=0.128	P=0.605	P=0.257	P=0.211
Cochran-Armitage test	P=0.109			
Fisher exact test		P=0.548	P=0.250	P=0.189
Pancreatic Islets: Adenoma				
Overall rates	2/79 (3%)	0/49 (0%)	3/50 (6%)	4/80 (5%)
Adjusted rates	3.9%	0.0%	13.0%	8.5%
Terminal rates	1/42 (2%)	0/25 (0%)	3/23 (13%)	3/42 (7%)
First incidence (days)	645	---	729 (T)	614
Life table tests	P=0.114	P=0.345N	P=0.249	P=0.342
Logistic regression tests	P=0.110	P=0.346N	P=0.284	P=0.341
Cochran-Armitage test	P=0.118			
Fisher exact test		P=0.379N	P=0.293	P=0.347
Pancreatic Islets: Adenoma or Carcinoma				
Overall rates	3/79 (4%)	1/49 (2%)	4/50 (8%)	5/80 (6%)
Adjusted rates	6.3%	4.0%	15.9%	10.4%
Terminal rates	2/42 (5%)	1/25 (4%)	3/23 (13%)	3/42 (7%)
First incidence (days)	645	729 (T)	702	614
Life table tests	P=0.165	P=0.491N	P=0.214	P=0.359
Logistic regression tests	P=0.159	P=0.475N	P=0.246	P=0.360
Cochran-Armitage test	P=0.173			
Fisher exact test		P=0.504N	P=0.261	P=0.367

Table A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
Parathyroid Gland: Adenoma				
Overall rates	4/77 (5%)	1/51 (2%)	1/49 (2%)	1/77 (1%)
Adjusted rates	9.4%	4.0%	4.3%	2.3%
Terminal rates	3/41 (7%)	1/25 (4%)	1/23 (4%)	0/39 (0%)
First incidence (days)	719	729 (T)	729 (T)	726
Life table tests	P=0.152N	P=0.360N	P=0.396N	P=0.193N
Logistic regression tests	P=0.156N	P=0.348N	P=0.375N	P=0.201N
Cochran-Armitage test	P=0.143N			
Fisher exact test		P=0.336N	P=0.352N	P=0.183N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	15/80 (19%)	9/50 (18%)	9/49 (18%)	13/80 (16%)
Adjusted rates	30.1%	26.7%	30.1%	23.4%
Terminal rates	10/42 (24%)	3/25 (12%)	4/22 (18%)	5/42 (12%)
First incidence (days)	417	623	404	464
Life table tests	P=0.406N	P=0.573N	P=0.499	P=0.430N
Logistic regression tests	P=0.379N	P=0.516N	P=0.571N	P=0.412N
Cochran-Armitage test	P=0.378N			
Fisher exact test		P=0.554N	P=0.575N	P=0.418N
Preputial Gland: Adenoma				
Overall rates	7/80 (9%)	4/51 (8%)	3/47 (6%)	4/80 (5%)
Adjusted rates	14.6%	14.4%	9.0%	8.3%
Terminal rates	4/42 (10%)	3/25 (12%)	1/23 (4%)	2/42 (5%)
First incidence (days)	669	673	603	646
Life table tests	P=0.204N	P=0.593N	P=0.464N	P=0.278N
Logistic regression tests	P=0.201N	P=0.539N	P=0.435N	P=0.269N
Cochran-Armitage test	P=0.198N			
Fisher exact test		P=0.563N	P=0.456N	P=0.267N
Preputial Gland: Carcinoma				
Overall rates	1/80 (1%)	3/51 (6%)	1/47 (2%)	4/80 (5%)
Adjusted rates	1.6%	8.4%	4.0%	7.7%
Terminal rates	0/42 (0%)	1/25 (4%)	0/23 (0%)	2/42 (5%)
First incidence (days)	648	638	718	607
Life table tests	P=0.258	P=0.176	P=0.628	P=0.186
Logistic regression tests	P=0.259	P=0.156	P=0.641	P=0.182
Cochran-Armitage test	P=0.259			
Fisher exact test		P=0.164	P=0.605	P=0.184
Preputial Gland: Adenoma or Carcinoma				
Overall rates	8/80 (10%)	7/51 (14%)	4/47 (9%)	8/80 (10%)
Adjusted rates	15.9%	22.0%	12.7%	15.6%
Terminal rates	4/42 (10%)	4/25 (16%)	1/23 (4%)	4/42 (10%)
First incidence (days)	648	638	603	607
Life table tests	P=0.422N	P=0.335	P=0.535N	P=0.594
Logistic regression tests	P=0.417N	P=0.379	P=0.504N	P=0.602N
Cochran-Armitage test	P=0.415N			
Fisher exact test		P=0.350	P=0.524N	P=0.603N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
Skin: Keratoacanthoma				
Overall rates	9/80 (11%)	2/51 (4%)	1/50 (2%)	8/80 (10%)
Adjusted rates	18.3%	8.0%	4.3%	16.8%
Terminal rates	6/42 (14%)	2/25 (8%)	1/23 (4%)	5/42 (12%)
First incidence (days)	549	729 (T)	729 (T)	661
Life table tests	P=0.545	P=0.141N	P=0.074N	P=0.510N
Logistic regression tests	P=0.540	P=0.114N	P=0.056N	P=0.499N
Cochran-Armitage test	P=0.543N			
Fisher exact test		P=0.123N	P=0.050N	P=0.500N
Skin: Trichoepithelioma and Keratoacanthoma				
Overall rates	9/80 (11%)	2/51 (4%)	2/50 (4%)	8/80 (10%)
Adjusted rates	18.3%	8.0%	8.7%	16.8%
Terminal rates	6/42 (14%)	2/25 (8%)	2/23 (9%)	5/42 (12%)
First incidence (days)	549	730 (T)	730 (T)	661
Life table tests	P=0.517	P=0.141N	P=0.166N	P=0.510N
Logistic regression tests	P=0.510	P=0.114N	P=0.132N	P=0.499N
Cochran-Armitage test	P=0.523			
Fisher exact test		P=0.123N	P=0.130N	P=0.500N
Skin: Papilloma or Squamous Papilloma				
Overall rates	1/80 (1%)	3/51 (6%)	1/50 (2%)	4/80 (5%)
Adjusted rates	2.4%	10.7%	4.3%	9.1%
Terminal rates	1/42 (2%)	2/25 (8%)	1/23 (4%)	3/42 (7%)
First incidence (days)	729 (T)	691	729 (T)	710
Life table tests	P=0.260	P=0.151	P=0.622	P=0.180
Logistic regression tests	P=0.247	P=0.163	P=0.622	P=0.171
Cochran-Armitage test	P=0.261			
Fisher exact test		P=0.164	P=0.623	P=0.184
Skin (Subcutaneous Tissue): Fibroma				
Overall rates	0/80 (0%)	2/51 (4%)	3/50 (6%)	4/80 (5%)
Adjusted rates	0.0%	6.0%	10.0%	7.8%
Terminal rates	0/42 (0%)	1/25 (4%)	0/23 (0%)	2/42 (5%)
First incidence (days)	---	584	668	587
Life table tests	P=0.076	P=0.152	P=0.045	P=0.067
Logistic regression tests	P=0.074	P=0.137	P=0.052	P=0.065
Cochran-Armitage test	P=0.074			
Fisher exact test		P=0.150	P=0.055	P=0.060
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rates	1/80 (1%)	2/51 (4%)	4/50 (8%)	4/80 (5%)
Adjusted rates	1.6%	6.0%	12.3%	7.8%
Terminal rates	0/42 (0%)	1/25 (4%)	0/23 (0%)	2/42 (5%)
First incidence (days)	646	584	648	587
Life table tests	P=0.140	P=0.360	P=0.062	P=0.187
Logistic regression tests	P=0.140	P=0.329	P=0.070	P=0.182
Cochran-Armitage test	P=0.139			
Fisher exact test		P=0.335	P=0.072	P=0.184

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
Spleen: Histiocytic Sarcoma				
Overall rates	0/79 (0%)	3/51 (6%)	0/50 (0%)	0/80 (0%)
Adjusted rates	0.0%	10.5%	0.0%	0.0%
Terminal rates	0/42 (0%)	1/25 (4%)	0/23 (0%)	0/42 (0%)
First incidence (days)	---	706	---	---
Life table tests	P=0.178N	P=0.049	-	-
Logistic regression tests	P=0.175N	P=0.056	-	-
Cochran-Armitage test	P=0.168N			
Fisher exact test		P=0.058	-	-
Testes: Adenoma				
Overall rates	70/80 (88%)	46/51 (90%)	46/50 (92%)	73/80 (91%)
Adjusted rates	100.0%	100.0%	97.9%	98.6%
Terminal rates	42/42 (100%)	25/25 (100%)	22/23 (96%)	41/42 (98%)
First incidence (days)	543	533	570	501
Life table tests	P=0.339	P=0.340	P=0.166	P=0.368
Logistic regression tests	P=0.172	P=0.527N	P=0.310	P=0.324
Cochran-Armitage test	P=0.257			
Fisher exact test		P=0.431	P=0.309	P=0.305
Thyroid Gland (C-Cell): Adenoma				
Overall rates	14/80 (18%)	10/51 (20%)	9/50 (18%)	12/80 (15%)
Adjusted rates	28.1%	33.1%	27.6%	22.8%
Terminal rates	9/42 (21%)	6/25 (24%)	3/23 (13%)	6/42 (14%)
First incidence (days)	571	669	607	561
Life table tests	P=0.343N	P=0.424	P=0.469	P=0.425N
Logistic regression tests	P=0.331N	P=0.504	P=0.561	P=0.411N
Cochran-Armitage test	P=0.321N			
Fisher exact test		P=0.467	P=0.560	P=0.415N
Thyroid Gland (C-Cell): Carcinoma				
Overall rates	1/80 (1%)	1/51 (2%)	0/50 (0%)	4/80 (5%)
Adjusted ratesa	2.2%	2.0%	0.0%	9.1%
Terminal rates	0/42 (0%)	0/25 (0%)	0/23 (0%)	3/42 (7%)
First incidence (days)	719	424	---	710
Life table tests	P=0.110	P=0.649	P=0.634N	P=0.180
Logistic regression tests	P=0.106	P=0.602	P=0.603N	P=0.172
Cochran-Armitage test	P=0.106			
Fisher exact test		P=0.629	P=0.615N	P=0.184
Thyroid Gland (C-Cell): Adenoma or Carcinoma				
Overall rates	15/80 (19%)	11/51 (22%)	9/50 (18%)	16/80 (20%)
Adjusted rates	29.7%	34.4%	27.6%	30.7%
Terminal rates	9/42 (21%)	6/25 (24%)	3/23 (13%)	9/42 (21%)
First incidence (days)	571	424	607	561
Life table tests	P=0.504	P=0.387	P=0.530	P=0.491
Logistic regression tests	P=0.511	P=0.467	P=0.556N	P=0.501
Cochran-Armitage test	P=0.521			
Fisher exact test		P=0.429	P=0.554N	P=0.500

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rates	1/80 (1%)	1/51 (2%)	1/50 (2%)	4/80 (5%)
Adjusted rates	2.0%	4.0%	4.3%	9.5%
Terminal rates	0/42 (0%)	1/25 (4%)	1/23 (4%)	4/42 (10%)
First incidence (days)	712	729 (T)	729 (T)	729 (T)
Life table tests	P=0.103	P=0.633	P=0.628	P=0.177
Logistic regression tests	P=0.096	P=0.658	P=0.641	P=0.171
Cochran-Armitage test	P=0.102			
Fisher exact test		P=0.629	P=0.623	P=0.184
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma[f]				
Overall rates	1/144 (1%)	1/70 (1%)	1/70 (1%)	5/100 (5%)
Adjusted rates	1.9%	4.0%	4.3%	10.6%
Interim sacrifice 1	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Interim sacrifice 2	0/9 (0%)	0/9 (0%)	0/10 (0%)	1/10 (10%)
Terminal rates	0/42 (0%)	1/25 (4%)	1/23 (4%)	4/42 (10%)
First incidence (days)	712	729 (T)	729 (T)	459 (I)
Life table tests	P=0.048	P=0.629	P=0.623	P=0.107
Logistic regression tests	P=0.027	P=0.630	P=0.613	P=0.055
Cochran-Armitage test	P=0.020			
Fisher exact test		P=0.548	P=0.548	P=0.044
All Organs: Histiocytic Sarcoma				
Overall rates	0/80 (0%)	3/51 (6%)	1/50 (2%)	1/80 (1%)
Adjusted rates	0.0%	10.5%	3.4%	1.5%
Terminal rates	0/42 (0%)	1/25 (4%)	0/23 (0%)	0/42 (0%)
First incidence (days)	---	706	715	614
Life table tests	P=0.506N	P=0.049	P=0.395	P=0.506
Logistic regression tests	P=0.500N	P=0.056	P=0.399	P=0.485
Cochran-Armitage test	P=0.498N			
Fisher exact test		P=0.057	P=0.385	P=0.500
All Organs: Leukemia (Lymphocytic, Monocytic, Mononuclear, or Undifferentiated)				
Overall rates	54/80 (68%)	23/51 (45%)	18/50 (36%)	47/80 (59%)
Adjusted rates	77.5%	55.7%	47.0%	69.1%
Terminal rates	27/42 (64%)	9/25 (36%)	6/23 (26%)	22/42 (52%)
First incidence (days)	325	422	570	389
Life table tests	P=0.336N	P=0.053N	P=0.014N	P=0.261N
Logistic regression tests	P=0.252N	P=0.008N	P<0.001N	P=0.150N
Cochran-Armitage test	P=0.253N			
Fisher exact test		P=0.009N	P<0.001N	P=0.163N
All Organs: Osteosarcoma				
Overall rates	0/80 (0%)	0/51 (0%)	1/50 (2%)	4/80 (5%)
Adjusted rates	0.0%	0.0%	4.3%	7.6%
Terminal rates	0/42 (0%)	0/25 (0%)	1/23 (4%)	2/42 (5%)
First incidence (days)	---	---	729 (T)	388
Life table tests	P=0.012	-	P=0.380	P=0.066
Logistic regression tests	P=0.010	-	P=0.380	P=0.057
Cochran-Armitage test	P=0.011			
Fisher exact test		-	P=0.385	P=0.060

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
All Organs: Benign Tumors				
Overall rates	74/80 (93%)	49/51 (96%)	47/50 (94%)	76/80 (95%)
Adjusted rates	100.0%	100.0%	97.9%	100.0%
Terminal rates	42/42 (100%)	25/25 (100%)	22/23 (96%)	42/42 (100%)
First incidence (days)	417	533	404	464
Life table tests	P=0.417	P=0.327	P=0.252	P=0.420
Logistic regression tests	P=0.370	P=0.693	P=0.589	P=0.497
Cochran-Armitage test	P=0.389			
Fisher exact test		P=0.332	P=0.521	P=0.373
All Organs: Malignant Tumors				
Overall rates	58/80 (73%)	31/51 (61%)	26/50 (52%)	62/80 (78%)
Adjusted rates	81.3%	66.2%	62.9%	81.2%
Terminal rates	29/42 (69%)	10/25 (40%)	9/23 (39%)	28/42 (67%)
First incidence (days)	325	422	570	282
Life table tests	P=0.271	P=0.257N	P=0.131N	P=0.345
Logistic regression tests	P=0.215	P=0.102N	P=0.013N	P=0.300
Cochran-Armitage test	P=0.215			
Fisher exact test		P=0.114N	P=0.015N	P=0.292
All Organs: Benign and Malignant Tumors				
Overall rates	76/80 (95%)	51/51 (100%)	48/50 (96%)	80/80 (100%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	42/42 (100%)	25/25 (100%)	23/23 (100%)	42/42 (100%)
First incidence (days)	325	422	404	282
Life table tests	P=0.349	P=0.294	P=0.265	P=0.335
Logistic regression tests	P=0.126	P=0.355	P=0.694	P=0.132
Cochran-Armitage test	P=0.099			
Fisher exact test		P=0.135	P=0.577	P=0.060

(I)Interim sacrifice
(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals necropsied or examined microscopically for this tumor type
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly to the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] No tumors in dosed group or control group; statistical test not performed.
[f] Includes paired controls and animals examined at interim sacrifices
[g] Observed incidence at interim sacrifice (interim 1: 184 days; interim 2: 459 days)

TABLE A4a
Historical Incidence of Osteosarcoma in Untreated Male F344/N Rats

Study	Incidence of Osteosarcomas in Controls
Historical Incidence at Battelle Columbus Laboratory[a]	
Chlorobenzene	0/50
N-phenyl-2-naphthylamine	1/50
Rotenone	0/50
l-ascorbic acid	1/50
2,4-Dichlorophenol	0/50
Diphenylhydantoin	0/50
Ethylenethiourea	0/50
Total	2/350 (0.6%)
Standard deviation	1.0%
Range	0%-2%
Overall Historical Incidence[b]	
Total	10/2106 (0.5%)
Standard deviation	1.2%
Range	0%-6%

[a] Data as of 1 January 1990
[b] No osteomas reported in 2106 untreated controls.

TABLE A4b
Historical Incidence of Oral Cavity Tumors in Untreated Male F344/N Rats

Study	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Papilloma or Carcinoma
Historical Incidence at Battelle Columbus Laboratory[a]			
Chlorobenzene	0/50	0/50	0/50
N-phenyl-2-naphthylamine	0/50	0/50	0/50
Rotenone	1/50	0/50	1/50
l-ascorbic acid	0/50	0/50	0/50
2,4-Dichlorophenol	0/50	0/50	0/50
Diphenylhydantoin	0/50	0/50	0/50
Ethylenethiourea	0/50	0/50	0/50
Total	1/350 (0.3%)	0/350 (0%)	1/350 (0.3%)
Standard deviation	0.8%	0%	0.8%
Range	0%-2%	0%-0%	0%-2%
Overall Historical Incidence			
Total	8/2106 (0.4%)	6/2106 (0.3%)	14/2106 (0.7%)
Standard deviation	1.0%	0.7%	1.3%
Range	0%-4%	0%-2%	0%-4%

[a] Data as of 1 January 1990

TABLE A4c
Historical Incidence of Thyroid Gland Follicular Cell Neoplasms in Untreated Male F344/N Rats

Study	Incidence in Controls		
	Adenoma	Carcinoma[a]	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratory[b]			
Chlorobenzene	1/49	0/49	1/49
N-phenyl-2-naphthylamine	1/49	0/49	1/49
Rotenone	0/50	1/50	1/50
l-ascorbic acid	0/49	1/49	1/49
2,4-Dichlorophenol	0/50	0/50	0/50
Diphenylhydantoin	0/50	1/50	1/50
Ethylenethiourea	0/50	1/50	1/50
Total	2/347 (0.6%)	4/347 (1.2%)	6/347 (1.7%)
Standard deviation	1.0%	1.1%	0.8%
Range	0%-2%	0%-2%	0%-2%
Overall Historical Incidence			
Total	13/2086 (0.6%)	13/2086 (0.6%)	26/2086 (1.2%)
Standard deviation	1.2%	0.9%	1.5%
Range	0%-5%	0%-2%	0%-6%

[a] Including adenocarcinoma
[b] Data as of 1 January 1990

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

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Disposition Summary					
Animals initially in study	100	50	70	70	100
Early deaths					
Moribund sacrifice	21	12	13	13	19
Natural death	17	6	13	13	19
Survivors					
Terminal sacrifice	42	5	25	23	42
Paired control		27			
Animals examined microscopically	80	45	51	50	80
Alimentary System					
Intestine large, cecum	(79)	(45)	(50)	(50)	(80)
Congestion	1 (1%)				
Ulcer		1 (2%)			
Intestine large, colon	(79)	(45)	(51)	(50)	(80)
Ulcer			1 (2%)		
Serosa, inflammation, chronic active			1 (2%)		
Intestine large, rectum	(79)	(45)	(51)	(50)	(80)
Muscularis, inflammation, chronic active					1 (1%)
Intestine small, duodenum	(80)	(45)	(51)	(50)	(80)
Ulcer		1 (2%)			
Intestine small, jejunum	(80)	(45)	(51)	(50)	(80)
Inflammation, granulomatous, chronic active			1 (2%)		
Liver	(80)	(45)	(51)	(50)	(80)
Angiectasis		2 (4%)			2 (3%)
Basophilic focus	15 (19%)	5 (11%)	22 (43%)	15 (30%)	22 (28%)
Clear cell focus	22 (28%)	2 (4%)	19 (37%)	15 (30%)	18 (23%)
Congestion				2 (4%)	1 (1%)
Eosinophilic focus	5 (6%)	1 (2%)	3 (6%)	3 (6%)	5 (6%)
Hepatodiaphragmatic nodule	7 (9%)	6 (13%)	4 (8%)	4 (8%)	9 (11%)
Hyperplasia	4 (5%)	1 (2%)	3 (6%)	3 (6%)	9 (11%)
Infarct				1 (2%)	
Inflammation, chronic active	3 (4%)	3 (7%)	2 (4%)	3 (6%)	2 (3%)
Mixed cell focus			3 (6%)		1 (1%)
Necrosis					2 (3%)
Vacuolization cytoplasmic	24 (30%)	28 (62%)	18 (35%)	13 (26%)	22 (28%)
Bile duct, hyperplasia	65 (81%)	37 (82%)	39 (76%)	38 (76%)	70 (88%)
Hepatocyte, cytomegaly, focal			1 (2%)		
Hepatocyte, degeneration, cystic	13 (16%)	3 (7%)	8 (16%)	10 (20%)	14 (18%)
Serosa, fibrosis				1 (2%)	1 (1%)
Subserosa, congestion			1 (2%)		
Mesentery	(13)	(6)	(9)	(5)	(16)
Artery, thrombus				1 (20%)	
Fat, hemorrhage		1 (17%)			
Fat, inflammation, chronic active	12 (92%)	4 (67%)	7 (78%)	2 (40%)	15 (94%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Alimentary System (continued)					
Pancreas	(79)	(45)	(50)	(50)	(79)
Acinus, atrophy	25 (32%)	18 (40%)	15 (30%)	18 (36%)	18 (23%)
Acinus, hyperplasia	1 (1%)	1 (2%)		1 (2%)	
Artery, inflammation, chronic active	5 (6%)	2 (4%)	5 (10%)		6 (8%)
Duct, cyst				2 (4%)	
Duct, hyperplasia					1 (1%)
Vein, thrombus	1 (1%)				
Salivary glands	(80)	(45)	(50)	(50)	(80)
Acinus, atrophy					1 (1%)
Stomach, forestomach	(79)	(45)	(51)	(50)	(80)
Acanthosis	9 (11%)	2 (4%)	3 (6%)	4 (8%)	2 (3%)
Inflammation, acute	1 (1%)				
Inflammation, chronic active	3 (4%)	1 (2%)		1 (2%)	2 (3%)
Mineralization	1 (1%)				
Ulcer	8 (10%)	3 (7%)	8 (16%)	3 (6%)	3 (4%)
Submucosa, ectopic tissue				1 (2%)	
Stomach, glandular	(79)	(45)	(51)	(49)	(80)
Cyst epithelial inclusion			1 (2%)		
Dysplasia	2 (3%)				
Erosion				1 (2%)	
Hyperplasia	1 (1%)				
Inflammation, chronic active				1 (2%)	
Mineralization	3 (4%)	1 (2%)		2 (4%)	1 (1%)
Necrosis	4 (5%)		3 (6%)	3 (6%)	6 (8%)
Pigmentation, hemosiderin			3 (6%)	4 (8%)	2 (3%)
Ulcer	7 (9%)	3 (7%)	3 (6%)	1 (2%)	1 (1%)
Tongue			(2)		
Mucosa, hyperplasia, squamous			1 (50%)		
Tooth	(80)	(45)	(51)	(50)	(80)
Dentine, incisor, dysplasia	4 (5%)		7 (14%)	14 (28%)	30 (38%)
Dentine, incisor, necrosis, focal			1 (2%)		
Dentine, incisor, necrosis, multifocal	75 (94%)	33 (73%)	42 (82%)	44 (88%)	73 (91%)
Incisor, odontoblast, degeneration			1 (2%)	2 (4%)	4 (5%)
Incisor, ameloblast, degeneration			1 (2%)	7 (14%)	23 (29%)
Peridontal tissue, fibrosis					1 (1%)
Peridontal tissue, incisor, inflammation, suppurative					2 (3%)
Peridontal tissue, molar, inflammation, suppurative, chronic	1 (1%)				1 (1%)
Peridontal tissue, molar, lower, inflammation, suppurative, chronic	27 (34%)	22 (49%)	21 (41%)	19 (38%)	33 (41%)
Pulp, incisor, inflammation, necrotizing, chronic			1 (2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Cardiovascular System					
Blood vessel	(1)				
Aorta, mineralization	1 (100%)				
Heart	(80)	(45)	(51)	(50)	(80)
Degeneration, chronic	73 (91%)	35 (78%)	47 (92%)	43 (86%)	67 (84%)
Mineralization	2 (3%)	1 (2%)			
Thrombus	6 (8%)	1 (2%)	2 (4%)	3 (6%)	4 (5%)
Atrium, dilatation			1 (2%)	1 (2%)	1 (1%)
Endocrine System					
Adrenal gland	(80)	(45)	(51)	(50)	(80)
Accessory adrenal cortical nodule	1 (1%)				
Hyperplasia	1 (1%)				
Capsule, spindle cell, hyperplasia			1 (2%)		
Adrenal gland, cortex	(80)	(45)	(51)	(50)	(80)
Congestion				1 (2%)	
Hemorrhage	1 (1%)				
Hyperplasia	9 (11%)	3 (7%)	12 (24%)	12 (24%)	12 (15%)
Hypertrophy			1 (2%)	2 (4%)	4 (5%)
Vacuolization cytoplasmic, focal	6 (8%)	1 (2%)	3 (6%)	6 (12%)	8 (10%)
Bilateral, degeneration, cystic, focal			1 (2%)		
Adrenal gland, medulla	(80)	(45)	(51)	(50)	(80)
Hemorrhage	1 (1%)				
Hyperplasia	33 (41%)	11 (24%)	21 (41%)	16 (32%)	28 (35%)
Islets, pancreatic	(79)	(45)	(49)	(50)	(80)
Hyperplasia	1 (1%)		3 (6%)	1 (2%)	2 (3%)
Parathyroid gland	(77)	(43)	(51)	(49)	(77)
Hyperplasia	1 (1%)			2 (4%)	1 (1%)
Pituitary gland	(80)	(44)	(50)	(49)	(80)
Pars distalis, congestion	2 (3%)		3 (6%)	5 (10%)	6 (8%)
Pars distalis, cyst	4 (5%)	2 (5%)	3 (6%)	3 (6%)	2 (3%)
Pars distalis, hemorrhage	3 (4%)			1 (2%)	1 (1%)
Pars distalis, hyperplasia	14 (18%)	6 (14%)	8 (16%)	6 (12%)	7 (9%)
Pars distalis, inflammation, chronic active	1 (1%)				
Pars distalis, karyomegaly					1 (1%)
Pars distalis, vacuolization cytoplasmic, focal			1 (2%)		
Pars intermedia, cyst	3 (4%)	2 (5%)	1 (2%)	2 (4%)	2 (3%)
Thyroid gland	(80)	(45)	(51)	(50)	(80)
Metaplasia, osseous					1 (1%)
C-cell, hyperplasia	5 (6%)	3 (7%)	3 (6%)	4 (8%)	8 (10%)
Follicle, cyst	2 (3%)		1 (2%)	2 (4%)	2 (3%)
Follicular cell, hyperplasia	2 (3%)			1 (2%)	1 (1%)
General Body System					
None					

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Genital System					
Ductus deferens		(1)			
Hemorrhage		1 (100%)			
Epididymis	(80)	(45)	(51)	(50)	(80)
Dilatation	2 (3%)				
Hemorrhage		1 (2%)			
Inflammation, chronic active		2 (4%)			1 (1%)
Preputial gland	(80)	(45)	(51)	(47)	(80)
Hyperplasia, glandular		1 (2%)	1 (2%)		1 (1%)
Inflammation, chronic active	48 (60%)	30 (67%)	41 (80%)	33 (70%)	61 (76%)
Duct, cyst	4 (5%)	1 (2%)	5 (10%)	4 (9%)	6 (8%)
Prostate	(79)	(45)	(50)	(49)	(80)
Atrophy					1 (1%)
Dilatation	4 (5%)		1 (2%)	1 (2%)	4 (5%)
Hyperplasia					1 (1%)
Inflammation, chronic active	29 (37%)	11 (24%)	18 (36%)	13 (27%)	17 (21%)
Seminal vesicle	(78)	(45)	(51)	(49)	(77)
Atrophy	2 (3%)				3 (4%)
Dilatation				1 (2%)	
Inflammation, chronic active				1 (2%)	1 (1%)
Testes	(80)	(45)	(51)	(50)	(80)
Interstitial cell, hyperplasia	30 (38%)	30 (67%)	15 (29%)	14 (28%)	30 (38%)
Seminiferous tubule, atrophy	20 (25%)	5 (11%)	5 (10%)	10 (20%)	10 (13%)
Serosa, inflammation, chronic active		1 (2%)			
Hematopoietic System					
Bone marrow	(79)	(45)	(51)	(50)	(80)
Femoral, atrophy			1 (2%)		
Femoral, myelofibrosis	2 (3%)				
Lymph node	(79)	(45)	(51)	(50)	(80)
Mediastinal, congestion				1 (2%)	
Mediastinal, depletion lymphoid		1 (2%)			
Mediastinal, infiltration cellular, histiocytic		1 (2%)			
Mediastinal, inflammation, acute				1 (2%)	
Renal, angiectasis					1 (1%)
Renal, congestion					1 (1%)
Lymph node, mandibular	(79)	(45)	(50)	(50)	(80)
Angiectasis	1 (1%)		2 (4%)		2 (3%)
Congestion			1 (2%)		
Infiltration cellular, histiocytic		1 (2%)			1 (1%)
Inflammation, chronic active				1 (2%)	
Lymph node, mesenteric	(79)	(45)	(50)	(49)	(76)
Angiectasis			1 (2%)	1 (2%)	1 (1%)
Congestion					1 (1%)
Infiltration cellular, histiocytic		1 (2%)			
Inflammation, chronic active			1 (2%)	1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Hematopoietic System (continued)					
Spleen	(79)	(45)	(51)	(50)	(80)
Depletion lymphoid	1 (1%)	1 (2%)	1 (2%)	1 (2%)	
Fibrosis	10 (13%)	2 (4%)	6 (12%)	9 (18%)	9 (11%)
Hematopoietic cell proliferation			1 (2%)	1 (2%)	1 (1%)
Hyperplasia, reticulum cell		1 (2%)			
Necrosis				1 (2%)	1 (1%)
Capsule, cyst, multiple		1 (2%)			
Red pulp, atrophy	1 (1%)		1 (2%)		
Thymus	(69)	(43)	(48)	(42)	(76)
Depletion lymphoid	54 (78%)	19 (44%)	42 (88%)	38 (90%)	66 (87%)
Integumentary System					
Mammary gland	(75)	(43)	(48)	(47)	(72)
Hyperplasia, cystic	70 (93%)	37 (86%)	47 (98%)	46 (98%)	66 (92%)
Duct, hemorrhage					1 (1%)
Skin	(80)	(45)	(51)	(50)	(80)
Acanthosis	1 (1%)				
Cyst epithelial inclusion			2 (4%)		
Hyperkeratosis		1 (2%)	1 (2%)	1 (2%)	
Ulcer			1 (2%)		
Sebaceous gland, cyst			1 (2%)		
Subcutaneous tissue, foreign body		1 (2%)			
Subcutaneous tissue, inflammation, chronic active		1 (2%)	1 (2%)		2 (3%)
Subcutaneous tissue, metaplasia, osseous					1 (1%)
Musculoskeletal System					
Bone	(80)	(45)	(51)	(50)	(80)
Epiphysis, tibia, cyst			1 (2%)	1 (2%)	
Epiphysis, tibia, cyst, multifocal			1 (2%)		
Femur, fibrous osteodystrophy					1 (1%)
Femur, osteosclerosis					1 (1%)
Humerus, fibrous osteodystrophy	8 (10%)	2 (4%)	6 (12%)	8 (16%)	2 (3%)
Humerus, osteoporosis			1 (2%)		
Humerus, osteosclerosis	4 (5%)	1 (2%)	1 (2%)	1 (2%)	
Humerus, joint, cartilage, degeneration	1 (1%)			1 (2%)	1 (1%)
Humerus, joint, cartilage, degeneration, focal	1 (1%)				1 (1%)
Humerus, joint, cartilage, necrosis, focal	1 (1%)		1 (2%)	1 (2%)	
Humerus, epiphysis, cyst			1 (2%)		
Joint, cartilage, tibia, degeneration			1 (2%)		2 (3%)
Joint, cartilage, tibia, necrosis, focal	1 (1%)				
Mandible, fibrous osteodystrophy	1 (1%)	2 (4%)	1 (2%)	3 (6%)	1 (1%)
Maxilla, fibrous osteodystrophy	7 (9%)	2 (4%)	5 (10%)	4 (8%)	1 (1%)
Maxilla, fibrous osteodystrophy, multifocal					1 (1%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Musculoskeletal System					
Bone (continued)	(80)	(45)	(51)	(50)	(80)
Thoracic, periosteum, vertebra, hyperostosis	1 (1%)				
Thoracic, vertebra, fibrous osteodystrophy	7 (9%)	1 (2%)	3 (6%)	6 (12%)	3 (4%)
Thoracic, vertebra, osteosclerosis				1 (2%)	
Thoracic, vertebra, intervertebral disc, degeneration	1 (1%)				
Tibia, fibrous osteodystrophy	10 (13%)	3 (7%)	5 (10%)	5 (10%)	2 (3%)
Tibia, necrosis, focal					1 (1%)
Tibia, osteoporosis			1 (2%)		
Tibia, osteosclerosis	2 (3%)	1 (2%)	1 (2%)	4 (8%)	3 (4%)
Tibia, thrombus, chronic, focal			1 (2%)		
Nervous System					
Brain	(80)	(45)	(51)	(50)	(80)
Compression	2 (3%)	1 (2%)	3 (6%)	3 (6%)	2 (3%)
Degeneration	1 (1%)				
Hemorrhage					1 (1%)
Hydrocephalus	2 (3%)		2 (4%)	2 (4%)	1 (1%)
Necrosis, subacute	1 (1%)				
Vein, thrombus					1 (1%)
Peripheral nerve	(1)	(1)			(1)
Sciatic, degeneration		1 (100%)			1 (100%)
Respiratory System					
Lung	(80)	(45)	(51)	(50)	(80)
Hemorrhage		1 (2%)			
Inflammation, chronic active	1 (1%)	2 (4%)			2 (3%)
Mineralization	1 (1%)				
Alveolar epithelium, hyperplasia	2 (3%)	2 (4%)	2 (4%)	5 (10%)	3 (4%)
Pleura, hyperplasia					1 (1%)
Pleura, inflammation, chronic active			1 (2%)	1 (2%)	
Nose	(80)	(45)	(51)	(50)	(80)
Metaplasia, squamous	2 (3%)	1 (2%)			
Mucosa, inflammation, acute		7 (16%)	1 (2%)	2 (4%)	4 (5%)
Mucosa, inflammation, chronic active	25 (31%)	6 (13%)	17 (33%)	14 (28%)	22 (28%)
Mucosa, ulcer	1 (1%)	3 (7%)		2 (4%)	1 (1%)
Sinus, foreign body	20 (25%)	4 (9%)	15 (29%)	11 (22%)	21 (26%)
Special Senses System					
Ear	(3)	(1)		(1)	
Pinna, acanthosis	1 (33%)				
Eye	(22)	(3)	(7)	(14)	(16)
Cornea, hyperplasia, squamous			1 (14%)		
Cornea, inflammation, chronic active			1 (14%)		
Lens, cataract	20 (91%)	3 (100%)	7 (100%)	14 (100%)	16 (100%)
Retina, atrophy	21 (95%)	3 (100%)	5 (71%)	14 (100%)	16 (100%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Special Senses System (continued)					
Harderian gland	(1)	(2)			(1)
Hyperplasia		1 (50%)			
Zymbal's gland	(3)	(1)	(2)	(1)	(3)
Cyst, multiple			1 (50%)		
Urinary System					
Kidney	(79)	(45)	(51)	(50)	(80)
Hydronephrosis				1 (2%)	
Nephropathy, chronic	79 (100%)	44 (98%)	51 (100%)	49 (98%)	79 (99%)
Cortex, cyst	3 (4%)		2 (4%)	4 (8%)	2 (3%)
Renal tubule, necrosis, acute, multifocal					1 (1%)
Renal tubule, epithelium, hyperplasia, focal					1 (1%)
Urinary bladder	(79)	(44)	(51)	(48)	(80)
Calculus micro observation only	1 (1%)				
Ectasia				1 (2%)	
Mucosa, hyperplasia					1 (1%)
Submucosa, hemorrhage				1 (2%)	

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDIES OF SODIUM FLUORIDE

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Disposition Summary					
Animals initially in study	100	50	70	70	100
Early deaths					
Natural death	10	4	11	6	10
Moribund sacrifice	11	7	8	10	17
Survivors					
Terminal sacrifice	59	18	31	34	54
Paired control		21			
Animals examined microscopically	80	32	50	50	81
Alimentary System					
Intestine large, rectum	(80)	(32)	(49)	(50)	(81)
Adenocarcinoma		1 (3%)			
Leiomyosarcoma, metastatic, vagina			1 (2%)		
Intestine small, jejunum	(80)	(32)	(50)	(50)	(81)
Leiomyoma	1 (1%)				1 (1%)
Liver	(80)	(32)	(50)	(50)	(81)
Hepatocellular adenoma	2 (3%)			1 (2%)	1 (1%)
Mesentery	(3)	(1)	(3)	(2)	(2)
Histiocytic sarcoma, metastatic, skin				1 (50%)	
Oral mucosa	(1)				(2)
Gingival, squamous cell carcinoma	1 (100%)				2 (100%)
Pancreas	(80)	(32)	(50)	(50)	(80)
Histiocytic sarcoma, metastatic, skin				1 (2%)	
Acinus, adenoma	1 (1%)				
Pharynx			(1)	(2)	(1)
Palate, papilloma squamous			1 (100%)	1 (50%)	
Palate, squamous cell carcinoma					1 (100%)
Salivary glands	(80)	(32)	(50)	(50)	(78)
Histiocytic sarcoma, metastatic, skin				1 (2%)	
Stomach, glandular	(80)	(32)	(50)	(50)	(81)
Cardiovascular System					
Heart	(80)	(32)	(50)	(50)	(81)
Granulosa cell tumor malignant, metastatic, ovary	1 (1%)				
Endocrine System					
Adrenal gland, cortex	(80)	(32)	(50)	(50)	(81)
Adenoma	1 (1%)				1 (1%)
Adrenal gland, medulla	(80)	(32)	(50)	(50)	(81)
Granulosa cell tumor malignant, metastatic, ovary	1 (1%)				
Pheochromocytoma malignant				1 (2%)	1 (1%)
Pheochromocytoma benign	5 (6%)		2 (4%)	1 (2%)	5 (6%)
Bilateral, pheochromocytoma benign	1 (1%)				

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Endocrine System (continued)					
Islets, pancreatic	(80)	(32)	(50)	(50)	(80)
Adenoma	3 (4%)		1 (2%)	1 (2%)	
Carcinoma				1 (2%)	
Parathyroid gland	(79)	(32)	(46)	(46)	(80)
Adenoma				1 (2%)	1 (1%)
Pituitary gland	(80)	(32)	(50)	(50)	(81)
Pars distalis, adenoma	32 (40%)	7 (22%)	20 (40%)	19 (38%)	27 (33%)
Pars distalis, adenoma, multiple			1 (2%)	1 (2%)	4 (5%)
Pars distalis, carcinoma				2 (4%)	
Pars intermedia, adenoma			1 (2%)		
Pars intermedia, carcinoma	1 (1%)				
Thyroid gland	(80)	(32)	(50)	(50)	(81)
Bilateral, c-cell, adenoma					1 (1%)
Bilateral, follicular cell, carcinoma				1 (2%)	
C-cell, adenoma	13 (16%)	7 (22%)	3 (6%)	7 (14%)	12 (15%)
C-cell, carcinoma	1 (1%)			1 (2%)	1 (1%)
Follicular cell, adenoma				1 (2%)	1 (1%)
Follicular cell, carcinoma	2 (3%)			1 (2%)	1 (1%)
General Body System					
None					
Genital System					
Clitoral gland	(78)	(32)	(48)	(49)	(79)
Adenoma	9 (12%)		1 (2%)	5 (10%)	11 (14%)
Carcinoma	1 (1%)		1 (2%)		1 (1%)
Bilateral, adenoma	1 (1%)			1 (2%)	1 (1%)
Bilateral, carcinoma			1 (2%)		
Ovary	(80)	(32)	(50)	(50)	(81)
Granulosa cell tumor malignant	1 (1%)				
Periovarian tissue, lymphangioma		1 (3%)			
Uterus	(80)	(32)	(50)	(50)	(81)
Adenoma			1 (2%)		2 (2%)
Hemangioma					1 (1%)
Leiomyosarcoma		1 (3%)			
Lymphangiosarcoma					1 (1%)
Polyp stromal	12 (15%)	1 (3%)	4 (8%)	6 (12%)	2 (2%)
Cervix, carcinoma					1 (1%)
Cervix, fibroma					1 (1%)
Cervix, fibrosarcoma	1 (1%)				
Cervix, sarcoma stromal					1 (1%)
Vagina	(3)		(2)		
Fibrosarcoma	1 (33%)				
Leiomyosarcoma	1 (33%)		1 (50%)		

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Hematopoietic System					
Bone Marrow	(80)	(32)	(50)	(50)	(81)
Lymph node	(80)	(32)	(50)	(50)	(81)
Deep cervical, carcinoma, metastatic, thyroid gland					1 (1%)
Lymph node, mandibular	(80)	(32)	(50)	(50)	(81)
Fibrosarcoma, metastatic, skin				1 (2%)	
Histiocytic sarcoma, metastatic, skin				1 (2%)	
Lymph node, mesenteric	(80)	(31)	(50)	(49)	(81)
Spleen	(80)	(32)	(50)	(50)	(81)
Thymus	(70)	(29)	(48)	(47)	(76)
Thymoma benign	1 (1%)				
Integumentary System					
Mammary gland	(79)	(31)	(50)	(50)	(81)
Adenocarcinoma					1 (1%)
Adenocarcinoma, multiple			1 (2%)		
Adenoma			1 (2%)	1 (2%)	1 (1%)
Fibroadenoma	20 (25%)	6 (19%)	12 (24%)	12 (24%)	19 (23%)
Fibroadenoma, multiple	2 (3%)	2 (6%)	1 (2%)	3 (6%)	5 (6%)
Skin	(79)	(32)	(50)	(49)	(81)
Keratoacanthoma					2 (2%)
Keratoacanthoma, multiple					1 (1%)
Papilloma squamous		1 (3%)			
Trichoepithelioma	1 (1%)				
Subcutaneous tissue, fibroma			1 (2%)		
Subcutaneous tissue, fibrosarcoma				1 (2%)	1 (1%)
Subcutaneous tissue, granulosa cell tumor malignant, metastatic, ovary	1 (1%)				
Subcutaneous tissue, histiocytic sarcoma				1 (2%)	
Subcutaneous tissue, lipoma					1 (1%)
Subcutaneous tissue, schwannoma malignant, metastatic, eye		1 (3%)			
Sweat gland, adenoma					1 (1%)
Musculoskeletal System					
Skeletal muscle			(1)		
Nervous System					
Brain	(80)	(32)	(50)	(50)	(81)
Astrocytoma malignant	1 (1%)			1 (2%)	1 (1%)
Carcinoma, metastatic, pituitary gland				2 (4%)	
Carcinoma, metastatic, Zymbal's gland					1 (1%)
Glioma malignant				1 (2%)	
Histiocytic sarcoma, metastatic, skin				1 (2%)	
Oligodendroglioma malignant					1 (1%)

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Respiratory System					
Lung	(80)	(32)	(50)	(50)	(81)
Alveolar/bronchiolar adenoma	2 (3%)		1 (2%)		1 (1%)
Carcinoma, metastatic, thyroid gland				1 (2%)	
Fibrosarcoma, metastatic, skin				1 (2%)	
Granulosa cell tumor malignant, metastatic, ovary	1 (1%)				
Histiocytic sarcoma, metastatic, skin				1 (2%)	
Nose	(80)	(32)	(50)	(50)	(81)
Histiocytic sarcoma, metastatic, skin				1 (2%)	
Special Senses System					
Ear	(3)				(2)
Pinna, fibroma	1 (33%)				
Pinna, fibrosarcoma	2 (67%)				1 (50%)
Eye	(20)	(5)	(9)	(12)	(26)
Optic nerve, schwannoma malignant		1 (20%)			
Harderian gland				(1)	(1)
Fibrosarcoma, metastatic, skin				1 (100%)	
Zymbal's gland	(1)			(1)	(1)
Carcinoma	1 (100%)			1 (100%)	1 (100%)
Urinary System					
Kidney	(80)	(32)	(50)	(50)	(81)
Granulosa cell tumor malignant, metastatic, ovary	1 (1%)				
Mast cell tumor malignant			1 (2%)		
Urinary bladder	(80)	(32)	(49)	(50)	(81)
Leiomyosarcoma, metastatic, vagina			1 (2%)		
Systemic Lesions					
Multiple organs[a]	(80)	(32)	(50)	(50)	(81)
Histiocytic sarcoma				1 (2%)	
Leukemia mononuclear	26 (33%)	7 (22%)	15 (30%)	14 (28%)	18 (22%)
Tumor Summary					
Total animals with primary neoplasms[b]	73	22	41	48	71
Total primary neoplasms	148	35	71	87	137
Total animals with benign neoplasms	63	17	36	37	59
Total benign neoplasms	108	25	51	61	103
Total animals with malignant neoplasms	38	8	20	24	30
Total malignant neoplasms	40	10	20	26	34
Total animals with secondary neoplasms[c]	1	1	1	5	2
Total secondary neoplasms	5	1	2	13	2

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

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control

Number of Days on Study	260	376	400	463	509	620	630	634	643	646	647	663	674	677	682	683	683	691	710	719	719	729	729	729	729
Carcass ID Number	0901	0881	0961	0914	0794	0953	0895	0874	0855	0933	0884	0922	0873	0821	0875	0812	0964	0843	0955	0813	0962	0792	0834	0841	0853
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery														+											
Oral mucosa													+												
Gingival, squamous cell carcinoma													X												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Tooth	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary							X																		
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary							X																		
Pheochromocytoma benign																	X				X				
Bilateral, pheochromocytoma benign																				X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									

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

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	9	9	9	9	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	8	8	8	8	9	9	7	8	8	8	8	8	8	8	8	8	8	8	9	9	9	8	8	8	8
Carcass ID Number	6	6	8	9	0	2	9	0	0	0	0	1	1	1	2	2	3	3	7	7	8	3	3	4	4
	1	4	5	4	5	3	5	1	2	3	5	1	4	5	3	4	1	2	4	5	2	3	5	2	4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma														X											
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma													X												
Mesentery																									
Oral mucosa																									
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																					X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary																									
Pheochromocytoma benign								X								X									
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X						X			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733
Carcass ID Number	0845	0851	0854	0862	0863	0865	0871	0882	0883	0891	0892	0903	0911	0912	0913	0915	0921	0925	0931	0932	0934	0935	0942	0943	0944
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X													
Mesentery													+				+								
Oral mucosa																									
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary																									
Pheochromocytoma benign			X																						
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 9 4 5	0 9 5 2	0 9 5 4	0 9 6 3	0 9 6 5	**Total Tissues/ Tumors**
Alimentary System						
Esophagus	+	+	+	+	+	80
Intestine large	+	+	+	+	+	80
Intestine large, cecum	+	+	+	+	+	80
Intestine large, colon	+	+	+	+	+	80
Intestine large, rectum	+	+	+	+	+	80
Intestine small	+	+	+	+	+	80
Intestine small, duodenum	+	+	+	+	+	80
Intestine small, ileum	+	+	+	+	+	80
Intestine small, jejunum	+	+	+	+	+	80
Leiomyoma						1
Liver	+	+	+	+	+	80
Hepatocellular adenoma						2
Mesentery						3
Oral mucosa						1
Gingival, squamous cell carcinoma						1
Pancreas	+	+	+	+	+	80
Acinus, adenoma						1
Salivary glands	+	+	+	+	+	80
Stomach	+	+	+	+	+	80
Stomach, forestomach	+	+	+	+	+	80
Stomach, glandular	+	+	+	+	+	80
Tongue		+				1
Tooth	+	+	+	+	+	79
Cardiovascular System						
Heart	+	+	+	+	+	80
Granulosa cell tumor malignant, metastatic, ovary						1
Endocrine System						
Adrenal gland	+	+	+	+	+	80
Adrenal gland, cortex	+	+	+	+	+	80
Adenoma						1
Adrenal gland, medulla	+	+	+	+	+	80
Granulosa cell tumor malignant, metastatic, ovary						1
Pheochromocytoma benign						5
Bilateral, pheochromocytoma benign						1
Islets, pancreatic	+	+	+	+	+	80
Adenoma						3

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	260	376	400	463	509	620	630	634	643	646	647	663	674	677	682	683	683	691	710	719	719	729	729	729	729
Carcass ID Number	0901	0881	0961	0914	0794	0953	0895	0874	0855	0933	0884	0922	0873	0821	0875	0812	0964	0843	0955	0813	0962	0792	0834	0841	0853
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X				X			X			X						X	
Pars intermedia, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X							X				X	
C-cell, carcinoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+
Adenoma																					X			X	
Carcinoma																									
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant							X																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal		X			X							X	X												
Cervix, fibrosarcoma																									
Vagina								+				+													
Fibrosarcoma																									
Leiomyosarcoma								X																	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	M	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	9	9	9	9	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	8	8	8	8	9	9	7	8	8	8	8	8	8	8	8	8	8	8	9	9	9	8	8	8	8
Carcass ID Number	6	6	8	9	0	2	9	0	0	0	0	1	1	1	2	2	3	3	7	7	8	3	3	4	4
	1	4	5	4	5	3	5	1	2	3	5	1	4	5	3	4	1	2	4	5	2	3	5	2	4
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X		X			X	X						X		X			X	X	X			X
Pars intermedia, carcinoma																								X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma					X					X	X						X			X					
C-cell, carcinoma									X																
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Carcinoma																									
Bilateral, adenoma											X														
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal			X			X										X									
Cervix, fibrosarcoma																									
Vagina																									
Fibrosarcoma																									
Leiomyosarcoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+
Thymoma benign												X													

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	8	8	8	8	8	8	8	8	8	8	8	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Carcass ID Number	4	5	5	6	6	6	7	8	8	9	9	0	1	1	1	1	2	2	3	3	3	3	4	4	4
	5	1	4	2	3	5	1	2	3	1	2	3	1	2	3	5	1	5	1	2	4	5	2	3	4
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X	X	X	X		X	X	X	X	X					X			X		X		X		
Pars intermedia, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																						X		X	X
C-cell, carcinoma																									
Follicular cell, carcinoma										X				X											
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X			X	X								X										
Carcinoma																									X
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal														X									X	X	
Cervix, fibrosarcoma								X																	
Vagina								+																	
Fibrosarcoma								X																	
Leiomyosarcoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Thymoma benign																									

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 9 4 5	0 9 5 2	0 9 5 4	0 9 6 3	0 9 6 5	**Total Tissues/ Tumors**
Endocrine System (continued)						
Parathyroid gland	+	+	+	+	+	79
Pituitary gland	+	+	+	+	+	80
Pars distalis, adenoma	X				X	32
Pars intermedia, carcinoma						1
Thyroid gland	+	+	+	+	+	80
C-cell, adenoma			X	X		13
C-cell, carcinoma						1
Follicular cell, carcinoma						2
General Body System						
None						
Genital System						
Clitoral gland	+	+	+	+	+	78
Adenoma			X		X	9
Carcinoma						1
Bilateral, adenoma						1
Ovary	+	+	+	+	+	80
Granulosa cell tumor malignant						1
Uterus	+	+	+	+	+	80
Polyp stromal			X		X	12
Cervix, fibrosarcoma						1
Vagina						3
Fibrosarcoma						1
Leiomyosarcoma						1
Hematopoietic System						
Bone marrow	+	+	+	+	+	80
Lymph node	+	+	+	+	+	80
Lymph node, mandibular	+	+	+	+	+	80
Lymph node, mesenteric	+	+	+	+	+	80
Spleen	+	+	+	+	+	80
Thymus	+	+	+	+	+	70
Thymoma benign						1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	2 6 0	3 7 6	4 0 0	4 6 3	5 0 9	6 2 0	6 3 0	6 3 4	6 4 3	6 4 6	6 4 7	6 6 3	6 7 4	6 7 7	6 8 2	6 8 3	6 8 3	6 9 1	7 1 0	7 1 9	7 1 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 9 0 1	0 8 8 1	0 9 6 1	0 9 1 4	0 7 9 4	0 9 5 3	0 8 9 5	0 8 7 4	0 8 5 5	0 9 3 3	0 8 8 4	0 9 2 2	0 8 7 3	0 8 2 1	0 8 7 5	0 8 1 2	0 9 6 4	0 8 4 3	0 9 5 5	0 8 1 3	0 9 6 2	0 7 9 2	0 8 3 4	0 8 4 1	0 8 5 3
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma										X												X			
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma											X														
Subcutaneous tissue, granulosa cell tumor malignant, metastatic, ovary							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant		X																							
Spinal cord																			+						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Granulosa cell tumor malignant, metastatic, ovary							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear											+									+					
Pinna, fibroma																				X					
Pinna, fibrosarcoma											X														
Eye													+			+		+	+	+					+
Zymbal's gland						+																			
Carcinoma						X																			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary							X																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X				X		X			X		X	X	X	X		X	X	X		X		X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	9	9	9	9	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	8	8	8	8	9	9	7	8	8	8	8	8	8	8	8	8	8	8	9	9	9	8	8	8	8
Carcass ID Number	6	6	8	9	0	2	9	0	0	0	0	1	1	1	2	2	3	3	7	7	8	3	3	4	4
	1	4	5	4	5	3	5	1	2	3	5	1	4	5	3	4	1	2	4	5	2	3	5	2	4
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma			X						X				X	X	X				X	X				X	X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma																									
Subcutaneous tissue, granulosa cell tumor malignant, metastatic, ovary																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X							
Granulosa cell tumor malignant, metastatic, ovary																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear		+																							
Pinna, fibroma																									
Pinna, fibrosarcoma		X																							
Eye				+	+			+		+	+	+													
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X						X		X				X			X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	8	8	8	8	8	8	8	8	8	8	8	9	9	9	9	9	9	9	9	9	9	9	9	9	9
	4	5	5	6	6	6	7	8	8	9	9	0	1	1	1	1	2	2	3	3	3	3	4	4	4
	5	1	4	2	3	5	1	2	3	1	2	3	1	2	3	5	1	5	1	2	4	5	2	3	4
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma		X			X	X								X					X	X	X				
Fibroadenoma, multiple													X		X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma																									
Subcutaneous tissue, granulosa cell tumor malignant, metastatic, ovary																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Granulosa cell tumor malignant, metastatic, ovary																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Pinna, fibroma																									
Pinna, fibrosarcoma																									
Eye		+	+							+		+							+		+				
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X						X				X	X			X			X		X					

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 9 4 5	0 9 5 2	0 9 5 4	0 9 6 3	0 9 6 5	**Total Tissues/ Tumors**
Integumentary System						
Mammary gland	+	+	+	+	+	79
Fibroadenoma		X	X			20
Fibroadenoma, multiple						2
Skin	+	+	+	+	+	79
Trichoepithelioma						1
Subcutaneous tissue, granulosa cell tumor malignant, metastatic, ovary						1
Musculoskeletal System						
Bone	+	+	+	+	+	80
Nervous System						
Brain	+	+	+	+	+	80
Astrocytoma malignant						1
Spinal cord						1
Respiratory System						
Lung	+	+	+	+	+	80
Alveolar/bronchiolar adenoma		X				2
Granulosa cell tumor malignant, metastatic, ovary						1
Nose	+	+	+	+	+	80
Trachea	+	+	+	+	+	80
Special Senses System						
Ear						3
Pinna, fibroma						1
Pinna, fibrosarcoma						2
Eye		+	+			20
Zymbal's gland						1
Carcinoma						1
Urinary System						
Kidney	+	+	+	+	+	80
Granulosa cell tumor malignant, metastatic, ovary						1
Urinary bladder	+	+	+	+	+	80
Systemic Lesions						
Multiple organs	+	+	+	+	+	80
Leukemia mononuclear			X			26

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control

Number of Days on Study	320	338	379	402	415	451	463	515	557	561	568	579	584	599	609	614	620	628	632	633	641	643	643	646	661
Carcass ID Number	1082	0991	1055	1072	0993	1065	1081	1021	1074	1013	1035	0994	1032	1031	1014	1012	1024	1034	1054	1045	1001	1041	1083	1044	1003
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma			X																						
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																				+					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X							X						X				X		X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma								X						X			X					X			
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Periovarian tissue, lymphangioma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma			X																						
Polyp stromal																								X	

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

	6	6	6	7	7	7	7	
Number of Days on Study	7	7	9	0	1	1	2	
	0	7	8	5	0	6	6	
	1	1	1	1	1	0	1	
	0	0	0	0	0	9	0	**Total**
Carcass ID Number	3	2	5	0	7	9	7	**Tissues/**
	3	3	2	2	3	5	5	**Tumors**
Alimentary System								
Esophagus	+	+	+	+	M	+	+	31
Intestine large	+	+	+	+	+	+	+	32
Intestine large, cecum	+	+	+	+	+	+	+	32
Intestine large, colon	+	+	+	+	+	+	+	32
Intestine large, rectum	+	+	+	+	+	+	+	32
Adenocarcinoma								1
Intestine small	+	+	+	+	+	+	+	32
Intestine small, duodenum	+	+	+	+	+	+	+	32
Intestine small, ileum	+	+	+	+	+	+	+	32
Intestine small, jejunum	+	+	+	+	+	+	+	32
Liver	+	+	+	+	+	+	+	32
Mesentery								1
Pancreas	+	+	+	+	+	+	+	32
Salivary glands	+	+	+	+	+	+	+	32
Stomach	+	+	+	+	+	+	+	32
Stomach, forestomach	+	+	+	+	+	+	+	32
Stomach, glandular	+	+	+	+	+	+	+	32
Tooth	+	+	+	+	+	+	+	31
Cardiovascular System								
Heart	+	+	+	+	+	+	+	32
Endocrine System								
Adrenal gland	+	+	+	+	+	+	+	31
Adrenal gland, cortex	+	+	+	+	+	+	+	32
Adrenal gland, medulla	+	+	+	+	+	+	+	32
Islets, pancreatic	+	+	+	+	+	+	+	32
Parathyroid gland	+	+	+	+	+	+	+	32
Pituitary gland	+	+	+	+	+	+	+	32
Pars distalis, adenoma				X		X		7
Thyroid gland	+	+	+	+	+	+	+	32
C-cell, adenoma			X			X	X	7
General Body System								
None								
Genital System								
Clitoral gland	+	+	+	+	+	+	+	32
Ovary	+	+	+	+	+	+	+	32
Periovarian tissue, lymphangioma			X					1
Uterus	+	+	+	+	+	+	+	32
Leiomyosarcoma								1
Polyp stromal								1

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

	3	3	3	4	4	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6
Number of Days on Study	2	3	7	0	1	5	6	1	5	6	6	7	8	9	0	1	2	2	3	3	4	4	4	4	6
	0	8	9	2	5	1	3	5	7	1	8	9	4	9	9	4	0	8	2	3	1	3	3	6	1
	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
	0	9	0	0	9	0	0	0	0	0	0	9	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	8	9	5	7	9	6	8	2	7	1	3	9	3	3	1	1	2	3	5	4	0	4	8	4	0
	2	1	5	2	3	5	1	1	4	3	5	4	2	1	4	2	4	4	4	5	1	1	3	4	3
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma									X							X							X	X	
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																							X		
Subcutaneous tissue, schwannoma malignant, metastatic, eye	X																								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+																			+	+		+		
Optic nerve, schwannoma malignant	X																								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X											X	X				X	X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

	6	6	6	7	7	7	7	
Number of Days on Study	7	7	9	0	1	1	2	
	0	7	8	5	0	6	6	
	1	1	1	1	1	0	1	
	0	0	0	0	0	9	0	**Total**
Carcass ID Number	3	2	5	0	7	9	7	**Tissues/**
	3	3	2	2	3	5	5	**Tumors**
Hematopoietic System								
Bone marrow	+	+	+	+	+	+	+	32
Lymph node	+	+	+	+	+	+	+	32
Lymph node, mandibular	+	+	+	+	+	+	+	32
Lymph node, mesenteric	+	+	+	+	+	M	+	31
Spleen	+	+	+	+	+	+	+	32
Thymus	+	+	+	+	M	+	+	29
Integumentary System								
Mammary gland	+	+	+	+	+	+	+	31
Fibroadenoma	X			X				6
Fibroadenoma, multiple					X	X		2
Skin	+	+	+	+	+	+	+	32
Papilloma squamous								1
Subcutaneous tissue, schwannoma malignant, metastatic, eye								1
Musculoskeletal System								
Bone	+	+	+	+	+	+	+	32
Nervous System								
Brain	+	+	+	+	+	+	+	32
Respiratory System								
Lung	+	+	+	+	+	+	+	32
Nose	+	+	+	+	+	+	+	32
Trachea	+	+	+	+	+	+	+	32
Special Senses System								
Eye				+				5
Optic nerve, schwannoma malignant								1
Urinary System								
Kidney	+	+	+	+	+	+	+	32
Urinary bladder	+	+	+	+	+	+	+	32
Systemic Lesions								
Multiple organs	+	+	+	+	+	+	+	32
Leukemia mononuclear	X					X		7

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm

Number of Days on Study	451	565	582	618	620	631	639	659	677	677	696	702	704	709	715	718	719	719	719	729	729	729	729	729	729
Carcass ID Number	1133	1175	1134	1102	1192	1153	1143	1182	1154	1184	1201	1212	1213	1114	1152	1131	1171	1172	1173	1104	1122	1123	1124	1151	1162
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, vagina				X																					
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery									+				+												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																									
Palate, papilloma squamous																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign										X															
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Carcass ID Number	1181	1191	1201	1211	1092	1093	1095	1101	1105	1113	1135	1141	1142	1161	1163	1164	1174	1183	1185	1193	1203	1214	1215	1222	1225	Total Tissues/ Tumors
Number of Days on Study	729	729	729	729	730	730	730	730	730	731	731	731	731	731	732	732	732	732	732	732	733	733	733	733	733	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma, metastatic, vagina																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery										+																3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																						+				1
Palate, papilloma squamous																						X				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign													X													2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Number of Days on Study	451	565	582	618	620	631	639	659	677	677	696	702	704	709	715	718	719	719	719	729	729	729	729	729	729
Carcass ID Number	1133	1175	1134	1102	1192	1153	1143	1182	1154	1184	1201	1212	1213	1114	1152	1131	1171	1172	1173	1104	1122	1123	1124	1151	1162
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X			X		X	X		X	X				X			X	X			X		
Pars distalis, adenoma, multiple																								X	
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma		X																					X		
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma				X																					
Carcinoma												X													
Bilateral, carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Polyp stromal					X																				X
Vagina				+									+												
Leiomyosarcoma				X																					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	9	9	9	0	0	0	0	0	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	1	1	2	2	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	**Total**
Carcass ID Number	8	9	0	1	9	9	9	0	0	1	3	4	4	6	6	6	7	8	8	9	0	1	1	2	2	**Tissues/**
	1	1	2	1	2	3	5	1	5	3	5	1	2	1	3	4	4	3	5	3	3	4	5	2	5	**Tumors**
Endocrine System (continued)																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X			X			X		X				X		X					X	X	X		20
Pars distalis, adenoma, multiple																										1
Pars intermedia, adenoma												X														1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X																								3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Carcinoma																										1
Bilateral, carcinoma																X										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Polyp stromal	X												X													4
Vagina																										2
Leiomyosarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Number of Days on Study	4	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	5	6	8	1	2	3	3	5	7	7	9	0	0	0	1	1	1	1	1	2	2	2	2	2	2
	1	5	2	8	0	1	9	9	7	7	6	2	4	9	5	8	9	9	9	9	9	9	9	9	9
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	1	1	1	1	1	1	1	1	1	1	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1
	3	7	3	0	9	5	4	8	5	8	0	1	1	1	5	3	7	7	7	0	2	2	2	5	6
	3	5	4	2	2	3	3	2	4	4	1	2	3	4	2	1	1	2	3	4	2	3	4	1	2
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, multiple																									
Adenoma																									
Fibroadenoma				X				X									X		X	X	X		X		
Fibroadenoma, multiple						X																			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle													+												
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye						+			+											+		+		+	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, vagina				X																					
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X				X		X		X	X			X	X		X			X			X			X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Number of Days on Study	729	729	729	729	730	730	730	730	730	731	731	731	731	731	732	732	732	732	732	732	733	733	733	733	733	
Carcass ID Number	1181	1191	1202	1211	1092	1093	1095	1101	1105	1113	1135	1141	1142	1161	1163	1164	1174	1183	1185	1193	1203	1214	1215	1222	1225	**Total Tissues/ Tumors**
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, multiple									X																	1
Adenoma								X																		1
Fibroadenoma		X		X								X			X										X	12
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+							+											+			+			9
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant				X																						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma, metastatic, vagina																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear													X		X		X				X					15

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm

	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	6	6	7	7	4	4	4	4	4	6	6	7	0	1	1	1	2	3	3	3	3	3	3	3	3
	8	8	1	5	3	6	7	7	7	2	3	0	8	5	6	6	9	0	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	2	2	3	3	3	3	2	2	3	2	2	3	3	3	3	3	2	2	2	2	3	3	3	3	3
Carcass ID Number	4	7	0	0	3	1	4	9	4	3	3	2	0	4	5	5	8	5	7	8	0	1	2	4	5
	5	4	4	5	5	3	1	3	1	3	5	1	1	3	2	3	1	5	2	2	3	4	4	5	4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery											+								+						
Histiocytic sarcoma, metastatic, skin											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, skin											X														
Pharynx																		+							
Palate, papilloma squamous																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, skin											X														
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue														+											
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																X									
Pheochromocytoma benign																					X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	3	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	**Total**
Carcass ID Number	6	4	5	5	5	6	6	7	8	9	9	1	1	2	2	3	3	3	4	4	5	5	6	6	6	**Tissues/**
	3	3	1	2	3	3	5	5	4	1	4	2	5	2	3	1	2	4	2	4	1	5	1	2	5	**Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																						X				1
Mesentery																										2
Histiocytic sarcoma, metastatic, skin																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, skin																										1
Pharynx														+												2
Palate, papilloma squamous														X												1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, skin																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X												1
Carcinoma									X																	1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	3	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	**Total**
Carcass ID Number	6	4	5	5	5	6	6	7	8	9	9	1	1	2	2	3	3	3	4	4	5	5	6	6	6	**Tissues/**
	3	3	1	2	3	3	5	5	4	1	4	2	5	2	3	1	2	4	2	4	1	5	1	2	5	**Tumors**
Endocrine System (continued)																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X		X	X			X	X			X					X			X		X		19
Pars distalis, adenoma, multiple	X																									1
Pars distalis, carcinoma													X													2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, follicular cell, carcinoma											X															1
C-cell, adenoma									X				X					X								7
C-cell, carcinoma											X															1
Follicular cell, adenoma	X																									1
Follicular cell, carcinoma																					X					1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X											X			X									5
Bilateral, adenoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																									X	6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Histiocytic sarcoma, metastatic, skin																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

Number of Days on Study	568	568	571	575	643	646	647	647	647	662	663	670	708	715	716	719	729	730	730	730	730	730	730	730	730
Carcass ID Number	1245	1274	1304	1305	1335	1313	1241	1293	1341	1233	1235	1321	1301	1343	1352	1353	1281	1255	1272	1282	1303	1314	1324	1345	1354
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma						X		X												X		X			
Fibroadenoma, multiple															X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma										X															
Subcutaneous tissue, histiocytic sarcoma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant		X																							
Carcinoma, metastatic, pituitary gland									X																
Glioma malignant														X											
Histiocytic sarcoma, metastatic, skin											X														
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Fibrosarcoma, metastatic, skin										X															
Histiocytic sarcoma, metastatic, skin											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, skin											X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye			+					+			+														
Harderian gland										+															
Fibrosarcoma, metastatic, skin										X															
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Leukemia mononuclear			X		X							X	X					X			X		X	X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	3	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	**Total**
Carcass ID Number	6	4	5	5	5	6	6	7	8	9	9	1	1	2	2	3	3	3	4	4	5	5	6	6	6	**Tissues/**
	3	3	1	2	3	3	5	5	4	1	4	2	5	2	3	1	2	4	2	4	1	5	1	2	5	**Tumors**
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X													1
Fibroadenoma	X	X			X					X					X			X	X				X			12
Fibroadenoma, multiple																	X			X						3
Skin	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, histiocytic sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Carcinoma, metastatic, pituitary gland													X													2
Glioma malignant																										1
Histiocytic sarcoma, metastatic, skin																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland											X															1
Fibrosarcoma, metastatic, skin																										1
Histiocytic sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, skin																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+						+	+	+	+					+	+	+				+				12
Harderian gland																										1
Fibrosarcoma, metastatic, skin																										1
Zymbal's gland						+																				1
Carcinoma						X																				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear								X					X		X		X		X	X						14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm

Number of Days on Study	338	415	515	557	561	571	578	613	628	631	631	639	646	647	647	647	678	705	709	714	716	716	716	719	719
Carcass ID Number	1445	1373	1433	1424	1411	1404	1442	1455	1441	1391	1451	1502	1405	1383	1481	1483	1523	1412	1395	1524	1472	1474	1532	1491	1493
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery																									
Oral mucosa									+															+	
Gingival, squamous cell carcinoma									X															X	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx												+													
Palate, squamous cell carcinoma												X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																	X	X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	719	722	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731
Carcass ID Number	1494	1431	1414	1421	1444	1453	1464	1501	1504	1512	1533	1551	1375	1381	1382	1384	1385	1392	1394	1401	1402	1403	1413	1422	1425
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma										X															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery																									
Oral mucosa																									
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																									
Palate, squamous cell carcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant	X																								
Pheochromocytoma benign							X														X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733
Carcass ID Number	1432	1434	1435	1443	1452	1454	1462	1471	1473	1475	1503	1505	1514	1515	1521	1522	1531	1534	1535	1541	1542	1543	1545	1552	1553
Alimentary System																									
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery				+																					
Oral mucosa																									
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																									
Palate, squamous cell carcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																					+				
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																X									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	
	3	3	3	3	3	3	
	1	1	1	1	1	1	
	5	5	5	5	5	5	**Total**
Carcass ID Number	5	6	6	6	6	6	**Tissues/**
	4	1	2	3	4	5	**Tumors**
Alimentary System							
Esophagus	+	+	+	+	+	+	79
Intestine large	+	+	+	+	+	+	81
Intestine large, cecum	+	+	+	+	+	+	81
Intestine large, colon	+	+	+	+	+	+	81
Intestine large, rectum	+	+	+	+	+	+	81
Intestine small	+	+	+	+	+	+	81
Intestine small, duodenum	+	+	+	+	+	+	81
Intestine small, ileum	+	+	+	+	+	+	81
Intestine small, jejunum	+	+	+	+	+	+	81
Leiomyoma							1
Liver	+	+	+	+	+	+	81
Hepatocellular adenoma				X			1
Mesentery	+						2
Oral mucosa							2
Gingival, squamous cell carcinoma							2
Pancreas	+	+	+	+	+	+	80
Pharynx							1
Palate, squamous cell carcinoma							1
Salivary glands	+	+	+	+	+	+	78
Stomach	+	+	+	+	+	+	81
Stomach, forestomach	+	+	+	+	+	+	81
Stomach, glandular	+	+	+	+	+	+	81
Tongue							1
Tooth	+	+	+	+	+	+	81
Cardiovascular System							
Heart	+	+	+	+	+	+	81
Endocrine System							
Adrenal gland	+	+	+	+	+	+	81
Adrenal gland, cortex	+	+	+	+	+	+	81
Adenoma							1
Adrenal gland, medulla	+	+	+	+	+	+	81
Pheochromocytoma malignant							1
Pheochromocytoma benign							5
Islets, pancreatic	+	+	+	+	+	+	80

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	338	415	515	557	561	571	578	613	628	631	631	639	646	647	647	648	705	709	714	716	716	716	716	719	719
Carcass ID Number	1445	1373	1433	1424	1411	1404	1442	1455	1441	1391	1451	1502	1405	1383	1481	1483	1523	1412	1395	1524	1472	1474	1532	1491	1493
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X									X	X		X	X			X	X		X
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, c-cell, adenoma																									
C-cell, adenoma																				X		X			
C-cell, carcinoma																									
Follicular cell, adenoma																						X			
Follicular cell, carcinoma													X												
General Body System																									
Tissue NOS											+														
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Carcinoma																									
Bilateral, adenoma														X											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Hemangioma																	X								
Lymphangiosarcoma																				X					
Polyp stromal											X														
Cervix, carcinoma																								X	
Cervix, fibroma															X										
Cervix, sarcoma stromal	X																								
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, carcinoma, metastatic, thyroid gland																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	1	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	2	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	4	4	4	4	4	4	4	5	5	5	5	5	3	3	3	3	3	3	3	4	4	4	4	4	4
Carcass ID Number	9	3	1	2	4	5	6	0	0	1	3	5	7	8	8	8	8	9	9	0	0	0	1	2	2
	4	1	4	1	4	3	4	1	4	2	3	1	5	1	2	4	5	2	4	1	2	3	3	2	5
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X		X	X		X						X						X			X	X		
Pars distalis, adenoma, multiple								X				X		X											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, c-cell, adenoma																									
C-cell, adenoma										X					X										
C-cell, carcinoma																									
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
Tissue NOS																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma							X										X		X				X		
Carcinoma										X															
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Hemangioma																									
Lymphangiosarcoma																									
Polyp stromal					X																				
Cervix, carcinoma																									
Cervix, fibroma																									
Cervix, sarcoma stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, carcinoma, metastatic, thyroid gland																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	4	4	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Carcass ID Number	3	3	3	4	5	5	6	7	7	7	0	0	1	1	2	2	3	3	3	4	4	4	4	5	5
	2	4	5	3	2	4	2	1	3	5	3	5	4	5	1	2	1	4	5	1	2	3	5	2	3
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X			X				X		X			X		X	X	X				
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, c-cell, adenoma																									
C-cell, adenoma	X			X		X							X							X					X
C-cell, carcinoma											X														
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
Tissue NOS																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X	X		X				X			X	X					
Carcinoma																									
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X								X		
Hemangioma																									
Lymphangiosarcoma																									
Polyp stromal																									
Cervix, carcinoma																									
Cervix, fibroma																									
Cervix, sarcoma stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, carcinoma, metastatic, thyroid gland											X														
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 5 5 4	1 5 6 1	1 5 6 2	1 5 6 3	1 5 6 4	1 5 6 5	**Total Tissues/ Tumors**
Endocrine System (continued)							
Parathyroid gland	+	+	+	+	+	+	80
Adenoma							1
Pituitary gland	+	+	+	+	+	+	81
Pars distalis, adenoma	X						27
Pars distalis, adenoma, multiple					X		4
Thyroid gland	+	+	+	+	+	+	81
Bilateral, c-cell, adenoma					X		1
C-cell, adenoma	X	X					12
C-cell, carcinoma							1
Follicular cell, adenoma							1
Follicular cell, carcinoma							1
General Body System							
Tissue NOS							1
Genital System							
Clitoral gland	+	+	+	+	+	+	79
Adenoma							11
Carcinoma							1
Bilateral, adenoma							1
Ovary	+	+	+	+	+	+	81
Uterus	+	+	+	+	+	+	81
Adenoma							2
Hemangioma							1
Lymphangiosarcoma							1
Polyp stromal							2
Cervix, carcinoma							1
Cervix, fibroma							1
Cervix, sarcoma stromal							1
Hematopoietic System							
Bone marrow	+	+	+	+	+	+	81
Lymph node	+	+	+	+	+	+	81
Deep cervical, carcinoma, metastatic, thyroid gland							1
Lymph node, mandibular	+	+	+	+	+	+	81
Lymph node, mesenteric	+	+	+	+	+	+	81
Spleen	+	+	+	+	+	+	81
Thymus	+	+	+	+	+	+	76

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	338	415	515	557	561	571	578	613	628	631	631	639	646	647	647	647	678	705	709	714	716	716	716	719	719
Carcass ID Number	1445	1373	1433	1424	1411	1404	1442	1455	1441	1391	1451	1502	1405	1383	1481	1483	1523	1412	1395	1524	1472	1474	1532	1491	1493
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																						X			
Adenoma																									
Fibroadenoma								X		X			X								X	X		X	
Fibroadenoma, multiple																									X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Keratoacanthoma, multiple																								X	
Subcutaneous tissue, fibrosarcoma																							X		
Subcutaneous tissue, lipoma																									
Sweat gland, adenoma						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Carcinoma, metastatic, Zymbal's gland								X																	
Oligodendroglioma malignant							X																		
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																+			+						
Pinna, fibrosarcoma																X									
Eye								+	+			+			+	+				+		+	+		+
Harderian gland																									
Zymbal's gland								+																	
Carcinoma								X																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X							X					X	X		X			X			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	1	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	2	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	4	4	4	4	4	4	4	5	5	5	5	5	3	3	3	3	3	3	3	4	4	4	4	4	4
Carcass ID Number	9	3	1	2	4	5	6	0	0	1	3	5	7	8	8	8	8	9	9	0	0	0	1	2	2
	4	1	4	1	4	3	4	1	4	2	3	1	5	1	2	4	5	2	4	1	2	3	3	2	5
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma													X												
Fibroadenoma	X			X	X									X			X				X	X			X
Fibroadenoma, multiple								X		X															
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma										X									X						
Keratoacanthoma, multiple																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, lipoma																									
Sweat gland, adenoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Carcinoma, metastatic, Zymbal's gland																									
Oligodendroglioma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Pinna, fibrosarcoma																									
Eye											+			+	+	+	+							+	
Harderian gland																									+
Zymbal's gland																									
Carcinoma																									
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 Studies of Sodium Fluoride: 175 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	4	4	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Carcass ID Number	3	3	3	4	5	5	6	7	7	7	0	0	1	1	2	2	3	3	3	4	4	4	4	5	5
	2	4	5	3	2	4	2	1	3	5	3	5	4	5	1	2	1	4	5	1	2	3	5	2	3
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma																									
Fibroadenoma	X													X					X				X		
Fibroadenoma, multiple							X						X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Keratoacanthoma, multiple																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, lipoma																									
Sweat gland, adenoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Carcinoma, metastatic, Zymbal's gland																									
Oligodendroglioma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Pinna, fibrosarcoma																									
Eye	+	+	+					+		+			+			+	+	+	+						
Harderian gland																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X			X								X											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	733	733	733	733	733	733	
Carcass ID Number	1554	1561	1562	1563	1564	1565	**Total Tissues/ Tumors**
Integumentary System							
Mammary gland	+	+	+	+	+	+	81
Adenocarcinoma							1
Adenoma							1
Fibroadenoma				X			19
Fibroadenoma, multiple							5
Skin	+	+	+	+	+	+	81
Keratoacanthoma							2
Keratoacanthoma, multiple							1
Subcutaneous tissue, fibrosarcoma							1
Subcutaneous tissue, lipoma		X					1
Sweat gland, adenoma							1
Musculoskeletal System							
Bone	+	+	+	+	+	+	81
Nervous System							
Brain	+	+	+	+	+	+	81
Astrocytoma malignant					X		1
Carcinoma, metastatic, Zymbal's gland							1
Oligodendroglioma malignant							1
Respiratory System							
Lung	+	+	+	+	+	+	81
Alveolar/bronchiolar adenoma							1
Nose	+	+	+	+	+	+	81
Trachea	+	+	+	+	+	+	79
Special Senses System							
Ear							2
Pinna, fibrosarcoma							1
Eye					+		26
Harderian gland							1
Zymbal's gland							1
Carcinoma							1
Urinary System							
Kidney	+	+	+	+	+	+	81
Urinary bladder	+	+	+	+	+	+	81
Systemic Lesions							
Multiple organs	+	+	+	+	+	+	81
Leukemia mononuclear	X		X				18

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

	Control	25 ppm	100 ppm	175 ppm
Adrenal Gland (Medulla): Pheochromocytoma Benign				
Overall rates[a]	6/80 (8%)	2/50 (4%)	1/50 (2%)	5/81 (6%)
Adjusted rates[b]	9.6%	5.5%	2.9%	8.5%
Terminal rates[c]	3/59 (5%)	1/31 (3%)	1/34 (3%)	3/54 (6%)
First incidence (days)	683	677	729 (T)	678
Life table tests[d]	P=0.479N	P=0.394N	P=0.203N	P=0.538N
Logistic regression tests[d]	P=0.459N	P=0.332N	P=0.175N	P=0.501N
Cochran-Armitage test[d]	P=0.451N			
Fisher exact test[d]		P=0.342N	P=0.172N	P=0.491N
Adrenal Gland (Medulla): Pheochromocytoma (Benign and Malignant)				
Overall rates	6/80 (8%)	2/50 (4%)	2/50 (4%)	6/81 (7%)
Adjusted rates	9.6%	5.5%	5.6%	10.0%
Terminal rates	3/59 (5%)	1/31 (3%)	1/34 (3%)	3/54 (6%)
First incidence (days)	683	677	716	678
Life table tests	P=0.459	P=0.394N	P=0.378N	P=0.577
Logistic regression tests	P=0.477	P=0.332N	P=0.340N	P=0.618
Cochran-Armitage test	P=0.485			
Fisher exact test		P=0.342N	P=0.342N	P=0.609N
Clitoral Gland: Adenoma				
Overall rates	10/78 (13%)	1/48 (2%)	6/49 (12%)	12/79 (15%)
Adjusted rates	16.9%	2.1%	15.9%	21.1%
Terminal rates	9/58 (16%)	0/31 (0%)	4/33 (12%)	10/53 (19%)
First incidence (days)	719	618	575	578
Life table tests	P=0.106	P=0.059N	P=0.575	P=0.331
Logistic regression tests	P=0.131	P=0.039N	P=0.573N	P=0.408
Cochran-Armitage test	P=0.134			
Fisher exact test		P=0.034N	P=0.577N	P=0.422
Clitoral Gland: Adenoma or Carcinoma				
Overall rates	11/78 (14%)	3/48 (6%)	6/49 (12%)	13/79 (16%)
Adjusted rates	18.6%	7.7%	15.9%	23.0%
Terminal rates	10/58 (17%)	1/31 (3%)	4/33 (12%)	11/53 (21%)
First incidence (days)	719	618	575	578
Life table tests	P=0.166	P=0.196N	P=0.563N	P=0.329
Logistic regression tests	P=0.201	P=0.141N	P=0.490N	P=0.409
Cochran-Armitage test	P=0.206			
Fisher exact test		P=0.142N	P=0.494N	P=0.426
Mammary Gland: Fibroadenoma				
Overall rates	22/80 (28%)	13/50 (26%)	15/50 (30%)	24/81 (30%)
Adjusted rates	36.5%	34.7%	39.9%	38.1%
Terminal rates	21/59 (36%)	8/31 (26%)	12/34 (35%)	16/54 (30%)
First incidence (days)	646	618	646	613
Life table tests	P=0.288	P=0.456	P=0.355	P=0.318
Logistic regression tests	P=0.331	P=0.515N	P=0.416	P=0.417
Cochran-Armitage test	P=0.357			
Fisher exact test		P=0.509N	P=0.455	P=0.451

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
Mammary Gland: Fibroadenoma or Adenoma				
Overall rates	22/80 (28%)	14/50 (28%)	16/50 (32%)	25/81 (31%)
Adjusted rates	36.5%	37.6%	42.6%	39.8%
Terminal rates	21/59 (36%)	9/31 (29%)	13/34 (38%)	17/54 (31%)
First incidence (days)	646	618	646	613
Life table tests	P=0.248	P=0.353	P=0.265	P=0.258
Logistic regression tests	P=0.287	P=0.547	P=0.319	P=0.349
Cochran-Armitage test	P=0.315			
Fisher exact test		P=0.553	P=0.361	P=0.384
Mammary Gland: Fibroadenoma, Adenoma, or Adenocarcinoma				
Overall rates	22/80 (28%)	15/50 (30%)	16/50 (32%)	25/81 (31%)
Adjusted rates	36.5%	40.4%	42.6%	39.8%
Terminal rates	21/59 (36%)	10/31 (32%)	13/34 (38%)	17/54 (31%)
First incidence (days)	646	618	646	613
Life table tests	P=0.278	P=0.260	P=0.265	P=0.258
Logistic regression tests	P=0.322	P=0.445	P=0.319	P=0.349
Cochran-Armitage test	P=0.351			
Fisher exact test		P=0.455	P=0.361	P=0.384
Oral Cavity (Pharynx): Squamous Papilloma				
Overall rates	0/80 (0%)	1/50 (2%)	1/50 (2%)	0/81 (0%)
Adjusted rates	0.0%	3.2%	2.9%	0.0%
Terminal rates	0/59 (0%)	1/31 (3%)	1/34 (3%)	0/54 (0%)
First incidence (days)	---	729 (T)	729 (T)	---
Life table tests	P=0.536N	P=0.372	P=0.390	–[e]
Logistic regression tests	P=0.536N	P=0.372	P=0.390	–
Cochran-Armitage test	P=0.523N			
Fisher exact test		P=0.385	P=0.385	–
Oral Cavity (Oral Mucosa or Pharynx): Squamous Papilloma or Squamous Cell Carcinoma				
Overall rates	1/80 (1%)	1/50 (2%)	1/50 (2%)	3/81 (4%)
Adjusted rates	1.5%	3.2%	2.9%	4.5%
Terminal rates	0/59 (0%)	1/31 (3%)	1/34 (3%)	0/54 (0%)
First incidence (days)	674	729 (T)	729 (T)	628
Life table tests	P=0.201	P=0.630	P=0.629	P=0.297
Logistic regression tests	P=0.211	P=0.654	P=0.654	P=0.303
Cochran-Armitage test	P=0.211			
Fisher exact test		P=0.623	P=0.623	P=0.315
Oral Cavity (Oral Mucosa or Pharynx): Squamous Papilloma or Squamous Cell Carcinoma[f]				
Overall rates	1/132 (1%)	1/70 (1%)	1/70 (1%)	3/100 (3%)
Adjusted rates	1.4%	3.2%	2.9%	4.5%
Interim sacrifice 1[g]	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Interim sacrifice 2[g]	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/9 (0%)
Terminal rates	0/59 (0%)	1/31 (3%)	1/34 (3%)	0/54 (0%)
First incidence (days)	674	729 (T)	729 (T)	628
Life table tests	P=0.185	P=0.620	P=0.619	P=0.259
Logistic regression tests	P=0.157	P=0.611	P=0.611	P=0.224
Cochran-Armitage test	P=0.141			
Fisher exact test		P=0.574	P=0.574	P=0.215

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	32/80 (40%)	21/50 (42%)	20/50 (40%)	31/81 (38%)
Adjusted rates	50.5%	52.5%	53.2%	48.0%
Terminal rates	28/59 (47%)	13/31 (42%)	17/34 (50%)	21/54 (39%)
First incidence (days)	634	582	568	571
Life table tests	P=0.502N	P=0.259	P=0.440	P=0.481
Logistic regression tests	P=0.420N	P=0.485	P=0.565	P=0.510N
Cochran-Armitage test	P=0.398N			
Fisher exact test		P=0.482	P=0.574N	P=0.475N
Pituitary Gland (Pars Distalis or Unspecified Site): Adenoma or Carcinoma				
Overall rates	32/80 (40%)	21/50 (42%)	22/50 (44%)	31/81 (38%)
Adjusted rates	50.5%	52.5%	57.0%	48.0%
Terminal rates	28/59 (47%)	13/31 (42%)	18/34 (53%)	21/54 (39%)
First incidence (days)	634	582	568	571
Life table tests	P=0.516	P=0.259	P=0.271	P=0.481
Logistic regression tests	P=0.449N	P=0.485	P=0.389	P=0.510N
Cochran-Armitage test	P=0.427N			
Fisher exact test		P=0.482	P=0.394	P=0.475N
Skin: Trichoepithelioma and Keratocanthoma				
Overall rates	1/80 (1%)	0/50 (0%)	0/50 (0%)	3/81 (4%)
Adjusted rates	1.4%	0.0%	0.0%	5.4%
Terminal rates	0/59 (0%)	0/31 (0%)	0/34 (0%)	2/54 (4%)
First incidence (days)	647	—	—	719
Life table tests	P=0.111	P=0.597N	P=0.593N	P=0.286
Logistic regression tests	P=0.115	P=0.619N	P=0.625N	P=0.310
Cochran-Armitage test	P=0.116			
Fisher exact test		P=0.615N	P=0.615N	P=0.315
Skin: Trichoepithelioma and Keratocanthoma[f]				
Overall rates	1/132 (1%)	0/70 (0%)	0/70 (0%)	3/100 (3%)
Adjusted rates	1.3%	0.0%	0.0%	5.4%
Interim sacrifice 1	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Interim sacrifice 2	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/9 (0%)
Terminal rates	0/59 (0%)	0/31 (0%)	0/34 (0%)	2/54 (4%)
First incidence (days)	647	—	—	719
Life table tests	P=0.107	P=0.619N	P=0.614N	P=0.275
Logistic regression tests	P=0.091	P=0.631N	P=0.631N	P=0.243
Cochran-Armitage test	P=0.077			
Fisher exact test		P=0.653N	P=0.653N	P=0.215
Thyroid Gland (C-Cell): Adenoma				
Overall rates	13/80 (16%)	3/50 (6%)	7/50 (14%)	13/81 (16%)
Adjusted rates	21.2%	8.4%	17.4%	22.9%
Terminal rates	11/59 (19%)	2/31 (6%)	3/34 (9%)	11/54 (20%)
First incidence (days)	674	565	646	714
Life table tests	P=0.276	P=0.120N	P=0.530N	P=0.499
Logistic regression tests	P=0.304	P=0.072N	P=0.461N	P=0.564
Cochran-Armitage test	P=0.317			
Fisher exact test		P=0.069N	P=0.467N	P=0.571N

Table B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
Thyroid Gland (C-Cell): Adenoma or Carcinoma				
Overall rates	14/80 (18%)	3/50 (6%)	8/50 (16%)	14/81 (17%)
Adjusted rates	22.8%	8.4%	20.1%	24.7%
Terminal rates	12/59 (20%)	2/31 (6%)	4/34 (12%)	12/54 (22%)
First incidence (days)	674	565	646	714
Life table tests	P=0.248	P=0.091N	P=0.579N	P=0.492
Logistic regression tests	P=0.275	P=0.052N	P=0.509N	P=0.561
Cochran-Armitage test	P=0.289			
Fisher exact test		P=0.048N	P=0.512N	P=0.568N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rates	2/80 (3%)	0/50 (0%)	3/50 (6%)	2/81 (2%)
Adjusted rates	3.4%	0.0%	8.8%	3.1%
Terminal rates	2/59 (3%)	0/31 (0%)	3/34 (9%)	0/54 (0%)
First incidence (days)	729 (T)	—	729 (T)	646
Life table tests	P=0.351	P=0.389N	P=0.262	P=0.674
Logistic regression tests	P=0.363	P=0.389N	P=0.262	P=0.690N
Cochran-Armitage test	P=0.368			
Fisher exact test		P=0.377N	P=0.288	P=0.685N
Uterus: Stromal Polyp				
Overall rates	12/80 (15%)	4/50 (8%)	6/50 (12%)	2/81 (2%)
Adjusted rates	18.2%	11.6%	14.8%	3.2%
Terminal rates	8/59 (14%)	3/31 (10%)	3/34 (9%)	1/54 (2%)
First incidence (days)	376	620	568	631
Life table tests	P=0.016N	P=0.256N	P=0.462N	P=0.009N
Logistic regression tests	P=0.011N	P=0.197N	P=0.454N	P=0.006N
Cochran-Armitage test	P=0.011N			
Fisher exact test		P=0.183N	P=0.419N	P=0.004N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rates	12/80 (15%)	4/50 (8%)	6/50 (12%)	3/81 (4%)
Adjusted rates	18.2%	11.6%	14.8%	4.4%
Terminal rates	8/59 (14%)	3/31 (10%)	3/34 (9%)	1/54 (2%)
First incidence (days)	376	620	568	338
Life table tests	P=0.033N	P=0.256N	P=0.462N	P=0.023N
Logistic regression tests	P=0.024N	P=0.197N	P=0.454N	P=0.014N
Cochran-Armitage test	P=0.024N			
Fisher exact test		P=0.183N	P=0.419N	P=0.013N
Uterus: Stromal Polyp or Stromal Sarcoma[f]				
Overall rates	13/132 (10%)	4/70 (6%)	7/70 (10%)	3/100 (3%)
Adjusted rates	18.4%	11.6%	16.3%	4.3%
Interim sacrifice 1	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Interim sacrifice 2	0/10 (0%)	0/10 (0%)	1/10 (10%)	0/9 (0%)
Terminal rates	8/59 (14%)	3/31 (10%)	3/34 (9%)	1/54 (2%)
First incidence (days)	376	620	460 (I)	338
Life table tests	P=0.039N	P=0.236N	P=0.541N	P=0.022N
Logistic regression tests	P=0.060N	P=0.241N	P=0.565N	P=0.035N
Cochran-Armitage test	P=0.067N			
Fisher exact test		P=0.233N	P=0.576N	P=0.034N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
All Organs: Leukemia (Lymphocytic, Monocytic, Mononuclear, or Undifferentiated)				
Overall rates	26/80 (33%)	15/50 (30%)	14/50 (28%)	18/81 (22%)
Adjusted rates	36.8%	35.7%	35.9%	28.1%
Terminal rates	15/59 (25%)	6/31 (19%)	10/34 (29%)	11/54 (20%)
First incidence (days)	400	451	571	338
Life table tests	P=0.131N	P=0.536	P=0.464N	P=0.177N
Logistic regression tests	P=0.079N	P=0.468N	P=0.362N	P=0.099N
Cochran-Armitage test	P=0.080N			
Fisher exact test		P=0.461N	P=0.367N	P=0.099N
All Organs: Benign Tumors				
Overall rates	63/80 (79%)	36/50 (72%)	37/50 (74%)	59/81 (73%)
Adjusted rates	88.7%	79.5%	85.7%	79.7%
Terminal rates	51/59 (86%)	22/31 (71%)	28/34 (82%)	39/54 (72%)
First incidence (days)	376	565	568	571
Life table tests	P=0.491N	P=0.435	P=0.548	P=0.540
Logistic regression tests	P=0.283N	P=0.210N	P=0.283N	P=0.234N
Cochran-Armitage test	P=0.282N			
Fisher exact test		P=0.251N	P=0.338N	P=0.245N
All Organs: Malignant Tumors				
Overall rates	38/80 (48%)	20/50 (40%)	24/50 (48%)	30/81 (37%)
Adjusted rates	50.4%	46.1%	53.9%	41.7%
Terminal rates	22/59 (37%)	9/31 (29%)	14/34 (41%)	14/54 (26%)
First incidence (days)	376	451	568	338
Life table tests	P=0.269N	P=0.454N	P=0.434	P=0.248N
Logistic regression tests	P=0.158N	P=0.269N	P=0.536	P=0.117N
Cochran-Armitage test	P=0.163N			
Fisher exact test		P=0.256N	P=0.549	P=0.118N
All Organs: Benign and Malignant Tumors				
Overall rates	73/80 (91%)	41/50 (82%)	48/50 (96%)	71/81 (88%)
Adjusted rates	93.6%	85.1%	96.0%	91.0%
Terminal rates	54/59 (92%)	24/31 (77%)	32/34 (94%)	47/54 (87%)
First incidence (days)	376	451	568	338
Life table tests	P=0.338	P=0.504	P=0.184	P=0.402
Logistic regression tests	P=0.528	P=0.088N	P=0.303	P=0.285N
Cochran-Armitage test	P=0.523			
Fisher exact test		P=0.100N	P=0.253	P=0.314N

(I)Interim sacrifice
(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals necropsied or examined microscopically for this tumor type
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly to the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] No tumors in dosed group or control group; statistical test not performed.
[f] Includes paired controls and animals examined at interim sacrifices
[g] Observed incidence at interim sacrifice (interim 1: 184 days; interim 2: 459 days)

TABLE B4a
Historical Incidence of Oral Cavity Tumors in Untreated Female F344/N Rats

Study	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Papilloma or Carcinoma
Historical Incidence at Battelle Columbus Laboratory[a]			
Chlorobenzene	0/49	0/49	0/49
N-phenyl-2-naphthylamine	0/49	0/49	0/49
Rotenone	0/50	0/50	0/50
l-ascorbic acid	0/50	1/50	1/50
2,4-Dichlorophenol	0/50	0/50	0/50
Diphenylhydantoin	0/50	0/50	0/50
Ethylenethiourea	1/50	0/50	1/50
Total	1/348 (0.3%)	1/348 (0.3%)	2/348 (0.6%)
Standard deviation	0.8%	0.8%	1.0%
Range	0%-2%	0%-2%	0%-2%
Overall Historical Incidence			
Total	8/2153 (0.4%)	4/2153 (0.2%)	12/2153 (0.6%)
Standard deviation	0.9%	0.6%	1.0%
Range	0%-4%	0%-2%	0%-4%

[a] Data as of 1 January 1990

TABLE B4b
Historical Incidence of Keratoacanthoma, Trichoepithelioma, or Squamous Cell Papilloma in Untreated Female F344/N Rats

Study	Incidence in Controls Keratoacanthoma	Trichoepithelioma	Squamous Cell Papilloma
Historical Incidence at Battelle Columbus Laboratory[a]			
Chlorobenzene	0/49	0/49	0/49
N-phenyl-2-naphthylamine	0/49	0/49	0/49
Rotenone	0/50	1/50	0/50
l-ascorbic acid	0/50	0/50	0/50
2,4-Dichlorophenol	0/50	0/50	1/50
Diphenylhydantoin	1/50	1/50	0/50
Ethylenethiourea	1/50	0/50	0/50
Total	2/348 (0.6%)	2/348 (0.6%)	1/348 (0.3%)
Standard deviation	1.0%	1.0%	0.8%
Range	0%-2%	0%-2%	0%-2%
Overall Historical Incidence[b]			
Total	13/2153 (0.6%)	2/2153 (0.1%)	6/2153 (0.3%)
Standard deviation	1.1%	0.4%	0.7%
Range	0%-4%	0%-2%	0%-2%

[a] Data as of 1 January 1990
[b] For keratoacanthoma, trichoepithelioma, or squamous cell papilloma (combined), overall historical control incidence is 21/2153 (1.0%) with a range of 0%-4%.

TABLE B4c
Historical Incidence of Uterine Tumors in Untreated Female F344/N Rats

Study	Incidence in Controls: Stromal Polyp	Stromal Sarcoma	Stromal Polyp or Sarcoma
Historical Incidence at Battelle Columbus Laboratory[a]			
Chlorobenzene	9/49	0/49	9/49
N-phenyl-2-naphthylamine	6/50	0/50	6/50
Rotenone	5/50	0/50	5/50
L-ascorbic acid	13/50	0/50	13/50
2,4-Dichlorophenol	12/50	1/50	13/50
Diphenylhydantoin	6/50	0/50	6/50
Ethylenethiourea	9/50	0/50	9/50
Total	60/349 (17%)	1/349 (0.3%)	61/349 (17%)
Standard deviation	6.2%	0.8%	6.6%
Range	10%-26%	0%-2%	10%-26%
Overall Historical Incidence			
Total	369/1782 (21%)	24/1782 (1%)	390/1782 (22%)[b]
Standard deviation	7.2%	1.9%	7.3%
Range	8%-36%	0%-6%	8%-38%

[a] Data as of 1 January 1990
[b] Numerator does not include 1 sarcoma NOS

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

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Disposition Summary					
Animals initially in study	100	50	70	70	100
Early deaths					
Natural death	10	4	11	6	10
Moribund sacrifice	11	7	8	10	17
Survivors					
Terminal sacrifice	59	18	31	34	54
Paired control		21			
Animals examined microscopically	80	32	50	50	81
Alimentary System					
Intestine small, duodenum	(80)	(32)	(50)	(50)	(81)
Necrosis			1 (2%)		
Intestine small, jejunum	(80)	(32)	(50)	(50)	(81)
Inflammation, chronic			1 (2%)		
Liver	(80)	(32)	(50)	(50)	(81)
Angiectasis	1 (1%)		1 (2%)		
Basophilic focus	52 (65%)	13 (41%)	32 (64%)	32 (64%)	49 (60%)
Clear cell focus	13 (16%)	1 (3%)	8 (16%)	9 (18%)	8 (10%)
Congestion	1 (1%)		1 (2%)	2 (4%)	
Eosinophilic focus	4 (5%)	1 (3%)	6 (12%)	7 (14%)	9 (11%)
Hepatodiaphragmatic nodule	7 (9%)	5 (16%)	7 (14%)	8 (16%)	13 (16%)
Hepatodiaphragmatic nodule, multiple				1 (2%)	1 (1%)
Hyperplasia	1 (1%)		2 (4%)	3 (6%)	
Inflammation, chronic active	18 (23%)	11 (34%)	13 (26%)	11 (22%)	19 (23%)
Mixed cell focus				1 (2%)	2 (2%)
Vacuolization cytoplasmic	11 (14%)	6 (19%)	8 (16%)	7 (14%)	19 (23%)
Bile duct, hyperplasia	24 (30%)	12 (38%)	10 (20%)	14 (28%)	22 (27%)
Centrilobular, necrosis	1 (1%)		1 (2%)	1 (2%)	
Hepatocyte, degeneration, cystic				1 (2%)	
Mesentery	(3)	(1)	(3)	(2)	(2)
Fat, congestion, acute				1 (50%)	
Fat, inflammation, chronic active	3 (100%)		2 (67%)		2 (100%)
Pancreas	(80)	(32)	(50)	(50)	(80)
Acinus, atrophy	19 (24%)	6 (19%)	7 (14%)	7 (14%)	19 (24%)
Acinus, cytomegaly, focal				1 (2%)	
Artery, inflammation, chronic active	1 (1%)				
Pharynx			(1)	(2)	(1)
Hyperplasia, squamous				1 (50%)	
Salivary glands	(80)	(32)	(50)	(50)	(78)
Acinus, atrophy				1 (2%)	
Acinus, cytomegaly	1 (1%)				
Stomach, forestomach	(80)	(32)	(50)	(50)	(81)
Acanthosis	3 (4%)	1 (3%)	3 (6%)	2 (4%)	3 (4%)
Inflammation, chronic active				1 (2%)	2 (2%)
Ulcer	1 (1%)		3 (6%)	3 (6%)	6 (7%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Alimentary System (continued)					
Stomach, glandular	(80)	(32)	(50)	(50)	(81)
Cyst epithelial inclusion	1 (1%)				
Erosion			1 (2%)		
Hyperplasia	1 (1%)				
Mineralization	1 (1%)				
Necrosis	2 (3%)	2 (6%)	1 (2%)	1 (2%)	3 (4%)
Pigmentation			1 (2%)		
Pigmentation, hemosiderin			1 (2%)	1 (2%)	1 (1%)
Ulcer		1 (3%)	1 (2%)	1 (2%)	3 (4%)
Tongue	(1)			(1)	(1)
Hyperplasia, squamous	1 (100%)			1 (100%)	1 (100%)
Tooth	(79)	(31)	(50)	(50)	(81)
Dentine, incisor, dysplasia		2 (6%)	8 (16%)	4 (8%)	10 (12%)
Dentine, incisor, necrosis, focal	5 (6%)			4 (8%)	4 (5%)
Dentine, incisor, necrosis, multifocal	55 (70%)	16 (52%)	34 (68%)	26 (52%)	53 (65%)
Incisor, odontoblast, degeneration					2 (2%)
Incisor, ameloblast, degeneration				1 (2%)	7 (9%)
Peridontal tissue, incisor, inflammation, necrotizing	1 (1%)				
Peridontal tissue, incisor, lower, inflammation, suppurative, chronic			1 (2%)		
Peridontal tissue, molar, inflammation, suppurative	2 (3%)				1 (1%)
Peridontal tissue, molar, lower, inflammation, suppurative, chronic	20 (25%)	5 (16%)	7 (14%)	10 (20%)	21 (26%)
Cardiovascular System					
Heart	(80)	(32)	(50)	(50)	(81)
Degeneration, chronic	63 (79%)	18 (56%)	42 (84%)	38 (76%)	63 (78%)
Inflammation, chronic active					1 (1%)
Thrombus		1 (3%)	1 (2%)		
Endocrine System					
Adrenal gland	(80)	(31)	(50)	(50)	(81)
Accessory adrenal cortical nodule	1 (1%)		1 (2%)		1 (1%)
Adrenal gland, cortex	(80)	(32)	(50)	(50)	(81)
Congestion	1 (1%)				
Degeneration, cystic	5 (6%)		1 (2%)	1 (2%)	3 (4%)
Hyperplasia	17 (21%)	2 (6%)	12 (24%)	18 (36%)	15 (19%)
Hypertrophy	2 (3%)	1 (3%)	5 (10%)	5 (10%)	9 (11%)
Necrosis			1 (2%)		
Vacuolization cytoplasmic, focal	7 (9%)		1 (2%)	2 (4%)	7 (9%)
Bilateral, degeneration, cystic				1 (2%)	
Bilateral, hyperplasia	1 (1%)				
Adrenal gland, medulla	(80)	(32)	(50)	(50)	(81)
Cyst					1 (1%)
Hemorrhage	1 (1%)				
Hyperplasia	3 (4%)		3 (6%)	8 (16%)	6 (7%)
Hypertrophy				1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Endocrine System (continued)					
Islets, pancreatic	(80)	(32)	(50)	(50)	(80)
Hyperplasia					1 (1%)
Pituitary gland	(80)	(32)	(50)	(50)	(81)
Pars distalis, congestion	21 (26%)	1 (3%)	12 (24%)	17 (34%)	22 (27%)
Pars distalis, cyst	17 (21%)	6 (19%)	19 (38%)	15 (30%)	29 (36%)
Pars distalis, hemorrhage	1 (1%)	1 (3%)	2 (4%)		5 (6%)
Pars distalis, hyperplasia	15 (19%)	7 (22%)	11 (22%)	7 (14%)	17 (21%)
Pars intermedia, congestion			1 (2%)		
Pars intermedia, cyst	2 (3%)		1 (2%)		4 (5%)
Pars intermedia, hyperplasia	1 (1%)			1 (2%)	
Rathke's cleft, cyst	1 (1%)				
Thyroid gland	(80)	(32)	(50)	(50)	(81)
C-cell, hyperplasia	8 (10%)	1 (3%)	6 (12%)	9 (18%)	7 (9%)
Follicle, cyst		1 (3%)			2 (2%)
Follicular cell, hyperplasia		1 (3%)		1 (2%)	4 (5%)
General Body System					
None					
Genital System					
Clitoral gland	(78)	(32)	(48)	(49)	(79)
Hyperplasia, glandular	4 (5%)	1 (3%)	7 (15%)	6 (12%)	6 (8%)
Inflammation, chronic active	13 (17%)	2 (6%)	8 (17%)	11 (22%)	17 (22%)
Duct, cyst	8 (10%)		3 (6%)	2 (4%)	5 (6%)
Duct, hyperplasia, squamous					2 (3%)
Ovary	(80)	(32)	(50)	(50)	(81)
Infiltration cellular, lymphocytic			1 (2%)		
Bilateral, periovarian tissue, cyst					1 (1%)
Follicle, cyst	1 (1%)	2 (6%)		1 (2%)	1 (1%)
Periovarian tissue, cyst	2 (3%)		6 (12%)	2 (4%)	3 (4%)
Periovarian tissue, hemorrhage			1 (2%)		
Uterus	(80)	(32)	(50)	(50)	(81)
Hemorrhage					1 (1%)
Infarct, chronic				1 (2%)	
Cervix, cyst	2 (3%)	1 (3%)	1 (2%)	2 (4%)	4 (5%)
Endometrium, hyperplasia, cystic, glandular	8 (10%)	4 (13%)	10 (20%)	7 (14%)	10 (12%)
Lumen, hemorrhage				2 (4%)	
Vagina	(3)		(2)		
Exudate	1 (33%)		1 (50%)		
Prolapse	1 (33%)				

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Hematopoietic System					
Bone marrow	(80)	(32)	(50)	(50)	(81)
Femoral, atrophy				1 (2%)	
Femoral, myelofibrosis			1 (2%)		1 (1%)
Lymph node	(80)	(32)	(50)	(50)	(81)
Mediastinal, angiectasis		1 (3%)			
Mediastinal, congestion	1 (1%)		1 (2%)		
Renal, angiectasis		1 (3%)			
Renal, pigmentation, hemosiderin		1 (3%)			
Lymph node, mandibular	(80)	(32)	(50)	(50)	(81)
Congestion			3 (6%)		
Necrosis			1 (2%)		
Lymph node, mesenteric	(80)	(31)	(50)	(49)	(81)
Angiectasis					1 (1%)
Infiltration cellular, histiocytic	1 (1%)		1 (2%)		
Inflammation, chronic active	1 (1%)				
Spleen	(80)	(32)	(50)	(50)	(81)
Depletion lymphoid			1 (2%)	1 (2%)	2 (2%)
Fibrosis	2 (3%)	1 (3%)	1 (2%)	2 (4%)	
Hematopoietic cell proliferation	1 (1%)		1 (2%)		1 (1%)
Hyperplasia, lymphoid, nodular	1 (1%)				
Hyperplasia, reticulum cell	2 (3%)		1 (2%)		
Infiltration cellular, lipocyte	1 (1%)				
Inflammation, granulomatous					1 (1%)
Necrosis	2 (3%)			1 (2%)	
Thrombus					1 (1%)
Capsule, fibrosis			1 (2%)		1 (1%)
Red pulp, atrophy			1 (2%)	1 (2%)	
Thymus	(70)	(29)	(48)	(47)	(76)
Depletion lymphoid	62 (89%)	10 (34%)	42 (88%)	42 (89%)	73 (96%)
Integumentary System					
Mammary gland	(79)	(31)	(50)	(50)	(81)
Hyperplasia, cystic	74 (94%)	24 (77%)	46 (92%)	47 (94%)	74 (91%)
Mineralization	1 (1%)				
Skin	(79)	(32)	(50)	(49)	(81)
Ulcer	1 (1%)		1 (2%)		
Subcutaneous tissue, inflammation, chronic active			1 (2%)		
Musculoskeletal System					
Bone	(80)	(32)	(50)	(50)	(81)
Cranium, osteosclerosis				1 (2%)	
Femur, fibrous osteodystrophy					1 (1%)
Humerus, fibrous osteodystrophy			1 (2%)		
Humerus, osteosclerosis	4 (5%)	4 (13%)	5 (10%)	3 (6%)	11 (14%)
Joint, cartilage, tibia, degeneration				1 (2%)	
Maxilla, fibrous osteodystrophy		1 (3%)			
Maxilla, osteosclerosis				1 (2%)	3 (4%)
Thoracic, vertebra, osteosclerosis	5 (6%)	1 (3%)	7 (14%)	4 (8%)	15 (19%)
Tibia, osteosclerosis	6 (8%)	2 (6%)	10 (20%)	7 (14%)	15 (19%)
Skeletal muscle			(1)		
Necrosis			1 (100%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Nervous System					
Brain	(80)	(32)	(50)	(50)	(81)
Compression	6 (8%)	2 (6%)	4 (8%)	7 (14%)	10 (12%)
Hemorrhage	1 (1%)				1 (1%)
Hydrocephalus	5 (6%)	1 (3%)	3 (6%)	5 (10%)	6 (7%)
Necrosis					1 (1%)
Spinal cord	(1)				
Myelin, degeneration	1 (100%)				
Respiratory System					
Lung	(80)	(32)	(50)	(50)	(81)
Foreign body	1 (1%)				
Inflammation, chronic active	1 (1%)		1 (2%)	1 (2%)	
Mineralization			1 (2%)		
Alveolar epithelium, hyperplasia	3 (4%)	1 (3%)	4 (8%)	2 (4%)	5 (6%)
Nose	(80)	(32)	(50)	(50)	(81)
Metaplasia, squamous	1 (1%)		1 (2%)		
Mucosa, inflammation, acute	2 (3%)	1 (3%)		1 (2%)	1 (1%)
Mucosa, inflammation, chronic active	12 (15%)	4 (13%)	7 (14%)	5 (10%)	18 (22%)
Mucosa, ulcer	2 (3%)				2 (2%)
Sinus, foreign body	6 (8%)	2 (6%)	5 (10%)	4 (8%)	15 (19%)
Special Senses System					
Ear	(3)				(2)
Pinna, inflammation, chronic active					1 (50%)
Eye	(20)	(5)	(9)	(12)	(26)
Anterior chamber, hemorrhage	1 (5%)				1 (4%)
Cornea, inflammation, acute					1 (4%)
Lens, cataract	19 (95%)	5 (100%)	9 (100%)	12 (100%)	25 (96%)
Retina, atrophy	19 (95%)	5 (100%)	9 (100%)	12 (100%)	25 (96%)
Urinary System					
Kidney	(80)	(32)	(50)	(50)	(81)
Hydronephrosis					1 (1%)
Inflammation, acute, focal			1 (2%)		
Nephropathy, chronic	72 (90%)	27 (84%)	48 (96%)	46 (92%)	76 (94%)
Cortex, cyst	1 (1%)	1 (3%)			
Cortex, infarct, chronic, multifocal					1 (1%)
Renal tubule, atrophy				1 (2%)	
Renal tubule, inflammation, chronic active				1 (2%)	
Urinary bladder	(80)	(32)	(49)	(50)	(81)
Dilatation			1 (2%)		

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR DRINKING WATER STUDIES OF SODIUM FLUORIDE

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

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Disposition Summary					
Animals initially in study	99	50	70	70	100
Early deaths					
Natural death	16	3	8	6	11
Moribund sacrifice	5	9	3	8	4
Survivors					
Natural death	2				
Terminal sacrifice	56	18	39	37	65
Paired control		20			
Animals examined microscopically	79	32	50	51	80
Alimentary System					
Intestine large, cecum	(79)	(32)	(50)	(50)	(80)
Adenocarcinoma, metastatic, intestine large					1 (1%)
Intestine large, colon	(79)	(32)	(50)	(50)	(80)
Adenocarcinoma					1 (1%)
Intestine small, duodenum	(79)	(32)	(50)	(50)	(80)
Polyp adenomatous				2 (4%)	1 (1%)
Intestine small, ileum	(78)	(32)	(50)	(49)	(80)
Adenocarcinoma, metastatic, intestine large					1 (1%)
Lymphoid tissue, lymphoma malignant lymphocytic		1 (3%)			
Intestine small, jejunum	(79)	(32)	(50)	(50)	(80)
Adenocarcinoma			1 (2%)	1 (2%)	
Lymphoma malignant mixed			1 (2%)	2 (4%)	
Lymphoma malignant undifferentiated cell type				1 (2%)	
Lymphoid tissue, lymphoma malignant mixed	1 (1%)				
Lymphoid tissue, lymphoma malignant undifferentiated cell type				1 (2%)	1 (1%)
Liver	(79)	(32)	(50)	(51)	(80)
Adenocarcinoma, metastatic, stomach				1 (2%)	
Fibrosarcoma, metastatic, prostate			1 (2%)		
Hemangiosarcoma	2 (3%)	1 (3%)		2 (4%)	2 (3%)
Hemangiosarcoma, multiple			1 (2%)		1 (1%)
Hemangiosarcoma, metastatic, heart			1 (2%)		
Hemangiosarcoma, metastatic, spleen					1 (1%)
Hemangiosarcoma, metastatic, multiple, liver		1 (3%)			
Hepatoblastoma			1 (2%)	1 (2%)	3 (4%)
Hepatocellular carcinoma	19 (24%)	7 (22%)	11 (22%)	13 (25%)	13 (16%)
Hepatocellular carcinoma, multiple	6 (8%)		4 (8%)		2 (3%)
Hepatocellular adenoma	14 (18%)	8 (25%)	17 (34%)	3 (6%)	23 (29%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Alimentary System					
Liver (continued)	(79)	(32)	(50)	(51)	(80)
Hepatocellular adenoma, multiple	36 (46%)	7 (22%)	17 (34%)	27 (53%)	30 (38%)
Histiocytic sarcoma		1 (3%)		1 (2%)	1 (1%)
Lymphoma malignant lymphocytic	2 (3%)				
Lymphoma malignant mixed				1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (1%)				
Mesentery	(8)	(2)	(4)	(7)	(4)
Adenocarcinoma, metastatic, intestine large					1 (25%)
Fibrosarcoma, metastatic, prostate			1 (25%)		
Hepatocellular carcinoma, metastatic, liver				1 (14%)	
Histiocytic sarcoma		1 (50%)			
Lymphoma malignant lymphocytic	1 (13%)				
Lymphoma malignant undifferentiated cell type	1 (13%)				
Pancreas	(78)	(32)	(50)	(51)	(80)
Fibrosarcoma, metastatic, prostate			1 (2%)		
Hemangioma			1 (2%)		
Lymphoma malignant lymphocytic	1 (1%)				
Lymphoma malignant undifferentiated cell type	1 (1%)				
Salivary glands	(78)	(32)	(50)	(51)	(80)
Histiocytic sarcoma				1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (1%)				
Stomach, forestomach	(79)	(32)	(50)	(51)	(79)
Papilloma squamous		2 (6%)			1 (1%)
Stomach, glandular	(79)	(32)	(50)	(51)	(80)
Adenocarcinoma				1 (2%)	
Adenoma			1 (2%)		
Fibrosarcoma, metastatic, prostate			1 (2%)		
Lymphoma malignant undifferentiated cell type	1 (1%)				
Tooth	(79)	(32)	(50)	(51)	(80)
Incisor, odontoma			1 (2%)		

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Cardiovascular System					
Blood vessel	(3)		(1)	(1)	(2)
Aorta, alveolar/bronchiolar carcinoma, metastatic, lung					1 (50%)
Heart	(79)	(32)	(50)	(50)	(80)
Hemangiosarcoma			1 (2%)		
Hemangiosarcoma, metastatic, skin	1 (1%)				
Hemangiosarcoma, metastatic, spleen					1 (1%)
Hepatocholangiocarcinoma, metastatic, liver					1 (1%)
Lymphoma malignant lymphocytic	1 (1%)				
Lymphoma malignant undifferentiated cell type	1 (1%)				
Endocrine System					
Adrenal gland, cortex	(79)	(32)	(50)	(51)	(80)
Adenoma	1 (1%)				
Bilateral, capsule, spindle cell, adenoma	2 (3%)	1 (3%)	1 (2%)	1 (2%)	
Capsule, spindle cell, adenoma	6 (8%)		6 (12%)	5 (10%)	6 (8%)
Capsule, spindle cell, adenoma, multiple			1 (2%)		
Adrenal gland, medulla	(78)	(32)	(50)	(51)	(80)
Pheochromocytoma malignant			1 (2%)		
Pheochromocytoma benign			1 (2%)		1 (1%)
Islets, pancreatic	(78)	(32)	(50)	(51)	(80)
Adenoma					2 (3%)
Thyroid gland	(79)	(32)	(50)	(51)	(80)
C-cell, adenoma	1 (1%)				
Follicular cell, adenoma	1 (1%)	1 (3%)	1 (2%)	3 (6%)	2 (3%)
General Body System					
None					
Genital System					
Epididymis	(79)	(32)	(50)	(51)	(79)
Hepatocellular carcinoma, metastatic, liver				1 (2%)	
Histiocytic sarcoma					1 (1%)
Lymphoma malignant lymphocytic	1 (1%)				
Lymphoma malignant mixed				1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (1%)				
Prostate	(79)	(32)	(50)	(51)	(79)
Fibrosarcoma			1 (2%)		
Lymphoma malignant lymphocytic	1 (1%)				
Lymphoma malignant mixed				1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (1%)				

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Genital System (continued)					
Seminal vesicle	(79)	(32)	(50)	(51)	(80)
Fibrosarcoma, metastatic, prostate			1 (2%)		
Hepatocellular carcinoma, metastatic, liver				1 (2%)	
Testes	(78)	(31)	(50)	(51)	(79)
Interstitial cell, adenoma			1 (2%)		1 (1%)
Hematopoietic System					
Blood	(2)				
Lymphoma malignant lymphocytic	1 (50%)				
Bone marrow	(79)	(32)	(50)	(51)	(80)
Femoral, hemangiosarcoma			1 (2%)	1 (2%)	
Femoral, hemangiosarcoma, metastatic, liver					1 (1%)
Femoral, hemangiosarcoma, metastatic, skin	1 (1%)	1 (3%)			
Femoral, hemangiosarcoma, metastatic, spleen					1 (1%)
Femoral, histiocytic sarcoma					1 (1%)
Humerus, hemangiosarcoma			2 (4%)		
Humerus, hemangiosarcoma, metastatic, skin	1 (1%)				
Tibia, hemangiosarcoma, metastatic, skin	1 (1%)				
Lymph node	(79)	(32)	(50)	(51)	(80)
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung					1 (1%)
Inguinal, lymphoma malignant mixed	1 (1%)				
Inguinal, lymphoma malignant undifferentiated cell type	1 (1%)				
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)		
Mediastinal, fibrosarcoma, metastatic, prostate			1 (2%)		
Mediastinal, hepatocellular carcinoma, metastatic, liver				1 (2%)	
Mediastinal, hepatocholangiocarcinoma, metastatic, liver					1 (1%)
Mediastinal, lymphoma malignant lymphocytic	1 (1%)				
Mediastinal, lymphoma malignant mixed				1 (2%)	
Pancreatic, hepatocholangiocarcinoma, metastatic, liver					1 (1%)
Renal, hepatocholangiocarcinoma, metastatic, liver					1 (1%)
Renal, lymphoma malignant mixed				1 (2%)	
Lymph node, mandibular	(78)	(31)	(50)	(50)	(80)
Lymphoma malignant lymphocytic	1 (1%)				
Lymphoma malignant undifferentiated cell type	1 (1%)				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Hematopoietic System (continued)					
Lymph node, mesenteric	(74)	(31)	(49)	(47)	(72)
Adenocarcinoma, metastatic, intestine large					1 (1%)
Hepatocellular carcinoma, metastatic, liver				1 (2%)	
Histiocytic sarcoma				1 (2%)	
Lymphoma malignant lymphocytic	2 (3%)	1 (3%)			
Lymphoma malignant mixed	1 (1%)			3 (6%)	
Lymphoma malignant undifferentiated cell type	1 (1%)			1 (2%)	
Spleen	(79)	(32)	(50)	(51)	(80)
Hemangiosarcoma				1 (2%)	1 (1%)
Hemangiosarcoma, metastatic, liver					1 (1%)
Hemangiosarcoma, metastatic, skin	1 (1%)				
Hepatocellular carcinoma, metastatic, liver				1 (2%)	
Histiocytic sarcoma	1 (1%)	1 (3%)		1 (2%)	
Lymphoma malignant lymphocytic	2 (3%)				
Lymphoma malignant mixed			1 (2%)	2 (4%)	
Lymphoma malignant undifferentiated cell type	1 (1%)			1 (2%)	
Thymus	(67)	(28)	(42)	(37)	(66)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver					1 (2%)
Lymphoma malignant lymphocytic	2 (3%)				
Lymphoma malignant undifferentiated cell type	1 (1%)				
Integumentary System					
Skin	(79)	(31)	(50)	(51)	(80)
Hepatocellular carcinoma, metastatic, liver				1 (2%)	
Lymphoma malignant lymphocytic	1 (1%)				
Papilloma squamous					1 (1%)
Subcutaneous tissue, fibrosarcoma		1 (3%)			
Subcutaneous tissue, hemangiosarcoma	1 (1%)	1 (3%)	1 (2%)		2 (3%)
Musculoskeletal System					
Bone	(79)	(32)	(50)	(51)	(80)
Cranium, schwannoma malignant, metastatic, brain					1 (1%)
Humerus, hemangiosarcoma			1 (2%)		
Maxilla, adenocarcinoma, metastatic, harderian gland			1 (2%)		
Skeletal muscle	(1)				(1)
Hepatocholangiocarcinoma, metastatic, liver					1 (100%)
Lymphoma malignant lymphocytic	1 (100%)				

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Nervous System					
Brain	(79)	(32)	(50)	(51)	(79)
Lymphoma malignant undifferentiated cell type	1 (1%)				
Olfactory lobe, schwannoma malignant					1 (1%)
Respiratory System					
Lung	(79)	(32)	(50)	(51)	(80)
Adenocarcinoma, metastatic, harderian gland			1 (2%)		
Alveolar/bronchiolar adenoma	9 (11%)	1 (3%)	4 (8%)	12 (24%)	9 (11%)
Alveolar/bronchiolar adenoma, multiple	2 (3%)				2 (3%)
Alveolar/bronchiolar carcinoma	12 (15%)	4 (13%)	8 (16%)	1 (2%)	7 (9%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)		
Alveolar/bronchiolar carcinoma, metastatic, lung	2 (3%)	1 (3%)		1 (2%)	2 (3%)
Fibrosarcoma, metastatic, skin		1 (3%)			
Hemangiosarcoma, metastatic, liver					1 (1%)
Hepatocellular carcinoma, metastatic, liver	8 (10%)	2 (6%)	2 (4%)	1 (2%)	1 (1%)
Hepatocholangiocarcinoma, metastatic, liver					1 (1%)
Histiocytic sarcoma		1 (3%)			
Lipoma			1 (2%)		
Lymphoma malignant lymphocytic	1 (1%)				
Lymphoma malignant mixed				1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (1%)				
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung					1 (1%)
Mediastinum, fibrosarcoma, metastatic, prostate			1 (2%)		
Nose	(79)	(32)	(50)	(51)	(80)
Adenocarcinoma, metastatic, harderian gland			1 (2%)		
Special Senses System					
Ear	(1)	(1)		(2)	(1)
Fibrosarcoma				1 (50%)	1 (100%)
Harderian gland	(65)	(27)	(42)	(43)	(59)
Adenocarcinoma	1 (2%)		1 (2%)		1 (2%)
Adenoma	7 (11%)		2 (5%)		1 (2%)

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Urinary System					
Kidney	(79)	(32)	(50)	(51)	(80)
Hepatocellular carcinoma, metastatic, liver				1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver					1 (1%)
Histiocytic sarcoma		1 (3%)		1 (2%)	
Lymphoma malignant lymphocytic	1 (1%)				
Lymphoma malignant mixed				1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (1%)				
Ureter			(1)		
Transitional epithelium, carcinoma			1 (100%)		
Urinary bladder	(78)	(32)	(50)	(50)	(80)
Lymphoma malignant lymphocytic	1 (1%)				
Lymphoma malignant mixed				1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (1%)				
Systemic Lesions					
Multiple organs[a]	(79)	(32)	(50)	(51)	(80)
Histiocytic sarcoma	1 (1%)	1 (3%)		2 (4%)	2 (3%)
Lymphoma malignant lymphocytic	2 (3%)	1 (3%)			
Lymphoma malignant mixed	1 (1%)		1 (2%)	3 (6%)	
Lymphoma malignant undifferentiated cell	1 (1%)			3 (6%)	1 (1%)
Tumor Summary					
Total animals with primary neoplasms[b]	71	24	45	43	69
Total primary neoplasms	125	36	93	83	118
Total animals with benign neoplasms	57	17	40	35	57
Total benign neoplasms	79	20	55	53	80
Total animals with malignant neoplasms	41	14	31	25	33
Total malignant neoplasms	46	16	38	30	38
Total animals with secondary neoplasms[c]	11	6	6	3	8
Total secondary neoplasms	15	6	15	11	25

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control

Number of Days on Study	420	496	571	578	591	625	626	641	645	662	669	684	691	696	698	701	704	715	720	721	721	729	729	729	729
Carcass ID Number	0671	0421	0401	0681	0311	0851	0221	0111	0031	0201	0501	0451	0561	0761	0631	0931	0611	0811	0381	0231	0411	0081	0281	0291	0371
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Hepatocellular carcinoma			X						X	X		X		X		X		X					X		
Hepatocellular carcinoma, multiple													X						X	X					
Hepatocellular adenoma																				X			X		
Hepatocellular adenoma, multiple	X			X							X	X		X			X								X
Mesentery		+					+														+				
Pancreas	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																			+						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, skin		X																							
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Bilateral, capsule, spindle cell, adenoma																									
Capsule, spindle cell, adenoma											X														
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined
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 Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	732	732
Carcass ID Number	0391	0491	0621	0821	0841	0881	0051	0061	0071	0091	0101	0121	0131	0151	0951	0161	0171	0181	0211	0251	0261	0301	0321	0331	0341
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma								X				X													X
Hepatocellular carcinoma, multiple	X																								
Hepatocellular adenoma				X			X		X			X									X				
Hepatocellular adenoma, multiple		X	X		X	X		X		X	X		X	X		X			X			X			
Mesentery				+							+														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, skin																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Bilateral, capsule, spindle cell, adenoma			X															X							
Capsule, spindle cell, adenoma							X						X												
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	732	732	732	732	732	732	733	733	733	733	733	733	733	733	736	736	736	736	736	736	736	736	737	737	737
Carcass ID Number	0351	0361	0431	0441	0461	0471	0481	0511	0521	0541	0571	0591	0631	0641	0651	0701	0711	0721	0731	0751	0771	0781	0801	0831	0891
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma					X																				
Hepatocellular carcinoma									X		X				X			X		X		X			X
Hepatocellular carcinoma, multiple																X	X								
Hepatocellular adenoma						X					X		X						X			X	X		
Hepatocellular adenoma, multiple	X	X	X	X			X	X	X	X		X		X	X	X		X		X	X				
Mesentery																		+					+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, skin																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Bilateral, capsule, spindle cell, adenoma																									
Capsule, spindle cell, adenoma							X				X								X						
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 9 1 1	0 9 2 1	0 9 7 1	0 9 8 1	**Total Tissues/ Tumors**
Alimentary System					
Esophagus	+	+	+	+	79
Gallbladder	+	+	+	+	76
Intestine large	+	+	+	+	79
Intestine large, cecum	+	+	+	+	79
Intestine large, colon	+	+	+	+	79
Intestine large, rectum	+	+	+	+	78
Intestine small	+	+	+	+	79
Intestine small, duodenum	+	+	+	+	79
Intestine small, ileum	+	+	+	+	78
Intestine small, jejunum	+	+	+	+	79
Liver	+	+	+	+	79
Hemangiosarcoma					2
Hepatocellular carcinoma			X		19
Hepatocellular carcinoma, multiple					6
Hepatocellular adenoma				X	14
Hepatocellular adenoma, multiple	X	X			36
Mesentery	+				8
Pancreas	+	+	+	+	78
Salivary glands	+	+	+	+	78
Stomach	+	+	+	+	79
Stomach, forestomach	+	+	+	+	79
Stomach, glandular	+	+	+	+	79
Tooth	+	+	+	+	79
Cardiovascular System					
Blood vessel	+				3
Heart	+	+	+	+	79
Hemangiosarcoma, metastatic, skin					1
Endocrine System					
Adrenal gland	+	+	+	+	79
Adrenal gland, cortex	+	+	+	+	79
Adenoma					1
Bilateral, capsule, spindle cell, adenoma					2
Capsule, spindle cell, adenoma					6
Adrenal gland, medulla	+	+	+	+	78
Islets, pancreatic	+	+	+	+	78

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	4 2 0	4 9 6	5 7 1	5 7 8	5 9 1	6 2 5	6 2 6	6 4 1	6 4 5	6 6 2	6 6 9	6 8 4	6 9 1	6 9 6	6 9 8	7 0 1	7 0 4	7 1 5	7 2 0	7 2 1	7 2 1	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 6 7 1	0 0 2 1	0 4 0 1	0 6 8 1	0 3 1 1	0 8 5 1	0 2 2 1	0 1 1 1	0 0 3 1	0 2 0 1	0 5 0 1	0 4 5 1	0 5 6 1	0 7 6 1	0 6 9 1	0 9 3 1	0 6 1 1	0 8 1 1	0 3 8 1	0 2 3 1	0 4 1 1	0 0 8 1	0 2 8 1	0 2 9 1	0 3 7 1
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M
Pituitary gland	+	I	+	+	+	I	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma												X													
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland					+		+	+	+	+		+	+	+		+	+	+			+	+	+	+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Blood										+											+				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma, metastatic, skin		X																							
Humerus, hemangiosarcoma, metastatic, skin		X																							
Tibia, hemangiosarcoma, metastatic, skin		X																							
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, skin		X																							
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	M	M	M	+	+	+	M	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	9	9	9	9	9	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	4	6	8	8	8	0	0	0	0	1	1	1	1	9	1	1	1	2	2	2	3	3	3	3
	9	9	2	2	4	8	5	6	7	9	0	2	3	5	5	6	7	8	1	5	6	0	2	3	4
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Endocrine System (continued)																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland	+	+		+	+	+		+		+	+	+	+	+		+	+	+	+	+	+	+	+	+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma, metastatic, skin																									
Humerus, hemangiosarcoma, metastatic, skin																									
Tibia, hemangiosarcoma, metastatic, skin																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, skin																									
Histiocytic sarcoma																									
Thymus	M	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	3	3	3	3	3	3	3	3	6	6	6	6	6	6	6	6	7	7	7
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	3	4	4	4	4	4	5	5	5	5	5	6	6	6	7	7	7	7	7	7	7	8	8	8
Carcass ID Number	5	6	3	4	6	7	8	1	2	4	7	9	3	4	5	0	1	2	3	5	7	8	0	3	9
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	I	+	+	I	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, adenoma																X									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland		+	+	+	+	+	+	+			+		+	+	+	+	+	+	+	+					+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma, metastatic, skin																									
Humerus, hemangiosarcoma, metastatic, skin																									
Tibia, hemangiosarcoma, metastatic, skin																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, skin																									
Histiocytic sarcoma																						X			
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 9 1 1	0 9 2 1	0 9 7 1	0 9 8 1	**Total Tissues/ Tumors**
Endocrine System (continued)					
Parathyroid gland	+	+	+	+	70
Pituitary gland	+	+	+	+	71
Thyroid gland	+	+	+	+	79
C-cell, adenoma					1
Follicular cell, adenoma					1
General Body System					
None					
Genital System					
Epididymis	+	+	+	+	79
Penis			+		1
Preputial gland	+	+		+	55
Prostate	+	+	+	+	79
Seminal vesicle	+	+	+	+	79
Testes	+	+	+	+	78
Hematopoietic System					
Blood					2
Bone marrow	+	+	+	+	79
Femoral, hemangiosarcoma, metastatic, skin					1
Humerus, hemangiosarcoma, metastatic, skin					1
Tibia, hemangiosarcoma, metastatic, skin					1
Lymph node	+	+	+	+	79
Lymph node, mandibular	+	+	+	+	78
Lymph node, mesenteric	+	+	+	+	74
Spleen	+	+	+	+	79
Hemangiosarcoma, metastatic, skin					1
Histiocytic sarcoma					1
Thymus	+	+	+	+	67

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	420	496	571	578	591	625	626	641	645	662	669	684	691	696	698	701	704	715	720	721	721	729	729	729	729
Carcass ID Number	0671	0021	0401	0681	0311	0851	0221	0111	0031	0201	0501	0451	0561	0761	0691	0931	0611	0811	0381	0231	0411	0081	0281	0291	0371
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	+	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma		X																							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																					+				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma				X			X																		
Alveolar/bronchiolar carcinoma, metastatic, lung							X																		
Hepatocellular carcinoma, metastatic, liver									X			X	X	X		X				X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye															+										
Harderian gland	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	M
Adenocarcinoma																									
Adenoma															X					X	X				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant lymphocytic					X																X				
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	9	9	9	9	9	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	2	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	4	6	8	8	8	0	0	0	0	1	1	1	1	9	1	1	1	2	2	2	3	3	3	3
	9	9	2	2	4	8	5	6	7	9	0	2	3	5	5	6	7	8	1	5	6	0	2	3	4
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X			X	X							X								
Alveolar/bronchiolar adenoma, multiple											X														
Alveolar/bronchiolar carcinoma							X	X					X							X					
Alveolar/bronchiolar carcinoma, metastatic, lung								X																	
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye						+														+					
Harderian gland	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenocarcinoma						X																			
Adenoma					X								X							X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type											X														

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	3	3	3	3	3	3	3	3	6	6	6	6	6	6	6	6	7	7	7
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	3	4	4	4	4	4	5	5	5	5	5	6	6	6	7	7	7	7	7	7	7	8	8	8
Carcass ID Number	5	6	3	4	6	7	8	1	2	4	7	9	3	4	5	0	1	2	3	5	7	8	0	3	9
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Integumentary System																									
Mammary gland	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	+	+	+	M	M	+	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X											X					X								X
Alveolar/bronchiolar adenoma, multiple																				X					
Alveolar/bronchiolar carcinoma										X			X	X	X			X			X				
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Hepatocellular carcinoma, metastatic, liver									X													X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear												+													
Eye																									+
Harderian gland	M	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+
Adenocarcinoma																									
Adenoma																									X
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	737	737	737	737	
Carcass ID Number	**0911**	**0921**	**0971**	**0981**	**Total Tissues/ Tumors**
Integumentary System					
Mammary gland	M	M	M	M	11
Skin	+	+	+	+	79
Subcutaneous tissue, hemangiosarcoma					1
Musculoskeletal System					
Bone	+	+	+	+	79
Skeletal muscle					1
Nervous System					
Brain	+	+	+	+	79
Respiratory System					
Lung	+	+	+	+	79
Alveolar/bronchiolar adenoma				X	9
Alveolar/bronchiolar adenoma, multiple					2
Alveolar/bronchiolar carcinoma					12
Alveolar/bronchiolar carcinoma, metastatic, lung					2
Hepatocellular carcinoma, metastatic, liver					8
Nose	+	+	+	+	79
Trachea	+	+	+	+	79
Special Senses System					
Ear					1
Eye					4
Harderian gland	+	+	+	+	65
Adenocarcinoma					1
Adenoma					7
Urinary System					
Kidney	+	+	+	+	79
Urinary bladder	+	+	+	+	78
Systemic Lesions					
Multiple organs	+	+	+	+	79
Histiocytic sarcoma					1
Lymphoma malignant lymphocytic					2
Lymphoma malignant mixed			X		1
Lymphoma malignant undifferentiated cell type					1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control

	0	2	2	2	3	3	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6
Number of Days on Study	1	0	4	7	5	8	2	2	3	8	0	1	2	2	3	4	6	6	7	9	9	0	1	2	5
	7	8	1	3	9	6	0	0	3	8	5	9	3	7	0	0	4	8	9	3	9	9	9	3	1
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	2	3	1	1	4	3	1	4	3	3	1	2	3	5	2	0	2	3	4	4	2	1	0	3	0
Carcass ID Number	2	9	9	7	1	2	3	2	0	7	5	0	3	0	8	5	9	1	8	9	1	8	3	6	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X										
Hemangiosarcoma, metastatic, multiple, liver															X										
Hepatocellular carcinoma												X							X	X		X	X		
Hepatocellular adenoma											X					X		X				X			X
Hepatocellular adenoma, multiple										X									X	X	X		X	X	
Histiocytic sarcoma					X																				
Mesentery					+							+													
Histiocytic sarcoma					X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous													X									X			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, capsule, spindle cell, adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

Number of Days on Study	657	660	684	687	698	706	713	
Carcass ID Number	1231	1161	1091	1251	1141	1071	1101	**Total Tissues/ Tumors**
Alimentary System								
Esophagus	+	+	+	+	+	+	+	32
Gallbladder	+	+	+	+	+	+	+	32
Intestine large	+	+	+	+	+	+	+	32
Intestine large, cecum	+	+	+	+	+	+	+	32
Intestine large, colon	+	+	+	+	+	+	+	32
Intestine large, rectum	+	+	+	+	+	+	+	31
Intestine small	+	+	+	+	+	+	+	32
Intestine small, duodenum	+	+	+	+	+	+	+	32
Intestine small, ileum	+	+	+	+	+	+	+	32
Intestine small, jejunum	+	+	+	+	+	+	+	32
Liver	+	+	+	+	+	+	+	32
Hemangiosarcoma								1
Hemangiosarcoma, metastatic, multiple, liver								1
Hepatocellular carcinoma	X					X		7
Hepatocellular adenoma		X	X		X			8
Hepatocellular adenoma, multiple				X				7
Histiocytic sarcoma								1
Mesentery								2
Histiocytic sarcoma								1
Pancreas	+	+	+	+	+	+	+	32
Salivary glands	+	+	+	+	+	+	+	32
Stomach	+	+	+	+	+	+	+	32
Stomach, forestomach	+	+	+	+	+	+	+	32
Papilloma squamous								2
Stomach, glandular	+	+	+	+	+	+	+	32
Tooth	+	+	+	+	+	+	+	32
Cardiovascular System								
Heart	+	+	+	+	+	+	+	32
Endocrine System								
Adrenal gland	+	+	+	+	+	+	+	32
Adrenal gland, cortex	+	+	+	+	+	+	+	32
Bilateral, capsule, spindle cell, adenoma							X	1
Adrenal gland, medulla	+	+	+	+	+	+	+	32
Islets, pancreatic	+	+	+	+	+	+	+	32

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

Number of Days on Study	0	2	2	2	3	3	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6
	1	0	4	7	5	8	2	2	3	8	0	1	2	2	3	4	6	6	7	9	9	0	1	2	5
	7	8	1	3	9	6	0	0	3	8	5	9	3	7	0	0	4	8	9	3	9	9	9	3	1
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	2	3	1	1	4	3	1	4	3	3	1	2	3	5	2	0	2	3	4	4	2	1	0	3	0
	2	9	9	7	1	2	3	2	0	7	5	0	3	0	8	5	9	1	8	9	1	8	3	6	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland									+			+								+	+	+	+		+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma, metastatic, skin																	X								
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

Number of Days on Study	657	660	684	687	698	706	713	
Carcass ID Number	1231	1161	1091	1251	1141	1071	1101	**Total Tissues/ Tumors**
Endocrine System (continued)								
Parathyroid gland	+	+	+	+	+	+	+	30
Pituitary gland	+	+	+	+	+	+	+	32
Thyroid gland	+	+	+	+	+	+	+	32
Follicular cell, adenoma			X					1
General Body System								
None								
Genital System								
Epididymis	+	+	+	+	+	+	+	32
Preputial gland			+	+	+	+	+	12
Prostate	+	+	+	+	+	+	+	32
Seminal vesicle	+	+	+	+	+	+	+	32
Testes	+	+	+	+	+	+	+	31
Hematopoietic System								
Bone marrow	+	+	+	+	+	+	+	32
Femoral, hemangiosarcoma, metastatic, skin								1
Lymph node	+	+	+	+	+	+	+	32
Lymph node, mandibular	+	+	+	+	+	M	+	31
Lymph node, mesenteric	+	+	+	+	+	+	+	31
Spleen	+	+	+	+	+	+	+	32
Histiocytic sarcoma								1
Thymus	+	+	+	+	+	M	+	28

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

	0	2	2	2	3	3	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6
Number of Days on Study	1	0	4	7	5	8	2	2	3	8	0	1	2	2	3	4	6	6	7	9	9	0	1	2	5
	7	8	1	3	9	6	0	0	3	8	5	9	3	7	0	0	4	8	9	3	9	9	9	3	1
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	2	3	1	1	4	3	1	4	3	3	1	2	3	5	2	0	2	3	4	4	2	1	0	3	0
Carcass ID Number	2	9	9	7	1	2	3	2	0	7	5	0	3	0	8	5	9	1	8	9	1	8	3	6	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
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	+
Skin	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma													X												
Subcutaneous tissue, hemangiosarcoma																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma									X										X						
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Fibrosarcoma, metastatic, skin													X												
Hepatocellular carcinoma, metastatic, liver												X										X			
Histiocytic sarcoma					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																					+				
Harderian gland	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Lymphoma malignant lymphocytic																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

Number of Days on Study	6 5 7	6 6 0	6 8 4	6 8 7	6 9 8	7 0 6	7 1 3	
Carcass ID Number	1 2 3 1	1 1 6 1	1 0 9 1	1 2 5 1	1 1 4 1	1 0 7 1	1 1 0 1	**Total Tissues/ Tumors**
Integumentary System								
Mammary gland	+	M	M	+	M	+	M	7
Skin	+	+	+	+	+	+	+	31
Subcutaneous tissue, fibrosarcoma								1
Subcutaneous tissue, hemangiosarcoma								1
Musculoskeletal System								
Bone	+	+	+	+	+	+	+	32
Nervous System								
Brain	+	+	+	+	+	+	+	32
Peripheral nerve								1
Respiratory System								
Lung	+	+	+	+	+	+	+	32
Alveolar/bronchiolar adenoma								1
Alveolar/bronchiolar carcinoma			X				X	4
Alveolar/bronchiolar carcinoma, metastatic, lung							X	1
Fibrosarcoma, metastatic, skin								1
Hepatocellular carcinoma, metastatic, liver								2
Histiocytic sarcoma								1
Nose	+	+	+	+	+	+	+	32
Trachea	+	+	+	+	+	+	+	32
Special Senses System								
Ear								1
Harderian gland	M	M	+	+	+	+	M	27
Urinary System								
Kidney	+	+	+	+	+	+	+	32
Histiocytic sarcoma								1
Urinary bladder	+	+	+	+	+	+	+	32
Systemic Lesions								
Multiple organs	+	+	+	+	+	+	+	32
Histiocytic sarcoma								1
Lymphoma malignant lymphocytic	X							1

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm

Number of Days on Study	208	540	619	624	659	656	657	684	707	709	728	729	729	729	729	729	729	729	729	729	729	730	730	730	730
Carcass ID Number	1571	2131	2031	1921	1831	2051	1961	2161	1781	1651	1821	1641	1661	1741	1761	1791	1881	1911	1931	1981	2091	1521	1531	1551	1581
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																						X			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, prostate								X																	
Hemangiosarcoma, multiple																X									
Hemangiosarcoma, metastatic, heart																									
Hepatoblastoma																									
Hepatocellular carcinoma				X				X		X			X										X		X
Hepatocellular carcinoma, multiple					X						X														
Hepatocellular adenoma			X			X					X	X		X				X			X		X		
Hepatocellular adenoma, multiple				X	X			X	X				X				X		X					X	X
Mesentery								+													+				
Fibrosarcoma, metastatic, prostate								X																	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, prostate								X																	
Hemangioma																						X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibrosarcoma, metastatic, prostate								X																	
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Incisor, odontoma																									
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Number of Days on Study	730	731	731	731	731	731	732	732	732	732	733	733	733	733	733	736	736	736	736	736	737	737	737	737	737	
Carcass ID Number	1601	1611	1621	1631	1671	1721	1731	1751	1771	1861	1891	1941	1951	1971	2011	2021	2061	2071	2081	2111	2151	2171	2181	2191	2201	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, prostate																										1
Hemangiosarcoma, multiple																										1
Hemangiosarcoma, metastatic, heart																							X			1
Hepatoblastoma																					X					1
Hepatocellular carcinoma		X						X	X				X			X										11
Hepatocellular carcinoma, multiple	X																						X			4
Hepatocellular adenoma			X	X	X							X		X	X	X		X					X			17
Hepatocellular adenoma, multiple	X						X			X							X		X	X	X	X				17
Mesentery										+						+										4
Fibrosarcoma, metastatic, prostate																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, prostate																										1
Hemangioma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															1
Fibrosarcoma, metastatic, prostate																										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Incisor, odontoma			X																							1
Cardiovascular System																										
Blood vessel												+														1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																							X			1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Number of Days on Study	208	540	619	624	629	656	657	684	707	709	728	729	729	729	729	729	729	729	729	729	729	730	730	730	730
Carcass ID Number	1571	2131	2031	1921	1831	2051	1961	2161	1781	1651	1821	1641	1661	1741	1761	1791	1881	1911	1931	1981	2091	1521	1531	1551	1581
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, capsule, spindle cell, adenoma									X																
Capsule, spindle cell, adenoma																X					X				
Capsule, spindle cell, adenoma, multiple																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		+	+			+		+		+	+	+		+	+	+	+	+	+			+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma								X																	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, prostate								X																	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma			X																						
Humerus, hemangiosarcoma			X															X							
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung						X																			
Mediastinal, fibrosarcoma, metastatic, prostate								X																	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung						X																			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	1	1	1	1	1	2	2	2	2	3	3	3	3	3	6	6	6	6	6	7	7	7	7	7	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	
	6	6	6	6	6	7	7	7	7	8	8	9	9	9	0	0	0	0	0	1	1	1	1	1	2	**Total**
Carcass ID Number	0	1	2	3	7	2	3	5	7	6	9	4	5	7	1	2	6	7	8	1	5	7	8	9	0	**Tissues/**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**Tumors**
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, capsule, spindle cell, adenoma																										1
Capsule, spindle cell, adenoma					X							X			X							X				6
Capsule, spindle cell, adenoma, multiple																									X	1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																		X								1
Pheochromocytoma benign															X											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma											X															1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland			+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+		+	+	+	+	+	38
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, prostate																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma															X											1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, hemangiosarcoma																										1
Humerus, hemangiosarcoma																										2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinal, fibrosarcoma, metastatic, prostate																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	M	+	M	+	+	+	+	42
Alveolar/bronchiolar carcinoma, metastatic, lung																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Number of Days on Study	2 0 8	5 4 0	6 1 9	6 2 4	6 2 9	6 5 6	6 5 7	6 8 4	7 0 7	7 0 9	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 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	1 5 7 1	2 1 3 1	2 0 3 1	1 9 2 1	1 8 3 1	2 0 5 1	1 9 6 1	2 1 6 1	1 7 8 1	1 6 5 1	1 8 2 1	1 6 4 1	1 6 6 1	1 7 4 1	1 7 6 1	1 7 9 1	1 8 8 1	1 9 1 1	1 9 3 1	1 9 8 1	2 0 9 1	1 5 2 1	1 5 3 1	1 5 5 1	1 5 8 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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Humerus, hemangiosarcoma			X																						
Maxilla, adenocarcinoma, metastatic, harderian gland		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+																						
Spinal cord			+																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland		X																							
Alveolar/bronchiolar adenoma													X						X						
Alveolar/bronchiolar carcinoma						X			X			X		X											
Alveolar/bronchiolar carcinoma, multiple															X										
Hepatocellular carcinoma, metastatic, liver																									X
Lipoma																									
Mediastinum, fibrosarcoma, metastatic, prostate								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland	+	+	M	M	+	M	+	+	+	M	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+
Adenocarcinoma		X																							
Adenoma																	X								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter																									
Transitional epithelium, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																			X						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	1	1	1	1	1	2	2	2	2	3	3	3	3	3	6	6	6	6	6	7	7	7	7	7	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	
	6	6	6	6	6	7	7	7	7	8	8	9	9	9	0	0	0	0	0	1	1	1	1	1	2	**Total**
Carcass ID Number	0	1	2	3	7	2	3	5	7	6	9	4	5	7	1	2	6	7	8	1	5	7	8	9	0	**Tissues/**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**Tumors**
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	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma												X														1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Humerus, hemangiosarcoma																										1
Maxilla, adenocarcinoma, metastatic, harderian gland																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, harderian gland																										1
Alveolar/bronchiolar adenoma									X		X															4
Alveolar/bronchiolar carcinoma	X			X								X			X											8
Alveolar/bronchiolar carcinoma, multiple																										1
Hepatocellular carcinoma, metastatic, liver								X																		2
Lipoma																					X					1
Mediastinum, fibrosarcoma, metastatic, prostate																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, harderian gland																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adenocarcinoma																										1
Adenoma								X																		2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter													+													1
Transitional epithelium, carcinoma													X													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm

Number of Days on Study	017	241	505	528	568	579	598	619	620	626	651	660	692	721	729	729	729	729	729	729	729	729	729	729	730	730
Carcass ID Number	2901	2301	2251	2321	2441	2681	2371	2561	2891	2351	2381	2471	2671	2451	2221	2241	2311	2421	2581	2621	2641	2821	2841	2861	2231	2291
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																										
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																										
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, stomach																										
Hemangiosarcoma																										
Hepatoblastoma																										
Hepatocellular carcinoma							X	X	X			X	X	X		X	X									
Hepatocellular adenoma												X														X
Hepatocellular adenoma, multiple						X			X						X	X		X	X		X	X	X		X	
Histiocytic sarcoma											X															
Mesentery												+					+								+	
Hepatocellular carcinoma, metastatic, liver																	X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X															
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																										
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel		+																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, capsule, spindle cell, adenoma																							X			
Capsule, spindle cell, adenoma															X	X									X	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3	3	6	6	6	6	7	7	7	7	
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	3	3	3	4	4	4	4	4	4	5	5	5	5	6	6	6	6	6	7	7	7	8	8	8	8	**Total**
Carcass ID Number	3	6	9	0	1	3	6	8	9	2	5	7	9	0	1	5	6	9	6	8	9	3	5	7	8	**Tissues/**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous			X																			X				2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																					X					1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenocarcinoma, metastatic, stomach																X										1
Hemangiosarcoma																				X	X					2
Hepatoblastoma																									X	1
Hepatocellular carcinoma					X							X		X									X		X	13
Hepatocellular adenoma																				X						3
Hepatocellular adenoma, multiple	X	X			X	X	X	X		X			X	X		X	X	X	X		X	X		X	X	27
Histiocytic sarcoma																										1
Mesentery		+		+														+				+				7
Hepatocellular carcinoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenocarcinoma																X										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, capsule, spindle cell, adenoma																										1
Capsule, spindle cell, adenoma		X																			X					5
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

Number of Days on Study	017	245	505	528	568	579	598	619	620	626	651	660	692	721	729	729	729	729	729	729	729	729	729	729	730	730
Carcass ID Number	2901	2301	2251	2321	2441	2681	2371	2561	2891	2351	2381	2471	2671	2451	2221	2241	2311	2421	2581	2621	2641	2821	2841	2861	2231	2291
Endocrine System (continued)																										
Parathyroid gland	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																										
General Body System																										
Tissue NOS																+										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																	X									
Penis				+																						
Preputial gland				+	+			+				+			+	+	+		+	+	+	+	+	+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																	X									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma						X																				
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, hepatocellular carcinoma, metastatic, liver																	X									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																	X									
Histiocytic sarcoma																										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																										
Hepatocellular carcinoma, metastatic, liver																	X									
Histiocytic sarcoma											X															
Thymus	+	I	+	+	+	M	+	M	+	+	M	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

Number of Days on Study	730	730	730	730	730	731	731	731	731	732	732	732	732	733	733	733	733	736	736	736	736	737	737	737	737	
Carcass ID Number	2331	2361	2391	2401	2411	2431	2461	2481	2491	2521	2551	2571	2591	2601	2611	2651	2661	2691	2761	2781	2791	2831	2851	2871	2881	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Follicular cell, adenoma									X								X								X	3
General Body System																										
Tissue NOS																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma, metastatic, liver																										1
Penis																										1
Preputial gland		+	+	+		+	+	+	+		+	+	+		+	+	+	+		+		+	+	+		31
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma, metastatic, liver																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Femoral, hemangiosarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Mediastinal, hepatocellular carcinoma, metastatic, liver																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma			X																							1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma							X																			1
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Thymus	+	+	+	+	M	+	+	+	M	+	+	M	M	M	+	+	+	+	+	+	M	+	+	+	M	37

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

	0	2	5	5	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	1	4	0	2	6	7	9	1	2	2	5	6	9	2	2	2	2	2	2	2	2	2	2	2	3	3
	7	1	5	8	8	9	8	9	0	6	1	0	2	1	9	9	9	9	9	9	9	9	9	9	0	0
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	9	3	2	3	4	6	3	5	8	3	3	4	6	4	2	2	3	4	5	6	6	8	8	8	2	2
Carcass ID Number	0	0	5	2	4	8	7	6	9	5	8	7	7	5	2	4	1	2	8	2	4	2	4	6	3	9
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																	X									
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X																X		X	X			
Alveolar/bronchiolar carcinoma																										
Alveolar/bronchiolar carcinoma, metastatic, lung																										
Hepatocellular carcinoma, metastatic, liver																	X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear		+																								
Fibrosarcoma																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																	X									
Histiocytic sarcoma											X															
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X															
Lymphoma malignant mixed																										
Lymphoma malignant undifferentiated cell type																									X	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3	3	6	6	6	6	7	7	7	7	
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	3	3	3	4	4	4	4	4	4	5	5	5	5	6	6	6	6	6	7	7	7	8	8	8	8	**Total**
Carcass ID Number	3	6	9	0	1	3	6	8	9	2	5	7	9	0	1	5	6	9	6	8	9	3	5	7	8	**Tissues/**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**Tumors**
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	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma, metastatic, liver																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma	X		X		X		X		X			X	X											X		12
Alveolar/bronchiolar carcinoma		X																								1
Alveolar/bronchiolar carcinoma, metastatic, lung		X																								1
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																										
Ear						+																				2
Fibrosarcoma						X																				1
Harderian gland	+	+	+	M	M	M	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	43
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma			X																							2
Lymphoma malignant mixed						X								X									X			3
Lymphoma malignant undifferentiated cell type								X							X											3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm

Number of Days on Study	273	386	488	527	529	593	609	623	684	691	705	714	714	719	721	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	3351	2961	3261	3431	3621	3781	3631	2991	3021	3831	3611	3291	3511	3081	3111	3101	3181	3211	3241	3371	3381	3561	3731	3761	3881
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, intestine large																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, intestine large																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																							
Hemangiosarcoma, multiple							X																		
Hemangiosarcoma, metastatic, spleen																									
Hepatoblastoma											X				X										
Hepatocellular carcinoma					X	X				X	X		X				X								
Hepatocellular carcinoma, multiple											X		X												
Hepatocellular adenoma						X									X										X
Hepatocellular adenoma, multiple							X									X	X		X	X		X	X	X	
Histiocytic sarcoma								X																	
Mesentery		+																							
Adenocarcinoma, metastatic, intestine large																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel						+																			
Aorta, alveolar/bronchiolar carcinoma, metastatic, lung						X																			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Hepatocholangiocarcinoma, metastatic, liver											X														

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732
Carcass ID Number	2931	2941	2951	2971	3011	3031	3051	3061	3071	3121	3131	3141	3151	3161	3191	3201	3221	3251	3271	3301	3311	3361	3401	3411	3441
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, intestine large	X																								
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma	X																								
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																	X								
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, intestine large	X																								
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, multiple																									
Hemangiosarcoma, metastatic, spleen																									
Hepatoblastoma																									
Hepatocellular carcinoma								X		X							X			X					X
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma		X				X	X			X	X					X	X		X		X		X		X
Hepatocellular adenoma, multiple			X		X				X					X										X	
Histiocytic sarcoma																									
Mesentery	+										+														
Adenocarcinoma, metastatic, intestine large	X																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous										X															
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Aorta, alveolar/bronchiolar carcinoma, metastatic, lung																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Hepatocholangiocarcinoma, metastatic, liver																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	733	733	733	733	733	733	733	733	733	733	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737
Carcass ID Number	3451	3461	3481	3491	3501	3521	3531	3551	3571	3591	3601	3641	3651	3661	3671	3681	3691	3711	3721	3741	3751	3791	3801	3811	3821
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, intestine large																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, intestine large																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																					X				
Hemangiosarcoma, multiple																									
Hemangiosarcoma, metastatic, spleen	X																								
Hepatoblastoma										X															
Hepatocellular carcinoma																X					X				
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma	X					X	X			X		X				X					X				
Hepatocellular adenoma, multiple		X	X		X			X	X		X		X	X	X		X		X	X		X	X	X	
Histiocytic sarcoma																									
Mesentery																									
Adenocarcinoma, metastatic, intestine large																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																			+						
Aorta, alveolar/bronchiolar carcinoma, metastatic, lung																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen			X																						
Hepatocholangiocarcinoma, metastatic, liver																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 8 4 1	3 8 6 1	3 8 7 1	3 8 9 1	3 9 0 1	**Total Tissues/ Tumors**
Alimentary System						
Esophagus	+	+	+	+	+	80
Gallbladder	+	+	+	+	+	80
Intestine large	+	+	+	+	+	80
Intestine large, cecum	+	+	+	+	+	80
Adenocarcinoma, metastatic, intestine large						1
Intestine large, colon	+	+	+	+	+	80
Adenocarcinoma						1
Intestine large, rectum	+	+	+	+	+	79
Intestine small	+	+	+	+	+	80
Intestine small, duodenum	+	+	+	+	+	80
Polyp adenomatous						1
Intestine small, ileum	+	+	+	+	+	80
Adenocarcinoma, metastatic, intestine large						1
Intestine small, jejunum	+	+	+	+	+	80
Liver	+	+	+	+	+	80
Hemangiosarcoma						2
Hemangiosarcoma, multiple						1
Hemangiosarcoma, metastatic, spleen						1
Hepatoblastoma						3
Hepatocellular carcinoma						13
Hepatocellular carcinoma, multiple						2
Hepatocellular adenoma				X	X	23
Hepatocellular adenoma, multiple	X		X			30
Histiocytic sarcoma						1
Mesentery					+	4
Adenocarcinoma, metastatic, intestine large						1
Pancreas	+	+	+	+	+	80
Salivary glands	+	+	+	+	+	80
Stomach	+	+	+	+	+	80
Stomach, forestomach	+	+	+	+	+	79
Papilloma squamous						1
Stomach, glandular	+	+	+	+	+	80
Tooth	+	+	+	+	+	80
Cardiovascular System						
Blood vessel						2
Aorta, alveolar/bronchiolar carcinoma, metastatic, lung						1
Heart	+	+	+	+	+	80
Hemangiosarcoma, metastatic, spleen						1
Hepatocholangiocarcinoma, metastatic, liver						1

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	273	386	488	527	529	593	609	623	684	691	705	714	714	719	721	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	3351	2961	3261	3431	3621	3781	3631	2991	3021	3831	3611	3291	3511	3081	3111	3101	3181	3211	3241	3371	3381	3561	3731	3761	3881
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, spindle cell, adenoma																					X		X		
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Penis				+																					
Preputial gland				+	+	+	+	+	+	+		+	+	+	+	+						+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma, metastatic, liver							X																		
Femoral, hemangiosarcoma, metastatic, spleen																									
Femoral, histiocytic sarcoma																						X			
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung						X																			
Mediastinal, hepatocholangiocarcinoma, metastatic, liver											X														
Pancreatic, hepatocholangiocarcinoma, metastatic, liver											X														
Renal, hepatocholangiocarcinoma, metastatic, liver											X														
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	M	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, intestine large																									

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732
Carcass ID Number	2931	2941	2951	2971	3011	3031	3051	3061	3071	3121	3131	3141	3151	3161	3191	3201	3221	3251	3271	3301	3311	3361	3401	3411	3441
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, spindle cell, adenoma			X																						
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																						X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	X
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Penis																									
Preputial gland				+	+	+	+				+	+	+	+	+		+	+		+		+	+	+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma, metastatic, liver																									
Femoral, hemangiosarcoma, metastatic, spleen																									
Femoral, histiocytic sarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung																									
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																									
Pancreatic, hepatocholangiocarcinoma, metastatic, liver																									
Renal, hepatocholangiocarcinoma, metastatic, liver																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, intestine large	X																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	733	733	733	733	733	733	733	733	733	733	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737
Carcass ID Number	3451	3461	3481	3491	3501	3521	3531	3551	3571	3591	3601	3641	3651	3661	3671	3681	3691	3711	3721	3741	3751	3791	3801	3811	3821
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, spindle cell, adenoma						X																X			
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																						X	X		
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Penis																									
Preputial gland	+	+		+		+	+	+	+	+	+	+			+		+	+	+	+	+	+	+	+	
Prostate	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma											X														
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma, metastatic, liver																									
Femoral, hemangiosarcoma, metastatic, spleen			X																						
Femoral, histiocytic sarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung																									
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																									
Pancreatic, hepatocholangiocarcinoma, metastatic, liver																									
Renal, hepatocholangiocarcinoma, metastatic, liver																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, intestine large																									

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 8 4 1	3 8 6 1	3 8 7 1	3 8 9 1	3 9 0 1	**Total Tissues/ Tumors**
Endocrine System						
Adrenal gland	+	+	+	+	+	80
Adrenal gland, cortex	+	+	+	+	+	80
Capsule, spindle cell, adenoma	X					6
Adrenal gland, medulla	+	+	+	+	+	80
Pheochromocytoma benign						1
Islets, pancreatic	+	+	+	+	+	80
Adenoma						2
Parathyroid gland	+	+	+	+	+	78
Pituitary gland	I	+	+	+	+	75
Thyroid gland	+	+	+	+	+	80
Follicular cell, adenoma						2
General Body System						
None						
Genital System						
Epididymis	+	+	+	+	+	79
Histiocytic sarcoma						1
Penis						1
Preputial gland		+		+	+	53
Prostate	+	+	+	+	+	79
Seminal vesicle	+	+	+	+	+	80
Testes	+	+	+	+	+	79
Interstitial cell, adenoma						1
Hematopoietic System						
Bone marrow	+	+	+	+	+	80
Femoral, hemangiosarcoma, metastatic, liver						1
Femoral, hemangiosarcoma, metastatic, spleen						1
Femoral, histiocytic sarcoma						1
Lymph node	+	+	+	+	+	80
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung						1
Mediastinal, hepatocholangio-carcinoma, metastatic, liver						1
Pancreatic, hepatocholangio-carcinoma, metastatic, liver						1
Renal, hepatocholangio-carcinoma, metastatic, liver						1
Lymph node, mandibular	+	+	+	+	+	80
Lymph node, mesenteric	+	+	+	+	+	72
Adenocarcinoma, metastatic, intestine large						1

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	2	3	4	5	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	7	8	8	2	2	9	0	2	8	9	0	1	1	1	2	2	2	2	2	2	2	2	2	2	2
	3	6	8	7	9	3	9	3	4	1	5	4	4	9	1	9	9	9	9	9	9	9	9	9	9
	3	2	3	3	3	3	3	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	3	9	2	4	6	7	6	9	0	8	6	2	5	0	1	1	1	2	2	3	3	5	7	7	8
Carcass ID Number	5	6	6	3	2	8	3	9	2	3	1	9	1	8	1	0	8	1	4	7	8	6	3	6	8
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hematopoietic System (continued)																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, liver							X																		
Thymus	+	+	+	M	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver											X														
Integumentary System																									
Mammary gland	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous										X															
Subcutaneous tissue, hemangiosarcoma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, schwannoma malignant, metastatic, brain															X										
Skeletal muscle											+														
Hepatocholangiocarcinoma, metastatic, liver											X														
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Olfactory lobe, schwannoma malignant															X										
Peripheral nerve									+																
Spinal cord									+																
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X							X					X			
Alveolar/bronchiolar adenoma, multiple																					X				
Alveolar/bronchiolar carcinoma						X																			
Alveolar/bronchiolar carcinoma, metastatic, lung						X																			
Hemangiosarcoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver																									
Hepatocholangiocarcinoma, metastatic, liver											X														
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732
Carcass ID Number	2931	2941	2951	2971	3011	3031	3051	3061	3071	3121	3131	3141	3151	3161	3191	3201	3221	3251	3271	3301	3311	3361	3401	3411	3441
Hematopoietic System (continued)																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, liver																									
Thymus	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M
Hepatocholangiocarcinoma, metastatic, liver																									
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	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Subcutaneous tissue, hemangiosarcoma			X																						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, schwannoma malignant, metastatic, brain																									
Skeletal muscle																									
Hepatocholangiocarcinoma, metastatic, liver																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Olfactory lobe, schwannoma malignant																									
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X			X											X									
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma							X				X									X		X			
Alveolar/bronchiolar carcinoma, metastatic, lung							X																		
Hemangiosarcoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver																									
Hepatocholangiocarcinoma, metastatic, liver																									
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	3	3	3	3	3	3	3	3	3	3	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	4	4	4	4	5	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	8	8	8
Carcass ID Number	5	6	8	9	0	2	3	5	7	9	0	4	5	6	7	8	9	1	2	4	5	9	0	1	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hematopoietic System (continued)																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X																						
Hemangiosarcoma, metastatic, liver																									
Thymus	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Integumentary System																									
Mammary gland	M	M	M	M	M	+	M	M	M	M	M	M	+	M	M	M	+	+	M	M	M	+	M	+	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, schwannoma malignant, metastatic, brain																									
Skeletal muscle																									
Hepatocholangiocarcinoma, metastatic, liver																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Olfactory lobe, schwannoma malignant																									
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X												X			X			
Alveolar/bronchiolar adenoma, multiple																		X							
Alveolar/bronchiolar carcinoma	X																								
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Hemangiosarcoma, metastatic, liver																					X				
Hepatocellular carcinoma, metastatic, liver																					X				
Hepatocholangiocarcinoma, metastatic, liver																									
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 8 4 1	3 8 6 1	3 8 7 1	3 8 9 1	3 9 0 1	**Total Tissues/ Tumors**
Hematopoietic System (continued)						
Spleen	+	+	+	+	+	80
Hemangiosarcoma						1
Hemangiosarcoma, metastatic, liver						1
Thymus	+	+	+	+	+	66
Hepatocholangiocarcinoma, metastatic, liver						1
Integumentary System						
Mammary gland	M	M	M	M	M	11
Skin	+	+	+	+	+	80
Papilloma squamous						1
Subcutaneous tissue, hemangiosarcoma						2
Musculoskeletal System						
Bone	+	+	+	+	+	80
Cranium, schwannoma malignant, metastatic, brain						1
Skeletal muscle						1
Hepatocholangiocarcinoma, metastatic, liver						1
Nervous System						
Brain	+	+	+	+	+	79
Olfactory lobe, schwannoma malignant						1
Peripheral nerve						1
Spinal cord						1
Respiratory System						
Lung	+	+	+	+	+	80
Alveolar/bronchiolar adenoma						9
Alveolar/bronchiolar adenoma, multiple						2
Alveolar/bronchiolar carcinoma		X				7
Alveolar/bronchiolar carcinoma, metastatic, lung						2
Hemangiosarcoma, metastatic, liver						1
Hepatocellular carcinoma, metastatic, liver						1
Hepatocholangiocarcinoma, metastatic, liver						1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung						1
Nose	+	+	+	+	+	80
Trachea	+	+	+	+	+	80

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	273	386	488	527	529	593	609	623	684	691	705	714	714	719	721	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	3351	2961	3261	3431	3621	3781	3631	2991	3021	3831	3611	3291	3511	3081	3111	3101	3181	3211	3241	3371	3381	3561	3731	3761	3881
Special Senses System																									
Ear																									
Fibrosarcoma																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	M
Adenocarcinoma																							X		
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver											X														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X														X			
Lymphoma malignant undifferentiated cell type																			X						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2
	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	9	9	9	0	0	0	0	0	1	1	1	1	1	1	2	2	2	2	3	3	3	4	4	4
Carcass ID Number	3	4	5	7	1	3	5	6	7	2	3	4	5	6	9	0	2	5	7	0	1	6	0	1	4
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Special Senses System																									
Ear																									
Fibrosarcoma																									
Harderian gland	M	+	+	+	+	+	+	M	+	M	+	M	+	+	M	+	+	+	+	+	+	+	M	M	M
Adenocarcinoma																									
Adenoma																	X								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant undifferentiated cell type																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	733	733	733	733	733	733	733	733	733	733	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737
Carcass ID Number	3451	3461	3481	3491	3501	3521	3531	3551	3571	3591	3601	3641	3651	3661	3671	3681	3691	3711	3721	3741	3751	3791	3801	3811	3821
Special Senses System																									
Ear							+																		
Fibrosarcoma							X																		
Harderian gland	+	M	+	+	+	+	+	+	M	+	M	M	M	+	M	+	+	+	M	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant undifferentiated cell type																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 8 4 1	3 8 6 1	3 8 7 1	3 8 9 1	3 9 0 1	**Total Tissues/ Tumors**
Special Senses System						
Ear						1
Fibrosarcoma						1
Harderian gland	+	M	+	M	+	59
Adenocarcinoma						1
Adenoma						1
Urinary System						
Kidney	+	+	+	+	+	80
Hepatocholangiocarcinoma, metastatic, liver						1
Urinary bladder	+	+	+	+	+	80
Systemic Lesions						
Multiple organs	+	+	+	+	+	80
Histiocytic sarcoma						2
Lymphoma malignant undifferentiated cell type						1

Table C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride

	Control	25 ppm	100 ppm	175 ppm
Adrenal Gland (Cortex): Adenoma				
Overall rates[a]	9/79 (11%)	8/50 (16%)	6/51 (12%)	6/80 (8%)
Adjusted rates[b]	15.0%	19.9%	16.2%	9.2%
Terminal rates[c]	8/58 (14%)	7/39 (18%)	6/37 (16%)	6/65 (9%)
First incidence (days)	669	707	729 (T)	729 (T)
Life table tests[d]	P=0.115N	P=0.359	P=0.571	P=0.221N
Logistic regression tests[d]	P=0.135N	P=0.325	P=0.524	P=0.258N
Cochran-Armitage test[d]	P=0.152N			
Fisher exact test[d]		P=0.310	P=0.579	P=0.286N
Harderian Gland: Adenoma				
Overall rates	7/79 (9%)	2/50 (4%)	0/51 (0%)	1/80 (1%)
Adjusted rates	11.4%	5.1%	0.0%	1.5%
Terminal rates	4/58 (7%)	2/39 (5%)	0/37 (0%)	1/65 (2%)
First incidence (days)	698	729 (T)	—	729 (T)
Life table tests	P=0.010N	P=0.222N	P=0.042N	P=0.026N
Logistic regression tests	P=0.011N	P=0.233N	P=0.044N	P=0.030N
Cochran-Armitage test	P=0.011N			
Fisher exact test		P=0.247N	P=0.027N	P=0.030N
Harderian Gland: Adenoma or Adenocarcinoma				
Overall rates	8/79 (10%)	3/50 (6%)	0/51 (0%)	2/80 (3%)
Adjusted rates	13.0%	7.1%	0.0%	3.1%
Terminal rates	5/58 (9%)	2/39 (5%)	0/37 (0%)	2/65 (3%)
First incidence (days)	698	540	—	729 (T)
Life table tests	P=0.014N	P=0.287N	P=0.028N	P=0.037N
Logistic regression tests	P=0.016N	P=0.311N	P=0.029N	P=0.043N
Cochran-Armitage test	P=0.016N			
Fisher exact test		P=0.317N	P=0.016N	P=0.047N
Harderian Gland: Adenoma or Adenocarcinoma[e]				
Overall rates	8/131 (6%)	3/60 (5%)	0/62 (0%)	3/100 (3%)
Adjusted rates	13.0%	7.1%	0.0%	4.2%
Interim sacrifice 1[f]	0/10 (0%)	0/0	0/2 (0%)	0/10 (0%)
Interim sacrifice 2[f]	0/10 (0%)	0/10 (0%)	0/9 (0%)	1/10 (10%)
Terminal rates	5/58 (9%)	2/39 (5%)	0/37 (0%)	2/65 (3%)
First incidence (days)	698	540	—	458 (I)
Life table tests	P=0.041N	P=0.298N	P=0.028N	P=0.083N
Logistic regression tests	P=0.073N	P=0.382N	P=0.034N	P=0.157N
Cochran-Armitage test	P=0.090N			
Fisher exact test		P=0.527N	P=0.042N	P=0.218N
Liver: Hepatocellular Adenoma				
Overall rates	50/79 (63%)	34/50 (68%)	30/51 (59%)	53/80 (66%)
Adjusted rates	76.7%	73.8%	74.8%	77.9%
Terminal rates	43/58 (74%)	27/39 (69%)	27/37 (73%)	50/65 (77%)
First incidence (days)	420	619	579	593
Life table tests	P=0.321N	P=0.519	P=0.425N	P=0.396N
Logistic regression tests	P=0.456	P=0.355	P=0.570N	P=0.418
Cochran-Armitage test	P=0.488			
Fisher exact test		P=0.362	P=0.371N	P=0.411

Table C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
Liver: Hepatocellular Carcinoma				
Overall rates	25/79 (32%)	15/50 (30%)	13/51 (25%)	15/80 (19%)
Adjusted rates	36.3%	33.9%	30.0%	20.6%
Terminal ratesa	15/58 (26%)	10/39 (26%)	7/37 (19%)	8/65 (12%)
First incidence (days)	571	624	598	529
Life table tests	P=0.028N	P=0.441N	P=0.356N	P=0.035N
Logistic regression tests	P=0.030N	P=0.503N	P=0.323N	P=0.045N
Cochran-Armitage test	P=0.029N			
Fisher exact test		P=0.502N	P=0.291N	P=0.045N
Liver: Hepatoblastoma or Hepatocellular Carcinoma				
Overall rates	25/79 (32%)	16/50 (32%)	13/51 (25%)	17/80 (21%)
Adjusted rates	36.3%	36.1%	30.0%	23.2%
Terminal rates	15/58 (26%)	11/39 (28%)	7/37 (19%)	9/65 (14%)
First incidence (days)	571	624	598	529
Life table tests	P=0.049N	P=0.525N	P=0.356N	P=0.072N
Logistic regression tests	P=0.056N	P=0.557	P=0.323N	P=0.096N
Cochran-Armitage test	P=0.054N			
Fisher exact test		P=0.558	P=0.291N	P=0.096N
Liver: Hepatocellular Adenoma, Hepatoblastoma, or Hepatocellular Carcinoma				
Overall rates	62/79 (78%)	39/50 (78%)	37/51 (73%)	61/80 (76%)
Adjusted rates	86.0%	82.9%	84.0%	82.4%
Terminal rates	48/58 (83%)	31/39 (79%)	30/37 (81%)	52/65 (80%)
First incidence (days)	420	619	579	529
Life table tests	P=0.168N	P=0.384N	P=0.401N	P=0.164N
Logistic regression tests	P=0.410N	P=0.581N	P=0.496N	P=0.470N
Cochran-Armitage test	P=0.354N			
Fisher exact test		P=0.558N	P=0.285N	P=0.442N
Liver: Hepatocellular Adenoma, Hepatoblastoma, or Hepatocellular Carcinoma[e]				
Overall rates	84/131 (64%)	44/60 (73%)	40/62 (65%)	66/100 (66%)
Adjusted rates	89.0%	84.4%	84.9%	83.4%
Interim sacrifice 1	0/10 (0%)	0/0	0/2 (0%)	0/10 (0%)
Interim sacrifice 2	4/10 (40%)	5/10 (50%)	3/9 (33%)	5/10 (50%)
Terminal rates	48/58 (83%)	31/39 (79%)	30/37 (81%)	52/65 (80%)
First incidence (days)	420	458 (I)	459 (I)	458 (I)
Life table tests	P=0.006N	P=0.043N	P=0.031N	P=0.004N
Logistic regression tests	P=0.308N	P=0.545	P=0.318N	P=0.395N
Cochran-Armitage test	P=0.489N			
Fisher exact test		P=0.137	P=0.545	P=0.438
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	11/79 (14%)	4/50 (8%)	12/51 (24%)	11/80 (14%)
Adjusted rates	19.0%	10.3%	31.2%	16.6%
Terminal rates	11/58 (19%)	4/39 (10%)	11/37 (30%)	10/65 (15%)
First incidence (days)	729 (T)	729 (T)	528	691
Life table tests	P=0.380	P=0.192N	P=0.110	P=0.479N
Logistic regression tests	P=0.314	P=0.192N	P=0.083	P=0.515N
Cochran-Armitage test	P=0.305			
Fisher exact test		P=0.232N	P=0.122	P=0.578N

Table C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
Lung: Alveolar/bronchiolar Carcinoma				
Overall rates	12/79 (15%)	9/50 (18%)	1/51 (2%)	7/80 (9%)
Adjusted rates	19.4%	21.7%	2.7%	10.4%
Terminal rates	10/58 (17%)	7/39 (18%)	1/37 (3%)	6/65 (9%)
First incidence (days)	578	656	729 (T)	593
Life table tests	P=0.026N	P=0.482	P=0.018N	P=0.117N
Logistic regression tests	P=0.035N	P=0.428	P=0.018N	P=0.158N
Cochran-Armitage test	P=0.033N			
Fisher exact test		P=0.425	P=0.011N	P=0.157N
Lung: Alveolar/bronchiolar Adenoma or Alveolar/bronchiolar Carcinoma				
Overall rates	23/79 (29%)	13/50 (26%)	13/51 (25%)	18/80 (23%)
Adjusted rates	37.9%	31.5%	33.8%	26.7%
Terminal rates	21/58 (36%)	11/39 (28%)	12/37 (32%)	16/65 (25%)
First incidence (days)	578	656	528	593
Life table tests	P=0.134N	P=0.353N	P=0.422N	P=0.132N
Logistic regression tests	P=0.205N	P=0.419N	P=0.490N	P=0.213N
Cochran-Armitage test	P=0.202N			
Fisher exact test		P=0.430N	P=0.404N	P=0.220N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rates	1/79 (1%)	1/50 (2%)	3/51 (6%)	2/80 (3%)
Adjusted rates	1.7%	2.6%	8.1%	3.1%
Terminal rates	1/58 (2%)	1/39 (3%)	3/37 (8%)	2/65 (3%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.353	P=0.670	P=0.163	P=0.540
Logistic regression tests	P=0.353	P=0.670	P=0.163	P=0.540
Cochran-Armitage test	P=0.320			
Fisher exact test		P=0.627	P=0.167	P=0.505
All Organs: Hemangiosarcoma				
Overall rates	3/79 (4%)	5/50 (10%)	4/51 (8%)	6/80 (8%)
Adjusted rates	4.4%	12.1%	10.1%	8.4%
Terminal rates	1/58 (2%)	4/39 (10%)	3/37 (8%)	3/65 (5%)
First incidence (days)	496	619	579	386
Life table tests	P=0.367	P=0.166	P=0.261	P=0.281
Logistic regression tests	P=0.351	P=0.161	P=0.320	P=0.308
Cochran-Armitage test	P=0.334			
Fisher exact test		P=0.148	P=0.270	P=0.254
All Organs: Hemangioma or Hemangiosarcoma				
Overall rates	3/79 (4%)	6/50 (12%)	4/51 (8%)	6/80 (8%)
Adjusted rates	4.4%	14.6%	10.1%	8.4%
Terminal rates	1/58 (2%)	5/39 (13%)	3/37 (8%)	3/65 (5%)
First incidence (days)	496	619	579	386
Life table tests	P=0.438	P=0.091	P=0.261	P=0.281
Logistic regression tests	P=0.421	P=0.083	P=0.320	P=0.308
Cochran-Armitage test	P=0.403			
Fisher exact test		P=0.079	P=0.270	P=0.254

Table C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rates	4/79 (5%)	1/50 (2%)	6/51 (12%)	1/80 (1%)
Adjusted rates	6.3%	2.6%	16.2%	1.5%
Terminal rates	2/58 (3%)	1/39 (3%)	6/37 (16%)	1/65 (2%)
First incidence (days)	591	729 (T)	729 (T)	729 (T)
Life table tests	P=0.307N	P=0.324N	P=0.139	P=0.159N
Logistic regression tests	P=0.343N	P=0.338N	P=0.121	P=0.176N
Cochran-Armitage test	P=0.341N			
Fisher exact test		P=0.355N	P=0.144	P=0.180N
All Organs: Malignant Lymphoma and Histiocytic Sarcoma				
Overall rates	5/79 (6%)	1/50 (2%)	8/51 (16%)	3/80 (4%)
Adjusted rates	8.0%	2.6%	20.9%	4.4%
Terminal rates	3/58 (5%)	1/39 (3%)	7/37 (19%)	2/65 (3%)
First incidence (days)	591	729 (T)	651	623
Life table tests	P=0.535N	P=0.225N	P=0.072	P=0.318N
Logistic regression tests	P=0.521	P=0.239N	P=0.061	P=0.347N
Cochran-Armitage test	P=0.525			
Fisher exact test		P=0.247N	P=0.077	P=0.353N
All Organs: Benign Tumors				
Overall rates	57/79 (72%)	40/50 (80%)	35/51 (69%)	57/80 (71%)
Adjusted rates	85.0%	86.9%	85.2%	82.6%
Terminal rates	48/58 (83%)	33/39 (85%)	31/37 (84%)	53/65 (82%)
First incidence (days)	420	619	528	593
Life table tests	P=0.102N	P=0.404	P=0.478N	P=0.181N
Logistic regression tests	P=0.329N	P=0.204	P=0.520	P=0.515N
Cochran-Armitage test	P=0.297N			
Fisher exact test		P=0.214	P=0.405N	P=0.520N
All Organs: Malignant Tumors				
Overall rates	41/79 (52%)	31/50 (62%)	25/51 (49%)	33/80 (41%)
Adjusted rates	55.1%	64.5%	55.5%	42.8%
Terminal rates	25/58 (43%)	22/39 (56%)	17/37 (46%)	21/65 (32%)
First incidence (days)	496	540	579	386
Life table tests	P=0.034N	P=0.298	P=0.521N	P=0.087N
Logistic regression tests	P=0.033N	P=0.175	P=0.482N	P=0.113N
Cochran-Armitage test	P=0.033N			
Fisher exact test		P=0.173	P=0.444N	P=0.118N
All Organs: Benign and Malignant Tumors				
Overall rates	71/79 (90%)	45/50 (90%)	43/51 (84%)	69/80 (86%)
Adjusted rates	92.2%	93.7%	93.5%	89.6%
Terminal rates	52/58 (90%)	36/39 (92%)	34/37 (92%)	57/65 (88%)
First incidence (days)	420	540	528	386
Life table tests	P=0.107N	P=0.388N	P=0.436N	P=0.115N
Logistic regression tests	P=0.268N	P=0.570	P=0.477N	P=0.358N
Cochran-Armitage test	P=0.214N			
Fisher exact test		P=0.615	P=0.250N	P=0.323N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

(I)Interim sacrifice
(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined at site
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly to the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Includes paired controls and animals examined at interim sacrifices
[f] Observed incidence at interim sacrifice (interim 1: 165 days; interim 2: 458 days)

Table C4
Historical Incidence of Hepatocellular Neoplasms in Untreated Male B6C3F$_1$ Mice

Study	Incidence in Controls Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratory[a]			
Chlorobenzene	7/50	14/50	19/50
N-phenyl-2-naphthylamine	6/47	6/47	11/47
Rotenone	7/47	6/47	12/47
l-ascorbic acid	6/50	10/50	16/50
2,4-Dichlorophenol	4/50	7/50	10/50
Diphenylhydantoin	19/50	13/50	29/50
Dowicide EC-7 pentachlorophenol	5/35	1/35	6/35
Ethylenethiourea	11/50	13/50	20/50
Technical grade pentachlorophenol	5/35	2/35	7/35
Total	70/414 (16.9%)	72/414 (17.4%)	130/414 (31.4%)
Standard deviation	8.9%	9.0%	13.2%
Range	8%-38%	3%-28%	17%-58%
Overall Historical Incidence			
Total	323/2197 (14.7%)	358/2197 (16.3%)	642/2197 (29.2%)
Standard deviation	7.9%	6.9%	9.0%
Range	4%-44%	3%-30%	15%-58%

[a] Data as of 1 January 1990

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Disposition Summary					
Animals initially in study	99	50	70	70	100
Early deaths					
Natural death	16	3	8	6	11
Moribund sacrifice	5	9	3	8	4
Survivors					
Natural death	2				
Terminal sacrifice	56	18	39	37	65
Paired control		20			
Animals examined microscopically	79	32	50	51	80
Alimentary System					
Gallbladder	(76)	(32)	(48)	(50)	(80)
Cyst		1 (3%)			
Intestine small, duodenum	(79)	(32)	(50)	(50)	(80)
Erosion			1 (2%)		
Intussusception				1 (2%)	
Intestine small, jejunum	(79)	(32)	(50)	(50)	(80)
Lymphoid tissue, hyperplasia			2 (4%)	1 (2%)	
Liver	(79)	(32)	(50)	(51)	(80)
Basophilic focus	9 (11%)	1 (3%)	6 (12%)	2 (4%)	5 (6%)
Clear cell focus	30 (38%)	7 (22%)	20 (40%)	29 (57%)	42 (53%)
Clear cell focus, multiple		1 (3%)			
Cytologic alterations	1 (1%)		1 (2%)		
Eosinophilic focus	7 (9%)	2 (6%)	7 (14%)	11 (22%)	6 (8%)
Fibrosis			1 (2%)		
Hyperplasia	1 (1%)		2 (4%)		
Inflammation, chronic active	2 (3%)	2 (6%)	7 (14%)	1 (2%)	
Mineralization			1 (2%)		1 (1%)
Mixed cell focus				1 (2%)	
Necrosis, coagulative	3 (4%)	3 (9%)	5 (10%)	4 (8%)	3 (4%)
Vacuolization cytoplasmic	16 (20%)	13 (41%)	9 (18%)	8 (16%)	18 (23%)
Bile duct, cyst				1 (2%)	
Bile duct, hyperplasia			1 (2%)		
Mesentery	(8)	(2)	(4)	(7)	(4)
Inflammation, chronic active					1 (25%)
Inflammation, necrotizing	6 (75%)	1 (50%)	3 (75%)	6 (86%)	2 (50%)
Mineralization	1 (13%)		2 (50%)	2 (29%)	1 (25%)
Pancreas	(78)	(32)	(50)	(51)	(80)
Acinus, amyloid deposition				1 (2%)	
Acinus, atrophy	1 (1%)		1 (2%)	1 (2%)	
Acinus, inflammation, chronic active	1 (1%)		1 (2%)		
Acinus, necrosis, coagulative			1 (2%)		
Stomach, forestomach	(79)	(32)	(50)	(51)	(79)
Acanthosis	2 (3%)		1 (2%)	1 (2%)	
Cyst epithelial inclusion				1 (2%)	1 (1%)
Diverticulum		1 (3%)		1 (2%)	2 (3%)
Inflammation, chronic active	1 (1%)		1 (2%)	1 (2%)	
Mineralization		1 (3%)			

Table C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Alimentary System (continued)					
Stomach, glandular	(79)	(32)	(50)	(51)	(80)
Erosion	1 (1%)		1 (2%)	1 (2%)	2 (3%)
Inflammation, chronic active	1 (1%)				
Mineralization	2 (3%)		2 (4%)		4 (5%)
Perivascular, inflammation, chronic active				1 (2%)	
Tooth	(79)	(32)	(50)	(51)	(80)
Dentine, incisor, concretion					1 (1%)
Dentine, incisor, degeneration			1 (2%)		
Dentine, incisor, dysplasia	62 (78%)	17 (53%)	44 (88%)	43 (84%)	73 (91%)
Dentine, incisor, necrosis	2 (3%)				2 (3%)
Gingiva, incisor, inflammation, suppurative			1 (2%)		
Incisor, lower, dysplasia	8 (10%)	6 (19%)	14 (28%)	17 (33%)	14 (18%)
Incisor, ameloblast, atrophy	42 (53%)	15 (47%)	29 (58%)	27 (53%)	50 (63%)
Peridontal tissue, incisor, inflammation, suppurative			1 (2%)		1 (1%)
Pulp, incisor, inflammation, suppurative				1 (2%)	
Cardiovascular System					
Blood vessel	(3)		(1)	(1)	(2)
Inflammation, chronic active			1 (100%)		
Aorta, inflammation, chronic active				1 (100%)	1 (50%)
Mesenteric artery, inflammation, chronic active	1 (33%)			1 (100%)	
Mesenteric artery, necrosis, fibrinoid	1 (33%)				
Renal artery, inflammation, chronic active	1 (33%)				
Thoracic, artery, inflammation, chronic active				1 (100%)	
Heart	(79)	(32)	(50)	(50)	(80)
Cardiomyopathy, chronic	2 (3%)		1 (2%)		1 (1%)
Mineralization		2 (6%)			
Perivascular, inflammation, chronic active				1 (2%)	
Endocrine System					
Adrenal gland	(79)	(32)	(50)	(51)	(80)
Accessory adrenal cortical nodule	2 (3%)		1 (2%)		1 (1%)
Cyst			1 (2%)		
Adrenal gland, cortex	(79)	(32)	(50)	(51)	(80)
Atrophy			1 (2%)		
Cyst	2 (3%)		1 (2%)	1 (2%)	
Hyperplasia	3 (4%)	1 (3%)	1 (2%)	4 (8%)	7 (9%)
Hypertrophy	34 (43%)	7 (22%)	16 (32%)	22 (43%)	32 (40%)
Bilateral, capsule, spindle cell, hyperplasia		1 (3%)		1 (2%)	2 (3%)
Capsule, spindle cell, hyperplasia	11 (14%)	1 (3%)	6 (12%)	8 (16%)	10 (13%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Endocrine System (continued)					
Adrenal gland, medulla	(78)	(32)	(50)	(51)	(80)
Hyperplasia			1 (2%)	1 (2%)	1 (1%)
Islets, pancreatic	(78)	(32)	(50)	(51)	(80)
Hyperplasia	13 (17%)	7 (22%)	7 (14%)	16 (31%)	14 (18%)
Parathyroid gland	(70)	(30)	(45)	(46)	(78)
Cyst	2 (3%)		1 (2%)		
Pituitary gland	(71)	(32)	(49)	(48)	(75)
Pars distalis, cyst	2 (3%)		6 (12%)	5 (10%)	4 (5%)
Pars distalis, hyperplasia	3 (4%)		1 (2%)	2 (4%)	
Pars intermedia, cyst			1 (2%)		
Thyroid gland	(79)	(32)	(50)	(51)	(80)
Cyst	1 (1%)				
Inflammation, chronic active	1 (1%)		1 (2%)	1 2(%)	1 (1%)
Ultimobranchial cyst		1 (3%)		2 (4%)	1 (1%)
Follicle, cyst					1 (1%)
Follicular cell, hyperplasia	6 (8%)	1 (3%)	10 (20%)	6 (12%)	12 (15%)
General Body System					
None					
Genital System					
Epididymis	(79)	(32)	(50)	(51)	(79)
Aspermia	1 (1%)				2 (3%)
Atrophy					2 (3%)
Granuloma sperm	2 (3%)		2 (4%)		4 (5%)
Inflammation, chronic active	2 (3%)	1 (3%)		1 (2%)	1 (1%)
Mineralization			1 (2%)	2 (4%)	
Duct, dilatation	1 (1%)				
Preputial gland	(55)	(12)	(38)	(31)	(53)
Atrophy	48 (87%)	11 (92%)	30 (79%)	27 (87%)	35 (66%)
Inflammation, chronic active	22 (40%)	5 (42%)	18 (47%)	14 (45%)	25 (47%)
Duct, dilatation	49 (89%)	11 (92%)	34 (89%)	30 (97%)	45 (85%)
Prostate	(79)	(32)	(50)	(51)	(79)
Atrophy					2 (3%)
Inflammation, chronic active	3 (4%)	1 (3%)	1 (2%)		1 (1%)
Seminal vesicle	(79)	(32)	(50)	(51)	(80)
Cyst			1 (2%)	1 (2%)	
Inflammation, chronic active	2 (3%)	1 (3%)	2 (4%)	1 (2%)	
Testes	(78)	(31)	(50)	(51)	(79)
Mineralization		1 (3%)		2 (4%)	
Necrosis, coagulative				1 (2%)	
Seminiferous tubule, atrophy					2 (3%)
Seminiferous tubule, degeneration			2 (4%)		3 (4%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Hematopoietic System					
Bone marrow	(79)	(32)	(50)	(51)	(80)
Femoral, myelofibrosis	1 (1%)		1 (2%)	5 (10%)	1 (1%)
Femoral, necrosis, coagulative					1 (1%)
Humerus, myelofibrosis			1 (2%)	2 (4%)	
Maxilla, myelofibrosis	1 (1%)		2 (4%)		
Thoracic, vertebra, myelofibrosis					1 (1%)
Tibia, myelofibrosis				1 (2%)	
Lymph node	(79)	(32)	(50)	(51)	(80)
Inguinal, hyperplasia, plasma cell					1 (1%)
Renal, sinus, ectasia			1 (2%)		
Lymph node, mandibular	(78)	(31)	(50)	(50)	(80)
Hyperplasia, plasma cell				2 (4%)	
Lymph node, mesenteric	(74)	(31)	(49)	(47)	(72)
Hematopoietic cell proliferation				1 (2%)	
Hyperplasia, lymphoid			2 (4%)		
Inflammation, chronic active					1 (1%)
Thrombus			1 (2%)		
Spleen	(79)	(32)	(50)	(51)	(80)
Atrophy				1 (2%)	2 (3%)
Hematopoietic cell proliferation	8 (10%)	3 (9%)	10 (20%)	7 (14%)	9 (11%)
Hyperplasia, lymphoid	1 (1%)				
Thymus	(67)	(28)	(42)	(37)	(66)
Atrophy			2 (5%)		
Cyst	10 (15%)	3 (11%)	8 (19%)	6 (16%)	11 (17%)
Hyperplasia, lymphoid					1 (2%)
Inflammation, chronic active	1 (1%)				
Thymocyte, necrosis					1 (2%)
Integumentary System					
Skin	(79)	(31)	(50)	(51)	(80)
Autolysis	1 (1%)				
Inflammation, chronic active	2 (3%)				1 (1%)
Musculoskeletal System					
Bone	(79)	(32)	(50)	(51)	(80)
Calvarium, hyperostosis					1 (1%)
Calvarium, osteosclerosis, focal				1 (2%)	
Humerus, osteosclerosis			1 (2%)		
Humerus, joint, cartilage, hyperplasia, focal					1 (1%)
Intervertebral disc, degeneration	6 (8%)	2 (6%)	10 (20%)	6 (12%)	8 (10%)
Joint, cartilage, tibia, degeneration					2 (3%)
Rib, cartilage, degeneration				1 (2%)	2 (3%)
Thoracic, vertebra, osteosclerosis	2 (3%)	1 (3%)			3 (4%)
Tibia, fracture healed		1 (3%)			
Tibia, osteosclerosis					1 (1%)
Nervous System					
None					

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Respiratory System					
Lung	(79)	(32)	(50)	(51)	(80)
Infiltration cellular, lymphocytic			1 (2%)		
Infiltration cellular, histiocytic					1 (1%)
Inflammation, chronic active	3 (4%)		2 (4%)	2 (4%)	4 (5%)
Leukocytosis	1 (1%)	1 (3%)			1 (1%)
Mineralization					1 (1%)
Pigmentation, hemosiderin	1 (1%)				
Thrombus					1 (1%)
Alveolar epithelium, hyperplasia	3 (4%)		3 (6%)	3 (6%)	3 (4%)
Bronchus, dilatation			1 (2%)		
Mediastinum, mineralization	1 (1%)				
Nose	(79)	(32)	(50)	(51)	(80)
Inflammation, chronic active	1 (1%)	1 (3%)			2 (3%)
Nasolacrimal duct, hyperplasia, squamous	1 (1%)				
Nasolacrimal duct, inflammation, suppurative	7 (9%)		4 (8%)	2 (4%)	2 (3%)
Special Senses System					
Ear	(1)	(1)		(2)	(1)
Middle ear, inflammation, suppurative				1 (50%)	
Eye	(4)				
Phthisis bulbi	1 (25%)				
Cornea, inflammation, chronic active	2 (50%)				
Lens, cataract	1 (25%)				
Harderian gland	(65)	(27)	(42)	(43)	(59)
Hyperplasia			1 (2%)		
Inflammation, chronic active				2 (5%)	
Urinary System					
Kidney	(79)	(32)	(50)	(51)	(80)
Cyst	17 (22%)	4 (13%)	9 (18%)	13 (25%)	11 (14%)
Hydronephrosis		2 (6%)	1 (2%)		
Inflammation, chronic active	2 (3%)	1 (3%)	2 (4%)		1 (1%)
Inflammation, necrotizing				1 (2%)	
Metaplasia, osseous				1 (2%)	
Mineralization	75 (95%)	28 (88%)	47 (94%)	44 (86%)	73 (91%)
Necrosis, coagulative	1 (1%)				1 (1%)
Nephropathy, chronic	66 (84%)	27 (84%)	46 (92%)	45 (88%)	69 (86%)
Artery, necrosis, fibrinoid	1 (1%)				
Pelvis, bacterium					1 (1%)
Renal tubule, epithelium, hyperplasia				1 (2%)	
Urinary bladder	(78)	(32)	(50)	(50)	(80)
Calculus gross observation			1 (2%)		
Calculus micro observation only				1 (2%)	
Inflammation, chronic active	2 (3%)			1 (2%)	

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDIES OF SODIUM FLUORIDE

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

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Disposition Summary					
Animals initially in study	100	50	70	70	99
Early deaths					
Natural death	13	7	5	7	16
Moribund sacrifice	14	6	9	9	12
Survivors					
Natural death				2	1
Terminal sacrifice	53	8	38	32	51
Paired control		29			
Animals examined microscopically	80	42	52	50	80
Alimentary System					
Gallbladder	(79)	(40)	(51)	(48)	(79)
Histiocytic sarcoma			1 (2%)		1 (1%)
Lymphoma malignant mixed					1 (1%)
Intestine large, cecum	(80)	(42)	(52)	(49)	(78)
Lymphoma malignant mixed				1 (2%)	
Intestine large, rectum	(79)	(42)	(52)	(49)	(79)
Histiocytic sarcoma				1 (2%)	
Intestine small, duodenum	(80)	(42)	(52)	(48)	(79)
Fibrosarcoma, metastatic, skin	1 (1%)				
Histiocytic sarcoma				1 (2%)	
Lymphoma malignant mixed				1 (2%)	
Intestine small, ileum	(78)	(42)	(52)	(49)	(78)
Fibrosarcoma, metastatic, skin		1 (2%)			
Histiocytic sarcoma				1 (2%)	
Intestine small, jejunum	(80)	(42)	(52)	(49)	(78)
Hemangiosarcoma				1 (2%)	
Histiocytic sarcoma				1 (2%)	
Lymphoma malignant mixed				1 (2%)	
Lymphoid tissue, lymphoma malignant lymphocytic					1 (1%)
Lymphoid tissue, lymphoma malignant mixed				1 (2%)	
Lymphoid tissue, lymphoma malignant undifferentiated cell type	1 (1%)				
Liver	(80)	(42)	(52)	(50)	(80)
Hemangioma	1 (1%)		1 (2%)		1 (1%)
Hemangiosarcoma	2 (3%)	1 (2%)			1 (1%)
Hepatoblastoma			1 (2%)		2 (3%)
Hepatocellular carcinoma	13 (16%)	3 (7%)	9 (17%)	7 (14%)	11 (14%)
Hepatocellular carcinoma, multiple	1 (1%)		2 (4%)	1 (2%)	1 (1%)
Hepatocellular adenoma	22 (28%)	4 (10%)	9 (17%)	10 (20%)	17 (21%)
Hepatocellular adenoma, multiple	27 (34%)	5 (12%)	19 (37%)	13 (26%)	17 (21%)
Hepatocholangiocarcinoma		1 (2%)			1 (1%)
Histiocytic sarcoma	4 (5%)		1 (2%)	2 (4%)	5 (6%)
Lymphoma malignant lymphocytic	1 (1%)			1 (2%)	3 (4%)
Lymphoma malignant mixed	3 (4%)		4 (8%)	4 (8%)	4 (5%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Alimentary System (continued)					
Lymphoma malignant undifferentiated cell type	5 (6%)	1 (2%)		2 (4%)	4 (5%)
Osteosarcoma, metastatic, bone	1 (1%)				
Osteosarcoma, metastatic, uncertain primary site			1 (2%)		
Mesentery	(28)	(6)	(15)	(15)	(28)
Fibrosarcoma, metastatic, skin	1 (4%)	1 (17%)	1 (7%)		
Hemangioma			1 (7%)		
Hepatocholangiocarcinoma, metastatic, liver					1 (4%)
Histiocytic sarcoma	2 (7%)		2 (13%)	1 (7%)	3 (11%)
Lipoma					1 (4%)
Lymphoma malignant lymphocytic					3 (11%)
Lymphoma malignant mixed	1 (4%)		1 (7%)	2 (13%)	3 (11%)
Lymphoma malignant undifferentiated cell type	2 (7%)	1 (17%)		2 (13%)	1 (4%)
Sarcoma, metastatic, uncertain primary site					1 (4%)
Pancreas	(80)	(42)	(52)	(49)	(79)
Fibrosarcoma, metastatic, skin	1 (1%)	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver					2 (3%)
Histiocytic sarcoma	2 (3%)		2 (4%)	1 (2%)	1 (1%)
Lymphoma malignant lymphocytic					1 (1%)
Lymphoma malignant mixed	1 (1%)		1 (2%)	3 (6%)	2 (3%)
Lymphoma malignant undifferentiated cell type	1 (1%)	1 (2%)		2 (4%)	1 (1%)
Acinus, adenocarcinoma	1 (1%)				
Salivary glands	(79)	(41)	(52)	(50)	(80)
Histiocytic sarcoma					1 (1%)
Lymphoma malignant lymphocytic					1 (1%)
Lymphoma malignant mixed	1 (1%)			1 (2%)	1 (1%)
Lymphoma malignant undifferentiated cell type	3 (4%)				
Stomach, forestomach	(80)	(42)	(52)	(49)	(79)
Lymphoma malignant undifferentiated cell type	1 (1%)			1 (2%)	
Mast cell tumor malignant				1 (2%)	
Papilloma squamous	3 (4%)		4 (8%)	2 (4%)	3 (4%)
Papilloma squamous, multiple					1 (1%)
Stomach, glandular	(80)	(42)	(52)	(49)	(79)
Histiocytic sarcoma				1 (2%)	
Lymphoma malignant lymphocytic					1 (1%)
Lymphoma malignant mixed				1 (2%)	

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Cardiovascular System					
Heart	(79)	(41)	(52)	(50)	(80)
Hemangiosarcoma			1 (2%)		
Hemangiosarcoma, metastatic, liver					1 (1%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)			1 (1%)
Histiocytic sarcoma	2 (3%)			1 (2%)	2 (3%)
Lymphoma malignant lymphocytic				1 (2%)	
Lymphoma malignant mixed				1 (2%)	1 (1%)
Lymphoma malignant undifferentiated cell type	1 (1%)			1 (2%)	
Pericardium, hepatocholangiocarcinoma, metastatic, liver					1 (1%)
Endocrine System					
Adrenal gland, cortex	(79)	(42)	(52)	(50)	(80)
Histiocytic sarcoma			1 (2%)	2 (4%)	1 (1%)
Lymphoma malignant lymphocytic				1 (2%)	2 (3%)
Lymphoma malignant mixed				1 (2%)	1 (1%)
Lymphoma malignant undifferentiated cell type		1 (2%)			
Sarcoma, metastatic, uncertain primary site					1 (1%)
Adrenal gland, medulla	(78)	(42)	(52)	(50)	(80)
Lymphoma malignant lymphocytic					1 (1%)
Lymphoma malignant undifferentiated cell type		1 (2%)			
Pheochromocytoma benign			1 (2%)	1 (2%)	1 (1%)
Bilateral, pheochromocytoma benign			1 (2%)		
Islets, pancreatic	(79)	(41)	(52)	(49)	(80)
Adenoma	1 (1%)		1 (2%)	1 (2%)	1 (1%)
Fibrosarcoma, metastatic, skin		1 (2%)			
Histiocytic sarcoma				1 (2%)	
Pituitary gland	(80)	(41)	(51)	(50)	(79)
Histiocytic sarcoma					2 (3%)
Pars distalis, adenoma	22 (28%)	3 (7%)	6 (12%)	8 (16%)	13 (16%)
Pars distalis, adenoma, multiple	3 (4%)		1 (2%)		
Thyroid gland	(80)	(42)	(52)	(50)	(80)
Lymphoma malignant lymphocytic					1 (1%)
C-cell, carcinoma				1 (2%)	
Follicular cell, adenoma	3 (4%)	2 (5%)			2 (3%)
Follicular cell, adenoma, multiple	1 (1%)				
General Body System					
None					

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Genital System					
Ovary	(78)	(41)	(50)	(50)	(80)
Cystadenoma, papillary	3 (4%)		1 (2%)		1 (1%)
Fibrosarcoma, metastatic, skin	1 (1%)	1 (2%)			
Granulosa cell tumor benign	1 (1%)				
Hemangiosarcoma			1 (2%)		
Histiocytic sarcoma	2 (3%)		1 (2%)	1 (2%)	3 (4%)
Luteoma	1 (1%)				
Lymphoma malignant lymphocytic					2 (3%)
Lymphoma malignant mixed				1 (2%)	1 (1%)
Lymphoma malignant undifferentiated cell type	1 (1%)	1 (2%)			
Sarcoma, metastatic, uncertain primary site					1 (1%)
Uterus	(80)	(42)	(52)	(50)	(80)
Hemangioma	2 (3%)				
Hemangiosarcoma		1 (2%)		1 (2%)	
Histiocytic sarcoma	4 (5%)		1 (2%)	1 (2%)	4 (5%)
Lymphoma malignant lymphocytic				1 (2%)	1 (1%)
Lymphoma malignant mixed					1 (1%)
Lymphoma malignant undifferentiated cell type	1 (1%)	1 (2%)			
Polyp stromal	2 (3%)		1 (2%)	1 (2%)	1 (1%)
Sarcoma stromal					1 (1%)
Hematopoietic System					
Blood	(2)	(1)			
Histiocytic sarcoma	1 (50%)				
Bone marrow	(80)	(42)	(52)	(50)	(80)
Femoral, hemangiosarcoma	1 (1%)		1 (2%)	1 (2%)	
Femoral, histiocytic sarcoma	2 (3%)			1 (2%)	2 (3%)
Femoral, lymphoma malignant lymphocytic				1 (2%)	
Femoral, lymphoma malignant mixed				1 (2%)	
Femoral, lymphoma malignant undifferentiated cell type	1 (1%)			2 (4%)	
Humerus, hemangiosarcoma				1 (2%)	
Humerus, histiocytic sarcoma	1 (1%)				
Maxilla, histiocytic sarcoma					1 (1%)
Thoracic, vertebra, histiocytic sarcoma					1 (1%)
Tibia, histiocytic sarcoma	2 (3%)				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Hematopoietic System (continued)					
Lymph node	(80)	(42)	(52)	(50)	(80)
Axillary, lymphoma malignant lymphocytic				1 (2%)	
Axillary, lymphoma malignant undifferentiated cell type				1 (2%)	
Deep cervical, lymphoma malignant lymphocytic					1 (1%)
Deep cervical, lymphoma malignant mixed					1 (1%)
Inguinal, histiocytic sarcoma					1 (1%)
Inguinal, lymphoma malignant mixed				1 (2%)	1 (1%)
Inguinal, lymphoma malignant undifferentiated cell type				2 (4%)	
Lumbar, fibrosarcoma, metastatic, skin		1 (2%)			
Lumbar, histiocytic sarcoma	1 (1%)				
Mediastinal, hepatocholangiocarcinoma, metastatic, liver		1 (2%)			1 (1%)
Mediastinal, histiocytic sarcoma	1 (1%)		2 (4%)	1 (2%)	2 (3%)
Mediastinal, lymphoma malignant lymphocytic				1 (2%)	3 (4%)
Mediastinal, lymphoma malignant mixed	3 (4%)		2 (4%)	3 (6%)	3 (4%)
Mediastinal, lymphoma malignant undifferentiated cell type	4 (5%)			2 (4%)	4 (5%)
Pancreatic, lymphoma malignant lymphocytic					1 (1%)
Pancreatic, lymphoma malignant mixed			1 (2%)	1 (2%)	1 (1%)
Pancreatic, lymphoma malignant undifferentiated cell type	1 (1%)				1 (1%)
Popliteal, lymphoma malignant mixed				1 (2%)	
Renal, fibrosarcoma, metastatic, skin		1 (2%)			
Renal, histiocytic sarcoma	1 (1%)				
Renal, lymphoma malignant mixed	1 (1%)		2 (4%)	1 (2%)	2 (3%)
Renal, lymphoma malignant undifferentiated cell type	2 (3%)			1 (2%)	1 (1%)
Lymph node, mandibular	(76)	(42)	(52)	(47)	(79)
Hemangioma	1 (1%)				
Histiocytic sarcoma	3 (4%)			1 (2%)	3 (4%)
Lymphoma malignant lymphocytic	1 (1%)			1 (2%)	3 (4%)
Lymphoma malignant mixed	1 (1%)		2 (4%)	4 (9%)	4 (5%)
Lymphoma malignant undifferentiated cell type	3 (4%)	1 (2%)		1 (2%)	1 (1%)
Lymph node, mesenteric	(79)	(40)	(49)	(49)	(77)
Fibrosarcoma, metastatic, skin		1 (3%)			
Hemangioma					1 (1%)
Histiocytic sarcoma	2 (3%)		1 (2%)	1 (2%)	3 (4%)
Lymphoma malignant lymphocytic	2 (3%)			1 (2%)	5 (6%)
Lymphoma malignant mixed	2 (3%)		2 (4%)	6 (12%)	7 (9%)
Lymphoma malignant undifferentiated cell type	5 (6%)	1 (3%)		2 (4%)	5 (6%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Hematopoietic System (continued)					
Spleen	(79)	(42)	(52)	(50)	(80)
Histiocytic sarcoma	1 (1%)		2 (4%)	1 (2%)	2 (3%)
Lymphoma malignant lymphocytic	1 (1%)			1 (2%)	4 (5%)
Lymphoma malignant mixed	3 (4%)		4 (8%)	7 (14%)	6 (8%)
Lymphoma malignant undifferentiated cell type	5 (6%)	1 (2%)		3 (6%)	6 (8%)
Thymus	(76)	(42)	(48)	(45)	(73)
Histiocytic sarcoma	1 (1%)		1 (2%)		2 (3%)
Lymphoma malignant lymphocytic					2 (3%)
Lymphoma malignant mixed	2 (3%)		3 (6%)	6 (13%)	3 (4%)
Lymphoma malignant undifferentiated cell type	4 (5%)	1 (2%)		3 (7%)	2 (3%)
Integumentary System					
Mammary gland	(78)	(41)	(51)	(50)	(80)
Adenocarcinoma	1 (1%)		1 (2%)		
Adenoma					1 (1%)
Histiocytic sarcoma				1 (2%)	
Skin	(80)	(42)	(52)	(50)	(80)
Histiocytic sarcoma				1 (2%)	
Lymphoma malignant lymphocytic					1 (1%)
Lymphoma malignant undifferentiated cell type		1 (2%)			
Subcutaneous tissue, fibrosarcoma	2 (3%)	2 (5%)	2 (4%)		5 (6%)
Subcutaneous tissue, hemangiosarcoma		1 (2%)			
Subcutaneous tissue, mast cell tumor malignant			1 (2%)		
Subcutaneous tissue, neurofibrosarcoma					1 (1%)
Musculoskeletal System					
Bone	(80)	(42)	(52)	(50)	(80)
Femur, osteosarcoma	1 (1%)				
Femur, synovial tissue, sarcoma	1 (1%)				
Humerus, hemangiosarcoma	1 (1%)				
Maxilla, adenocarcinoma, metastatic, harderian gland	1 (1%)				
Rib, osteoma	1 (1%)				
Skeletal muscle	(2)	(1)		(1)	(1)
Fibrosarcoma, metastatic, skin					1 (100%)
Histiocytic sarcoma	1 (50%)			1 (100%)	
Osteosarcoma, metastatic, bone	1 (50%)				
Nervous System					
Brain	(80)	(42)	(52)	(50)	(80)
Histiocytic sarcoma					1 (1%)
Lymphoma malignant mixed				1 (2%)	2 (3%)

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Respiratory System					
Lung	(80)	(42)	(52)	(50)	(80)
Adenocarcinoma, metastatic, harderian gland	1 (1%)		1 (2%)		
Alveolar/bronchiolar adenoma	5 (6%)	2 (5%)	3 (6%)	2 (4%)	4 (5%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)		
Alveolar/bronchiolar carcinoma	3 (4%)		2 (4%)	2 (4%)	3 (4%)
Fibrosarcoma, metastatic, skin					1 (1%)
Hepatoblastoma, metastatic, liver					1 (1%)
Hepatocellular carcinoma, metastatic, liver	1 (1%)		1 (2%)	1 (2%)	2 (3%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)			1 (1%)
Histiocytic sarcoma	3 (4%)		1 (2%)	2 (4%)	3 (4%)
Lymphoma malignant lymphocytic				1 (2%)	3 (4%)
Lymphoma malignant mixed	1 (1%)		2 (4%)	2 (4%)	4 (5%)
Lymphoma malignant undifferentiated cell type	1 (1%)	1 (2%)		1 (2%)	
Osteosarcoma, metastatic, bone	1 (1%)				
Osteosarcoma, metastatic, uncertain primary site			1 (2%)		
Mediastinum, fibrosarcoma, metastatic, skin	1 (1%)				
Mediastinum, hepatocellular carcinoma, metastatic, liver					1 (1%)
Mediastinum, lymphoma malignant undifferentiated cell type					1 (1%)
Nose	(80)	(42)	(52)	(50)	(80)
Adenocarcinoma, metastatic, harderian gland	1 (1%)				
Histiocytic sarcoma				1 (2%)	
Lymphoma malignant mixed				1 (2%)	
Special Senses System					
Ear			(1)	(1)	(1)
Fibrosarcoma			1 (100%)		
Papilloma squamous				1 (100%)	
Harderian gland	(49)	(36)	(42)	(37)	(34)
Adenocarcinoma	1 (2%)		1 (2%)		
Adenoma	4 (8%)	1 (3%)	2 (5%)	6 (16%)	2 (6%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Urinary System					
Kidney	(80)	(42)	(52)	(50)	(80)
Fibrosarcoma, metastatic, skin	1 (1%)				
Histiocytic sarcoma	3 (4%)		2 (4%)	1 (2%)	4 (5%)
Lymphoma malignant lymphocytic	1 (1%)			1 (2%)	3 (4%)
Lymphoma malignant mixed	1 (1%)		2 (4%)	4 (8%)	4 (5%)
Lymphoma malignant undifferentiated cell type	2 (3%)	1 (2%)		2 (4%)	
Urinary bladder	(80)	(42)	(52)	(50)	(78)
Histiocytic sarcoma	3 (4%)			1 (2%)	1 (1%)
Lymphoma malignant lymphocytic					2 (3%)
Lymphoma malignant mixed	1 (1%)		2 (4%)	4 (8%)	3 (4%)
Lymphoma malignant undifferentiated cell type	1 (1%)			1 (2%)	
Systemic Lesions					
Multiple organs[a]	(80)	(42)	(52)	(50)	(80)
Histiocytic sarcoma	5 (6%)		3 (6%)	2 (4%)	5 (6%)
Lymphoma malignant lymphocytic	2 (3%)			1 (2%)	5 (6%)
Lymphoma malignant mixed	4 (5%)		5 (10%)	7 (14%)	8 (10%)
Lymphoma malignant undifferentiated cell	5 (6%)	1 (2%)		3 (6%)	6 (8%)
Tumor Summary					
Total animals with primary neoplasms[b]	72	17	41	37	61
Total primary neoplasms	147	27	83	74	117
Total animals with benign neoplasms	65	12	34	29	45
Total benign neoplasms	103	17	52	45	67
Total animals with malignant neoplasms	34	9	25	25	43
Total malignant neoplasms	44	10	31	29	50
Total animals with secondary neoplasms[c]	5	2	4	1	8
Total secondary neoplasms	13	11	5	1	17
Total animals with malignant neoplasms			1		1

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control

Number of Days on Study	358	420	489	518	528	562	592	592	602	610	620	632	637	644	652	657	662	670	676	691	704	713	715	715	722
Carcass ID Number	4791	4661	4421	4251	4401	4571	4281	4691	4431	4501	4891	4261	4191	4201	4391	3961	4751	4061	4341	4591	4631	4881	4611	4641	3951
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																		X							
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma								X																	
Hemangiosarcoma				X																					
Hepatocellular carcinoma									X	X								X							X
Hepatocellular carcinoma, multiple																							X		
Hepatocellular adenoma	X			X										X											
Hepatocellular adenoma, multiple							X											X						X	
Histiocytic sarcoma						X			X												X				
Osteosarcoma, metastatic, bone		X																							
Mesentery	+	+			+	+					+			+	+			+			+			+	
Fibrosarcoma, metastatic, skin																		X							
Histiocytic sarcoma						X															X				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																		X							
Histiocytic sarcoma																					X				
Acinus, adenocarcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous														X											
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X															X				
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	722	722	729	729	729	729	729	729	729	729	729	729	730	730	730	731	731	731	731	731	731	731	731	732	732
Carcass ID Number	4171	4481	4051	4131	4181	4321	4381	4451	4491	4521	4601	4741	3911	3931	3941	3981	3991	4001	4011	4021	4071	4101	4111	4121	4141
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Intestine small, ileum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma						X																			
Hepatocellular carcinoma				X				X					X										X		
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma		X		X	X	X	X	X	X												X	X			X
Hepatocellular adenoma, multiple	X		X							X	X	X	X	X	X	X	X	X					X		
Histiocytic sarcoma																		X							
Osteosarcoma, metastatic, bone																									
Mesentery	+			+	+	+	+								+						+		+	+	
Fibrosarcoma, metastatic, skin																									
Histiocytic sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Histiocytic sarcoma																		X							
Acinus, adenocarcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																								X	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	3	3	3	3	3	3	3	3	6	6	6	6	6	6	6	6	7	7	7
	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	2	2	2	2	3	3	3	3	4	4	4	5	5	5	5	5	6	6	6	6	7	7	7	7	8
Carcass ID Number	2	3	7	9	0	1	3	6	1	4	7	1	3	5	6	8	2	5	7	8	2	3	7	8	0
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																									
Hepatocellular carcinoma										X			X			X							X		
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma		X		X					X								X	X	X						X
Hepatocellular adenoma, multiple	X				X	X	X	X		X			X		X					X				X	
Histiocytic sarcoma																									
Osteosarcoma, metastatic, bone																									
Mesentery			+				+			+						+	+			+					
Fibrosarcoma, metastatic, skin																									
Histiocytic sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Histiocytic sarcoma																									
Acinus, adenocarcinoma														X											
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																						+			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	
	7	7	7	7	7	
	4	4	4	4	4	
	8	8	8	8	9	**Total**
Carcass ID Number	1	2	4	5	0	**Tissues/**
	1	1	1	1	1	**Tumors**
Alimentary System						
Esophagus	+	+	+	+	+	79
Gallbladder	+	+	+	+	+	79
Intestine large	+	+	+	+	+	80
Intestine large, cecum	+	+	+	+	+	80
Intestine large, colon	+	+	+	+	+	80
Intestine large, rectum	+	+	+	+	+	79
Intestine small	+	+	+	+	+	80
Intestine small, duodenum	+	+	+	+	+	80
Fibrosarcoma, metastatic, skin						1
Intestine small, ileum	+	+	+	+	+	78
Intestine small, jejunum	+	+	+	+	+	80
Liver	+	+	+	+	+	80
Hemangioma						1
Hemangiosarcoma						2
Hepatocellular carcinoma					X	13
Hepatocellular carcinoma, multiple						1
Hepatocellular adenoma	X		X			22
Hepatocellular adenoma, multiple				X	X	27
Histiocytic sarcoma						4
Osteosarcoma, metastatic, bone						1
Mesentery	+		+	+		28
Fibrosarcoma, metastatic, skin						1
Histiocytic sarcoma						2
Pancreas	+	+	+	+	+	80
Fibrosarcoma, metastatic, skin						1
Histiocytic sarcoma						2
Acinus, adenocarcinoma						1
Salivary glands	+	+	+	+	+	79
Stomach	+	+	+	+	+	80
Stomach, forestomach	+	+	+	+	+	80
Papilloma squamous	X					3
Stomach, glandular	+	+	+	+	+	80
Tooth	+	+	+	+	+	80
Cardiovascular System						
Blood vessel						1
Heart	+	+	+	+	+	79
Histiocytic sarcoma						2
Endocrine System						
Adrenal gland	+	+	+	+	+	79
Adrenal gland, cortex	+	+	+	+	+	79

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	358	420	489	518	528	562	592	592	602	610	620	632	637	644	652	657	672	670	676	691	704	713	715	715	722
Carcass ID Number	4791	4661	4421	4251	4401	4571	4281	4691	4431	4501	4891	4261	4191	4201	4391	3961	4751	4061	4341	4591	4631	4881	4611	4641	3951
Endocrine System (continued)																									
Adrenal gland, medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X		X							X	X	X		X	X						
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																		X							
Follicular cell, adenoma, multiple														X											
General Body System																									
None																									
Genital System																									
Clitoral gland																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary																									
Fibrosarcoma, metastatic, skin																		X							
Granulosa cell tumor benign																									
Histiocytic sarcoma						X																			
Luteoma																				X					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Histiocytic sarcoma						X			X												X				
Polyp stromal																									
Hematopoietic System																									
Blood														+							+				
Histiocytic sarcoma																					X				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma																									
Femoral, histiocytic sarcoma									X																
Humerus, histiocytic sarcoma																									
Tibia, histiocytic sarcoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	9	9	9	9	9	9	9	9	9	9	0	0	0	1	1	1	1	1	1	1	1	2	2
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	3	3	3	3	3	4	4	4	4	4	4	4	4
	1	4	0	1	1	3	3	4	4	5	6	7	9	9	9	9	9	0	0	0	0	1	1	1	1
	7	8	5	3	8	2	8	5	9	2	0	4	1	3	4	8	9	0	1	2	7	0	1	2	4
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Endocrine System (continued)																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X				X			X			X		X				X	
Pars distalis, adenoma, multiple							X			X															
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
Follicular cell, adenoma, multiple																									
General Body System																									
None																									
Genital System																									
Clitoral gland																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary												X													
Fibrosarcoma, metastatic, skin																									
Granulosa cell tumor benign																									
Histiocytic sarcoma																		X							
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma		X												X											
Histiocytic sarcoma																		X							
Polyp stromal																									
Hematopoietic System																									
Blood																									
Histiocytic sarcoma																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma																		X							
Femoral, histiocytic sarcoma																		X							
Humerus, histiocytic sarcoma																									
Tibia, histiocytic sarcoma																		X							

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	732	732	732	732	732	732	733	733	733	733	733	733	733	733	736	736	736	736	736	736	736	736	737	737	737
Carcass ID Number	4221	4231	4271	4291	4301	4311	4331	4361	4411	4441	4471	4511	4531	4551	4561	4581	4621	4651	4671	4681	4721	4731	4771	4781	4801
Endocrine System (continued)																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X		X							X	X		X					X			
Pars distalis, adenoma, multiple																									X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																				X		X			
Follicular cell, adenoma, multiple																									
General Body System																									
None																									
Genital System																									
Clitoral gland						+																			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary				X									X												
Fibrosarcoma, metastatic, skin																									
Granulosa cell tumor benign					X																				
Histiocytic sarcoma																									
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Histiocytic sarcoma																									
Polyp stromal													X												
Hematopoietic System																									
Blood																									
Histiocytic sarcoma																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma																									
Femoral, histiocytic sarcoma																									
Humerus, histiocytic sarcoma																			X						
Tibia, histiocytic sarcoma																			X						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 8 1 1	4 8 2 1	4 8 4 1	4 8 5 1	4 9 0 1	**Total Tissues/ Tumors**
Endocrine System (continued)						
Adrenal gland, medulla	+	+	+	+	+	78
Islets, pancreatic	+	+	+	+	+	79
Adenoma						1
Parathyroid gland	M	+	+	+	+	73
Pituitary gland	+	+	+	+	+	80
Pars distalis, adenoma			X	X	X	22
Pars distalis, adenoma, multiple						3
Thyroid gland	+	+	+	+	+	80
Follicular cell, adenoma						3
Follicular cell, adenoma, multiple						1
General Body System						
None						
Genital System						
Clitoral gland				+		2
Ovary	+	+	+	+	+	78
Cystadenoma, papillary						3
Fibrosarcoma, metastatic, skin						1
Granulosa cell tumor benign						1
Histiocytic sarcoma						2
Luteoma						1
Uterus	+	+	+	+	+	80
Hemangioma						2
Histiocytic sarcoma						4
Polyp stromal		X				2
Hematopoietic System						
Blood						2
Histiocytic sarcoma						1
Bone marrow	+	+	+	+	+	80
Femoral, hemangiosarcoma						1
Femoral, histiocytic sarcoma						2
Humerus, histiocytic sarcoma						1
Tibia, histiocytic sarcoma						2

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	358	420	499	518	528	562	592	592	602	610	620	632	637	644	652	657	672	670	676	691	704	713	715	715	722
Carcass ID Number	4791	4661	4421	4251	4401	4571	4281	4691	4431	4501	4891	4261	4191	4201	4391	3961	4751	4061	4341	4591	4631	4881	4611	4641	3951
Hematopoietic System (continued)																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, histiocytic sarcoma																					X				
Mediastinal, histiocytic sarcoma																					X				
Renal, histiocytic sarcoma																					X				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Histiocytic sarcoma																					X				
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Integumentary System																									
Mammary gland	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma							X																		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma		X																							
Femur, synovial tissue, sarcoma																									
Humerus, hemangiosarcoma																									
Maxilla, adenocarcinoma, metastatic, harderian gland																									
Rib, osteoma																									
Skeletal muscle		+																			+				
Histiocytic sarcoma																					X				
Osteosarcoma, metastatic, bone		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve													+												
Spinal cord													+												

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	9	9	9	9	9	9	9	9	9	9	0	0	0	1	1	1	1	1	1	1	1	2	2
	4	4	4	4	4	4	4	4	4	4	4	4	3	3	3	3	3	4	4	4	4	4	4	4	4
	1	4	0	1	1	3	3	4	4	5	6	7	9	9	9	9	9	0	0	0	0	1	1	1	1
Carcass ID Number	7	8	5	3	8	2	8	5	9	2	0	4	1	3	4	8	9	0	1	2	7	0	1	2	4
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hematopoietic System (continued)																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, histiocytic sarcoma																									
Mediastinal, histiocytic sarcoma																									
Renal, histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Hemangioma																									
Histiocytic sarcoma																		X							
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma																									
Femur, synovial tissue, sarcoma																	X								
Humerus, hemangiosarcoma																		X							
Maxilla, adenocarcinoma, metastatic, harderian gland																						X			
Rib, osteoma					X																				
Skeletal muscle																									
Histiocytic sarcoma																									
Osteosarcoma, metastatic, bone																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	3	3	3	3	3	3	3	3	6	6	6	6	6	6	6	6	7	7	7
	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	2	2	2	2	3	3	3	3	4	4	4	5	5	5	5	5	6	6	6	6	7	7	7	7	8
Carcass ID Number	2	3	7	9	0	1	3	6	1	4	7	1	3	5	6	8	2	5	7	8	2	3	7	8	0
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hematopoietic System (continued)																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, histiocytic sarcoma																									
Mediastinal, histiocytic sarcoma																									
Renal, histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma			X																						
Histiocytic sarcoma																			X						
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Histiocytic sarcoma																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma																									
Femur, synovial tissue, sarcoma																									
Humerus, hemangiosarcoma																									
Maxilla, adenocarcinoma, metastatic, harderian gland																									
Rib, osteoma																									
Skeletal muscle																									
Histiocytic sarcoma																									
Osteosarcoma, metastatic, bone																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 8 1 1	4 8 2 1	4 8 4 1	4 8 5 1	4 9 0 1	**Total Tissues/ Tumors**
Hematopoietic System (continued)						
Lymph node	+	+	+	+	+	80
Lumbar, histiocytic sarcoma						1
Mediastinal, histiocytic sarcoma						1
Renal, histiocytic sarcoma						1
Lymph node, mandibular	M	+	+	+	+	76
Hemangioma						1
Histiocytic sarcoma						3
Lymph node, mesenteric	+	+	+	+	+	79
Histiocytic sarcoma						2
Spleen	+	+	+	+	+	79
Histiocytic sarcoma						1
Thymus	+	+	+	+	+	76
Histiocytic sarcoma						1
Integumentary System						
Mammary gland	+	+	+	+	+	78
Adenocarcinoma						1
Skin	+	+	+	+	+	80
Subcutaneous tissue, fibrosarcoma						2
Musculoskeletal System						
Bone	+	+	+	+	+	80
Femur, osteosarcoma						1
Femur, synovial tissue, sarcoma						1
Humerus, hemangiosarcoma						1
Maxilla, adenocarcinoma, metastatic, harderian gland						1
Rib, osteoma						1
Skeletal muscle						2
Histiocytic sarcoma						1
Osteosarcoma, metastatic, bone						1
Nervous System						
Brain	+	+	+	+	+	80
Peripheral nerve						1
Spinal cord						1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	3 5 8	4 2 0	4 8 9	5 1 8	5 2 8	5 6 2	5 9 2	5 9 2	6 0 2	6 1 0	6 2 0	6 3 2	6 3 7	6 4 4	6 5 2	6 5 7	6 7 2	6 7 0	6 7 6	6 9 1	7 0 4	7 1 3	7 1 5	7 1 5	7 2 2
Carcass ID Number	4 7 9 1	4 6 6 1	4 4 2 1	4 2 5 1	4 4 0 1	4 5 7 1	4 2 8 1	4 6 9 1	4 4 3 1	4 5 0 1	4 8 9 1	4 2 6 1	4 1 9 1	4 2 0 1	4 3 9 1	3 9 6 1	4 7 5 1	4 0 6 1	4 3 4 1	4 5 9 1	4 6 3 1	4 8 8 1	4 6 1 1	4 6 4 1	3 9 5 1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																									
Alveolar/bronchiolar adenoma							X																		X
Alveolar/bronchiolar carcinoma																				X			X		
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma									X												X				
Osteosarcoma, metastatic, bone		X																							
Mediastinum, fibrosarcoma, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear	I																								
Eye																									
Harderian gland	+	+	M	+	+	+	+	+	+	M	+	+	+	M	M	M	+	+	+	M	+	+	M	+	+
Adenocarcinoma																									
Adenoma		X											X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																		X							
Histiocytic sarcoma									X												X				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X															X				
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X			X												X				
Lymphoma malignant lymphocytic																							X	X	
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type															X										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	722	722	729	729	729	729	729	729	729	729	729	729	730	730	730	731	731	731	731	731	731	731	731	732	732
Carcass ID Number	4171	4481	4051	4131	4181	4321	4381	4451	4491	4521	4601	4741	3911	3931	3941	3981	3991	4001	4011	4021	4071	4101	4111	4121	4141
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																						X			
Alveolar/bronchiolar adenoma																		X							
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver													X												
Histiocytic sarcoma																		X							
Osteosarcoma, metastatic, bone																									
Mediastinum, fibrosarcoma, metastatic, skin																									X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																						X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																						+			
Harderian gland	+	M	M	M	M	M	+	M	+	+	+	+	I	M	M	M	M	M	+	+	M	+	+	+	+
Adenocarcinoma																						X			
Adenoma												X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Histiocytic sarcoma																		X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed				X									X				X								
Lymphoma malignant undifferentiated cell type					X																				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	3	3	3	3	3	3	3	3	6	6	6	6	6	6	6	6	7	7	7
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	2	2	2	2	3	3	3	3	4	4	4	5	5	5	5	5	6	6	6	6	7	7	7	7	8
	2	3	7	9	0	1	3	6	1	4	7	1	3	5	6	8	2	5	7	8	2	3	7	8	0
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																									
Alveolar/bronchiolar adenoma															X						X				
Alveolar/bronchiolar carcinoma			X																						
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Osteosarcoma, metastatic, bone																									
Mediastinum, fibrosarcoma, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																									
Harderian gland	M	+	+	+	+	+	+	M	+	+	M	+	+	+	M	M	+	+	+	+	I	+	+	M	M
Adenocarcinoma																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Histiocytic sarcoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed										X															
Lymphoma malignant undifferentiated cell type					X												X							X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Control (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	4 8 1 1	4 8 2 1	4 8 4 1	4 8 5 1	4 9 0 1	**Total Tissues/ Tumors**
Respiratory System						
Lung	+	+	+	+	+	80
Adenocarcinoma, metastatic, harderian gland						1
Alveolar/bronchiolar adenoma						5
Alveolar/bronchiolar carcinoma						3
Hepatocellular carcinoma, metastatic, liver						1
Histiocytic sarcoma						3
Osteosarcoma, metastatic, bone						1
Mediastinum, fibrosarcoma, metastatic, skin						1
Nose	+	+	+	+	+	80
Adenocarcinoma, metastatic, harderian gland						1
Trachea	+	+	+	+	+	80
Special Senses System						
Ear						
Eye						1
Harderian gland	M	+	M	+	M	49
Adenocarcinoma						1
Adenoma		X				4
Urinary System						
Kidney	+	+	+	+	+	80
Fibrosarcoma, metastatic, skin						1
Histiocytic sarcoma						3
Urinary bladder	+	+	+	+	+	80
Histiocytic sarcoma						3
Systemic Lesions						
Multiple organs	+	+	+	+	+	80
Histiocytic sarcoma						5
Lymphoma malignant lymphocytic						2
Lymphoma malignant mixed						4
Lymphoma malignant undifferentiated cell type						5

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control

	1	1	1	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4	4	4	5	5	5	5	5
Number of Days on Study	3	7	9	4	5	7	8	1	4	4	6	7	9	1	2	3	3	5	7	7	0	2	3	5	6
	5	9	8	1	9	8	6	3	9	9	1	9	5	1	0	3	7	6	7	8	0	7	4	2	6
	5	4	5	5	5	5	5	5	4	5	5	5	5	5	5	5	5	4	5	5	5	5	5	5	5
	2	9	1	1	0	3	2	0	9	1	3	0	0	1	2	0	3	9	1	4	0	3	2	0	1
Carcass ID Number	0	1	2	5	5	4	6	4	4	9	1	6	9	6	7	1	3	2	7	0	0	9	8	8	0
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma																									
Hepatocellular adenoma																				X					
Hepatocellular adenoma, multiple																								X	X
Hepatocholangiocarcinoma																									
Mesentery										+											+				
Fibrosarcoma, metastatic, skin																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma															X										
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

Number of Days on Study	5 6 8	5 7 1	5 7 9	5 8 7	6 0 3	6 1 1	6 1 7	6 3 1	6 4 8	6 5 2	6 6 6	6 7 6	6 8 0	6 9 1	6 9 8	7 0 6	7 1 3	
Carcass ID Number	5 3 8 1	5 3 2 1	5 3 6 1	5 1 8 1	4 9 7 1	5 2 9 1	5 2 3 1	5 2 1 1	5 3 5 1	4 9 3 1	5 1 3 1	5 1 4 1	5 2 4 1	4 9 8 1	4 9 6 1	5 0 2 1	5 0 3 1	**Total Tissues/ Tumors**
Alimentary System																		
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Fibrosarcoma, metastatic, skin																X		1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Hemangiosarcoma		X																1
Hepatocellular carcinoma							X	X									X	3
Hepatocellular adenoma						X		X								X		4
Hepatocellular adenoma, multiple									X					X			X	5
Hepatocholangiocarcinoma			X															1
Mesentery						+	+					+				+		6
Fibrosarcoma, metastatic, skin																X		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Fibrosarcoma, metastatic, skin																X		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	41
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Cardiovascular System																		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	41
Hepatocholangiocarcinoma, metastatic, liver			X															1
Endocrine System																		
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	41
Fibrosarcoma, metastatic, skin																X		1
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	41
Pars distalis, adenoma						X			X								X	3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Follicular cell, adenoma									X									2
General Body System																		
None																		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

Number of Days on Study	135	179	198	241	259	278	286	313	349	349	361	379	395	411	420	433	437	456	477	478	500	527	534	552	566
Carcass ID Number	5201	4911	5121	5151	5051	5341	5261	5041	4941	5191	5311	5061	5091	5161	5271	5011	5331	4921	5171	5401	5001	5391	5281	5081	5101
Genital System																									
Clitoral gland										M															
Ovary	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, fibrosarcoma, metastatic, skin																									
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																									
Renal, fibrosarcoma, metastatic, skin																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X							
Hepatocholangiocarcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye											+														
Harderian gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	I
Adenoma																									

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

Number of Days on Study	568	571	579	587	603	611	617	631	648	652	666	676	680	691	698	706	713	
Carcass ID Number	5381	5321	5361	5181	4971	5291	5231	5211	5351	4931	5131	5141	5241	4981	4961	5021	5031	**Total Tissues/ Tumors**
Genital System																		
Clitoral gland																		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Fibrosarcoma, metastatic, skin																X		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Hemangiosarcoma											X							1
Hematopoietic System																		
Blood														+				1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Lumbar, fibrosarcoma, metastatic, skin																X		1
Mediastinal, hepatocholangiocarcinoma, metastatic, liver			X															1
Renal, fibrosarcoma, metastatic, skin																X		1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Fibrosarcoma, metastatic, skin																X		1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Integumentary System																		
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Subcutaneous tissue, fibrosarcoma					X											X		2
Subcutaneous tissue, hemangiosarcoma																	X	1
Musculoskeletal System																		
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Skeletal muscle																		1
Nervous System																		
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Respiratory System																		
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Alveolar/bronchiolar adenoma																X		2
Hepatocholangiocarcinoma, metastatic, liver			X															1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Special Senses System																		
Eye																		1
Harderian gland	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	36
Adenoma							X											1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

Number of Days on Study	135	179	198	241	259	278	286	313	349	349	361	379	395	411	420	433	437	456	477	478	500	527	534	552	566
Carcass ID Number	5201	4911	5121	5151	5051	5341	5261	5041	4941	5191	5311	5061	5091	5161	5271	5011	5331	4921	5171	5401	5001	5391	5281	5081	5101
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: Paired Control (continued)

Number of Days on Study	568	571	579	587	603	611	617	631	648	652	666	676	680	691	698	706	713	
Carcass ID Number	5381	5321	5361	5181	4971	5291	5231	5211	5351	4931	5131	5141	5241	4981	4961	5021	5031	**Total Tissues/ Tumors**
Urinary System																		
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Systemic Lesions																		
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Lymphoma malignant undifferentiated cell type												X						1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm

Number of Days on Study	198	395	534	534	584	587	617	624	636	648	652	670	678	698	729	729	729	729	729	729	729	730	730	730	731	731	731
Carcass ID Number	5501	6001	5941	6041	5481	5991	5831	5741	5671	5651	5751	5931	5621	5961	5541	5571	5601	5701	5771	5841	6001	5461	5511	5631	5431	5441	5451
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Histiocytic sarcoma					X																						
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																		X									
Hepatoblastoma																		X									
Hepatocellular carcinoma													X	X								X				X	X
Hepatocellular carcinoma, multiple																									X		
Hepatocellular adenoma															X	X		X		X	X						
Hepatocellular adenoma, multiple						X					X			X									X		X	X	
Histiocytic sarcoma					X																						
Osteosarcoma, metastatic, uncertain primary site																											
Mesentery		+			+	+								+				+			+		+		+		+
Fibrosarcoma, metastatic, skin		X																									
Hemangioma																											
Histiocytic sarcoma					X																X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																X						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																	X	X									X
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																											
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	6	6	6	6	6	7	7	7	7	7	
	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	
	4	4	5	5	5	5	6	6	7	7	7	7	7	8	8	8	8	8	9	9	0	0	0	0	0	Total
Carcass ID Number	7	9	0	3	8	9	8	9	1	2	6	8	9	2	6	7	8	9	1	7	1	3	5	7	9	Tissues/
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangioma																										1
Hepatoblastoma																										1
Hepatocellular carcinoma										X								X			X			X		9
Hepatocellular carcinoma, multiple																						X				2
Hepatocellular adenoma												X	X	X							X					9
Hepatocellular adenoma, multiple	X	X		X			X		X	X	X				X	X			X	X		X	X			19
Histiocytic sarcoma																										1
Osteosarcoma, metastatic, uncertain primary site		X																								1
Mesentery		+	+	+			+							+					M			+				15
Fibrosarcoma, metastatic, skin																										1
Hemangioma							X																			1
Histiocytic sarcoma																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Papilloma squamous																			X							4
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangiosarcoma		X																								1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Number of Days on Study	198	395	534	534	584	587	617	624	636	648	652	670	678	698	729	729	729	729	729	729	729	730	730	730	731	731	731
Carcass ID Number	5551	6001	5941	6041	5481	5991	5831	5741	5671	5651	5751	5931	5621	5961	5541	5571	5601	5701	5771	5841	6101	5461	5511	5631	5431	5441	5451
Endocrine System (continued)																											
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																											
Bilateral, pheochromocytoma benign																											X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																				
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X										X		X									X		
Pars distalis, adenoma, multiple																											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																											
None																											
Genital System																											
Clitoral gland						+																					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary																											
Hemangiosarcoma														X													
Histiocytic sarcoma					X																						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																											
Polyp stromal																											
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma																											
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, histiocytic sarcoma					X																X						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	+
Histiocytic sarcoma																					X						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																X						
Thymus	+	I	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M
Histiocytic sarcoma					X																						
Integumentary System																											
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma		X																									
Subcutaneous tissue, mast cell tumor malignant																											X
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Number of Days on Study	731	731	731	732	732	732	732	732	732	733	733	733	733	733	733	736	736	736	736	736	737	737	737	737	737	
Carcass ID Number	5471	5491	5501	5531	5581	5591	5681	5691	5711	5721	5761	5781	5791	5821	5861	5871	5881	5891	5911	5971	6011	6031	6051	6071	6091	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pheochromocytoma benign																X										1
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	51
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma		X							X																	6
Pars distalis, adenoma, multiple				X																						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
General Body System																										
None																										
Genital System																										
Clitoral gland																			+							2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	50
Cystadenoma, papillary																									X	1
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma				X																						1
Polyp stromal		X																								1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Femoral, hemangiosarcoma																			X							1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Mediastinal, histiocytic sarcoma																										2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																										2
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenocarcinoma																							X			1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Subcutaneous tissue, fibrosarcoma																	X									2
Subcutaneous tissue, mast cell tumor malignant														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Number of Days on Study	198	395	534	534	584	587	617	624	636	648	652	670	678	698	729	729	729	729	729	729	729	730	730	730	731	731	731
Carcass ID Number	5551	6001	5941	6041	5481	5991	5831	5741	5671	5651	5751	5931	5621	5961	5541	5571	5601	5701	5771	5841	6101	5461	5511	5631	5431	5441	5451
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve									+																		
Spinal cord									+																		
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland										X																	
Alveolar/bronchiolar adenoma							X						X														
Alveolar/bronchiolar adenoma, multiple																											X
Alveolar/bronchiolar carcinoma																											
Hepatocellular carcinoma, metastatic, liver																						X					
Histiocytic sarcoma																					X						
Osteosarcoma, metastatic, uncertain primary site																											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																											
Ear																											
Fibrosarcoma																											
Eye		+																									
Harderian gland	+	M	+	+	+	+	+	+	M	+	+	M	+	M	M	M	+	M	+	+	+	+	+	+	M	M	+
Adenocarcinoma										X																	
Adenoma																											
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																X						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																X						
Lymphoma malignant mixed						X																					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 25 ppm (continued)

Number of Days on Study	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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 4 7 1	5 4 9 1	5 5 0 1	5 5 3 1	5 5 8 1	5 5 9 1	5 6 8 1	5 6 9 1	5 7 1 1	5 7 2 1	5 7 6 1	5 7 8 1	5 7 9 1	5 8 2 1	5 8 6 1	5 8 7 1	5 8 8 1	5 8 9 1	5 9 1 1	5 9 7 1	6 0 1 1	6 0 3 1	6 0 5 1	6 0 7 1	6 0 9 1	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenocarcinoma, metastatic, handerian gland																										1
Alveolar/bronchiolar adenoma									X																	3
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma															X										X	2
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Osteosarcoma, metastatic, uncertain primary site		X																								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	51
Special Senses System																										
Ear																	+									1
Fibrosarcoma																	X									1
Eye				+																						2
Harderian gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adenocarcinoma																										1
Adenoma				X																X						2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma				X																						3
Lymphoma malignant mixed		X																				X		X	X	5

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm

Number of Days on Study	313	379	411	478	527	552	587	611	617	634	653	657	684	692	724	724	730	730	730	730	730	730	730	730	730
Carcass ID Number	6201	6451	6341	6611	6371	6781	6121	6321	6491	6711	6171	6431	6671	6501	6231	6441	6241	6261	6281	6291	6331	6361	6651	6681	6691
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma														X											
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma										X			X											X	X
Hepatocellular carcinoma, multiple					X																				
Hepatocellular adenoma										X		X				X		X							
Hepatocellular adenoma, multiple															X		X						X		X
Histiocytic sarcoma							X							X											
Mesentery						+	+							+	+	+								+	+
Histiocytic sarcoma														X											
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																									
Papilloma squamous																	X								
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel						+																			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X							X											

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

Number of Days on Study	730	731	731	731	731	732	732	732	732	732	733	733	733	733	733	734	736	736	736	736	736	737	737	737	737	
Carcass ID Number	6771	6151	6161	6191	6221	6251	6271	6301	6311	6391	6461	6471	6481	6521	6531	6581	6541	6601	6621	6641	6661	6731	6741	6751	6801	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma	X																									1
Histiocytic sarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma									X			X								X						7
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma			X		X			X					X									X			X	10
Hepatocellular adenoma, multiple	X	X					X		X			X			X		X		X	X						13
Histiocytic sarcoma																										2
Mesentery	+		+				+	+						+		+			+				+			15
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mast cell tumor malignant																								X		1
Papilloma squamous							X																			2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

Number of Days on Study	313	379	411	478	527	552	587	611	617	634	653	657	684	692	724	724	730	730	730	730	730	730	730	730	730
Carcass ID Number	6201	6451	6341	6611	6371	6781	6121	6321	6491	6711	6171	6431	6671	6501	6231	6441	6241	6261	6281	6291	6331	6361	6651	6681	6691
Endocrine System (continued)																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Histiocytic sarcoma														X											
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																						X		X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, carcinoma																							X		
General Body System																									
None																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma														X											
Polyp stromal											X														
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma															X										
Femoral, histiocytic sarcoma														X											
Humerus, hemangiosarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, histiocytic sarcoma														X											
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Histiocytic sarcoma														X											
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+																		
Histiocytic sarcoma							X																		

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

Number of Days on Study	730	731	731	731	731	732	732	732	732	732	733	733	733	733	733	734	736	736	736	736	736	737	737	737	737	
Carcass ID Number	6771	6151	6161	6191	6221	6251	6271	6301	6311	6391	6461	6471	6481	6521	6531	6581	6541	6601	6621	6641	6661	6731	6741	6751	6801	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																			X							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																			X							1
Histiocytic sarcoma																										1
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X								X			X									X	X			X	8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																X										1
Histiocytic sarcoma																										1
Polyp stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, hemangiosarcoma																										1
Femoral, histiocytic sarcoma																										1
Humerus, hemangiosarcoma																									X	1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Histiocytic sarcoma																										1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

Number of Days on Study	313	379	411	478	527	552	587	611	617	634	653	657	684	692	724	724	730	730	730	730	730	730	730	730	730
Carcass ID Number	6201	6451	6341	6611	6371	6781	6121	6321	6491	6711	6171	6431	6671	6501	6231	6441	6241	6261	6281	6291	6331	6361	6651	6681	6691
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve				+		+						+													
Spinal cord				+		+						+													
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																X									
Hepatocellular carcinoma, metastatic, liver													X												
Histiocytic sarcoma							X							X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear		I			+																				
Papilloma squamous					X																				
Eye																							+		
Harderian gland	+	M	+	+	+	+	M	M	+	+	M	+	M	M	+	+	+	M	+	+	+	+	+	M	+
Adenoma										X							X						X		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X							X											
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed															X			X	X						
Lymphoma malignant undifferentiated cell type																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 100 ppm (continued)

Number of Days on Study	730	731	731	731	731	732	732	732	732	732	733	733	733	733	733	734	736	736	736	736	736	737	737	737	737	
Carcass ID Number	6771	6151	6161	6191	6221	6251	6271	6301	6311	6391	6461	6471	6481	6521	6531	6581	6541	6601	6621	6641	6661	6731	6741	6751	6801	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										3
Spinal cord																										3
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X												X									2
Alveolar/bronchiolar carcinoma												X														2
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Papilloma squamous																										1
Eye																	+									2
Harderian gland	I	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	37
Adenoma						X											X			X						6
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed												X		X			X		X							7
Lymphoma malignant undifferentiated cell type								X							X									X		3

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm

Number of Days on Study	1 3 5	1 7 9	2 4 1	2 7 8	2 8 6	3 1 4	3 4 9	3 6 1	4 3 3	4 7 7	5 0 0	5 6 6	5 6 8	5 7 3	5 7 9	5 8 4	6 0 6	6 1 0	6 1 9	6 3 2	6 6 6	6 8 4	6 8 8	7 0 5	7 0 7
Carcass ID Number	7 0 3 1	6 9 1 1	7 1 9 1	7 5 9 1	7 6 0 1	7 7 3 1	7 7 1 1	7 4 0 1	6 9 8 1	7 3 5 1	7 3 6 1	7 3 2 1	7 6 1 1	7 5 2 1	7 6 7 1	7 1 8 1	7 4 8 1	6 9 7 1	7 2 0 1	7 3 3 1	7 2 6 1	7 5 1 1	7 2 1 1	7 6 8 1	7 0 8 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Intestine large	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																									
Hepatoblastoma										X															
Hepatocellular carcinoma																				X					X
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																				X				X	
Hepatocholangiocarcinoma								X																	
Histiocytic sarcoma																X	X	X	X						
Mesentery			+					+		+				+			+	+	+		+		+		
Hepatocholangiocarcinoma, metastatic, liver								X																	
Histiocytic sarcoma																	X	X	X						
Lipoma																									
Sarcoma, metastatic, uncertain primary site																									
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver								X		X															
Histiocytic sarcoma																			X						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Stomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous										X															
Papilloma squamous, multiple												X													
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	1	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	2	5	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	2	2
Carcass ID Number	6	7	7	7	7	7	7	7	7	7	7	7	7	6	6	6	6	6	6	6	6	6	7	7	7
	8	1	7	0	0	0	1	2	2	3	3	4	7	8	8	8	8	9	9	9	9	9	6	0	0
	5	0	6	1	5	7	5	3	8	0	7	5	9	1	3	6	9	0	3	4	5	6	6	2	6
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																		X							
Hemangiosarcoma																									
Hepatoblastoma	X																								
Hepatocellular carcinoma				X										X										X	
Hepatocellular carcinoma, multiple																X									
Hepatocellular adenoma							X	X			X	X				X					X				
Hepatocellular adenoma, multiple	X	X			X	X				X			X							X		X			
Hepatocholangiocarcinoma																									
Histiocytic sarcoma																									
Mesentery		+	+	+							+		+	+					+			+		+	
Hepatocholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Lipoma													X												
Sarcoma, metastatic, uncertain primary site		X																							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Papilloma squamous, multiple																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	3	3	3	3	3	3	3	3	6	6	6	6	6	6	6	6	6	7	7
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	6	7	7	7	7	7	7	7	7	7	7
	0	1	1	1	1	1	2	2	2	2	2	3	3	3	8	4	4	4	4	4	5	5	5	6	6
Carcass ID Number	9	2	3	4	6	7	2	4	5	7	9	1	8	9	8	1	2	3	7	9	0	4	8	2	3
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																					X				
Hepatoblastoma																									
Hepatocellular carcinoma	X			X											X				X			X			
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma		X						X		X	X					X				X	X		X		
Hepatocellular adenoma, multiple						X	X		X					X	X		X					X			
Hepatocholangiocarcinoma																									
Histiocytic sarcoma																									X
Mesentery		+	+		+	+	+				+					+							+		
Hepatocholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Lipoma																									
Sarcoma, metastatic, uncertain primary site																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous		X																	X						
Papilloma squamous, multiple																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	737	737	737	737	737	
Carcass ID Number	**7651**	**7721**	**7741**	**7751**	**7781**	**Total Tissues/ Tumors**
Alimentary System						
Esophagus	+	+	+	+	+	80
Gallbladder	+	+	+	+	+	79
Histiocytic sarcoma						1
Intestine large	+	+	+	+	+	79
Intestine large, cecum	+	+	+	+	+	78
Intestine large, colon	+	+	+	+	+	79
Intestine large, rectum	+	+	+	+	+	79
Intestine small	+	+	+	+	+	79
Intestine small, duodenum	+	+	+	+	+	79
Intestine small, ileum	+	+	+	+	+	78
Intestine small, jejunum	+	+	+	+	+	78
Liver	+	+	+	+	+	80
Hemangioma						1
Hemangiosarcoma						1
Hepatoblastoma						2
Hepatocellular carcinoma			X			11
Hepatocellular carcinoma, multiple						1
Hepatocellular adenoma		X	X	X		17
Hepatocellular adenoma, multiple						17
Hepatocholangiocarcinoma						1
Histiocytic sarcoma						5
Mesentery		+		+		28
Hepatocholangiocarcinoma, metastatic, liver						1
Histiocytic sarcoma						3
Lipoma						1
Sarcoma, metastatic, uncertain primary site						1
Pancreas	+	+	+	+	+	79
Hepatocholangiocarcinoma, metastatic, liver						2
Histiocytic sarcoma						1
Salivary glands	+	+	+	+	+	80
Histiocytic sarcoma						1
Stomach	+	+	+	+	+	79
Stomach, forestomach	+	+	+	+	+	79
Papilloma squamous						3
Papilloma squamous, multiple						1
Stomach, glandular	+	+	+	+	+	79
Tooth	+	+	+	+	+	80

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	1	1	2	2	2	3	3	3	4	4	5	5	5	5	5	5	6	6	6	6	6	6	6	7	7
Number of Days on Study	3	7	4	7	8	1	4	6	3	7	0	6	6	7	7	8	0	1	1	3	6	8	8	0	0
	5	9	1	8	6	4	9	1	3	7	0	6	8	3	9	4	6	0	9	2	6	4	8	5	7
	7	6	7	7	7	7	7	7	6	7	7	7	7	7	7	7	7	6	7	7	7	7	7	7	7
	0	9	1	5	6	7	7	4	9	3	3	3	6	5	6	1	4	9	2	3	2	5	2	6	0
Carcass ID Number	3	1	9	9	0	3	1	0	8	5	6	2	1	2	7	8	8	7	0	3	6	1	1	8	8
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver																									
Hepatocholangiocarcinoma, metastatic, liver										X															
Histiocytic sarcoma																	X		X						
Pericardium, hepatocholangiocarcinoma, metastatic, liver								X																	
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Sarcoma, metastatic, uncertain primary site																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X		X						
Pars distalis, adenoma																	X								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									X
General Body System																									
None																									
Genital System																									
Clitoral gland																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary																									
Histiocytic sarcoma																X	X		X						
Sarcoma, metastatic, uncertain primary site																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X	X	X						
Polyp stromal							X																		
Sarcoma stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, histiocytic sarcoma																X			X						
Maxilla, histiocytic sarcoma																			X						
Thoracic, vertebra, histiocytic sarcoma																			X						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	0	1	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	2	5	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	2	2
	6	7	7	7	7	7	7	7	7	7	7	7	7	6	6	6	6	6	6	6	6	6	7	7	7
	8	1	7	0	0	0	1	2	2	3	3	4	7	8	8	8	8	9	9	9	9	9	6	0	0
Carcass ID Number	5	0	6	1	5	7	5	3	8	0	7	5	9	1	3	6	9	0	3	4	5	6	6	2	6
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver																									
Hepatocholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Pericardium, hepatocholangiocarcinoma, metastatic, liver																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Sarcoma, metastatic, uncertain primary site		X																							
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Pars distalis, adenoma											X			X		X					X	X	X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma		X																							
General Body System																									
None																									
Genital System																									
Clitoral gland			M									+									+				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary																									
Histiocytic sarcoma																									
Sarcoma, metastatic, uncertain primary site		X																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Polyp stromal																									
Sarcoma stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, histiocytic sarcoma																									
Maxilla, histiocytic sarcoma																									
Thoracic, vertebra, histiocytic sarcoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	3	3	3	3	3	3	3	3	6	6	6	6	6	6	6	6	6	7	7
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	6	7	7	7	7	7	7	7	7	7	7
	0	1	1	1	1	1	2	2	2	2	2	3	3	3	8	4	4	4	4	4	5	5	5	6	6
Carcass ID Number	9	2	3	4	6	7	2	4	5	7	9	1	8	9	8	1	2	3	7	9	0	4	8	2	3
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver																					X				
Hepatocholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Pericardium, hepatocholangiocarcinoma, metastatic, liver																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Sarcoma, metastatic, uncertain primary site																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign										X															
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Pars distalis, adenoma						X										X	X	X			X	X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland															+										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary																									
Histiocytic sarcoma																									
Sarcoma, metastatic, uncertain primary site																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Polyp stromal																									
Sarcoma stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, histiocytic sarcoma																									
Maxilla, histiocytic sarcoma																									
Thoracic, vertebra, histiocytic sarcoma																									

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	737	737	737	737	737	
Carcass ID Number	7651	7721	7741	7751	7781	**Total Tissues/ Tumors**
Cardiovascular System						
Heart	+	+	+	+	+	80
Hemangiosarcoma, metastatic, liver						1
Hepatocholangiocarcinoma, metastatic, liver						1
Histiocytic sarcoma						2
Pericardium, hepatocholangiocarcinoma, metastatic, liver						1
Endocrine System						
Adrenal gland	+	+	+	+	+	80
Adrenal gland, cortex	+	+	+	+	+	80
Histiocytic sarcoma						1
Sarcoma, metastatic, uncertain primary site						1
Adrenal gland, medulla	+	+	+	+	+	80
Pheochromocytoma benign						1
Islets, pancreatic	+	+	+	+	+	80
Adenoma						1
Parathyroid gland	+	+	+	+	+	75
Pituitary gland	+	+	+	+	+	79
Histiocytic sarcoma						2
Pars distalis, adenoma						13
Thyroid gland	+	+	+	+	+	80
Follicular cell, adenoma						2
General Body System						
None						
Genital System						
Clitoral gland						3
Ovary	+	+	+	+	+	80
Cystadenoma, papillary			X			1
Histiocytic sarcoma						3
Sarcoma, metastatic, uncertain primary site						1
Uterus	+	+	+	+	+	80
Histiocytic sarcoma						4
Polyp stromal						1
Sarcoma stromal			X			1
Hematopoietic System						
Bone marrow	+	+	+	+	+	80
Femoral, histiocytic sarcoma						2
Maxilla, histiocytic sarcoma						1
Thoracic, vertebra, histiocytic sarcoma						1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	135	179	241	278	286	314	349	361	433	477	500	566	568	573	579	584	606	610	619	632	666	684	688	705	707
Carcass ID Number	7031	6911	7191	7591	7601	7731	7711	7401	6981	7351	7361	7321	7611	7521	7671	7181	7481	6971	7201	7331	7261	7511	7211	7681	7081
Hematopoietic System (continued)																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, histiocytic sarcoma																	X								
Mediastinal, hepatocholangiocarcinoma, metastatic, liver										X															
Mediastinal, histiocytic sarcoma																X	X								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X	X		X						
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Hemangioma																									
Histiocytic sarcoma																	X	X	X						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X		X						
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Histiocytic sarcoma																X			X						
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																								X	
Subcutaneous tissue, neurofibrosarcoma												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Fibrosarcoma, metastatic, skin																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Peripheral nerve				+																					
Spinal cord				+																					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic, skin																								X	
Hepatoblastoma, metastatic, liver										X															
Hepatocellular carcinoma, metastatic, liver																				X					
Hepatocholangiocarcinoma, metastatic, liver								X																	
Histiocytic sarcoma																X	X		X						
Mediastinum, hepatocellular carcinoma, metastatic, liver																				X					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	0	1	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	2	5	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	2	2
	6	7	7	7	7	7	7	7	7	7	7	7	7	6	6	6	6	6	6	6	6	6	7	7	7
	8	1	7	0	0	0	1	2	2	3	3	4	7	8	8	8	8	9	9	9	9	9	6	0	0
Carcass ID Number	5	0	6	1	5	7	5	3	8	0	7	5	9	1	3	6	9	0	3	4	5	6	6	2	6
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hematopoietic System (continued)																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, histiocytic sarcoma																									
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																									
Mediastinal, histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Hemangioma	X																								
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma								X																	
Subcutaneous tissue, neurofibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle								+																	
Fibrosarcoma, metastatic, skin								X																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X								X											
Alveolar/bronchiolar carcinoma										X						X									
Fibrosarcoma, metastatic, skin																									
Hepatoblastoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver				X																					
Hepatocholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Mediastinum, hepatocellular carcinoma, metastatic, liver																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	732	732	732	732	732	732	733	733	733	733	733	733	733	733	736	736	736	736	736	736	736	736	736	737	737
Carcass ID Number	7091	7121	7131	7141	7161	7171	7221	7241	7251	7271	7291	7311	7381	7391	6881	7411	7421	7431	7471	7491	7501	7541	7581	7621	7631
Hematopoietic System (continued)																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, histiocytic sarcoma																									
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																									
Mediastinal, histiocytic sarcoma																									
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma		X						X																	
Subcutaneous tissue, neurofibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Fibrosarcoma, metastatic, skin																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic, skin																									
Hepatoblastoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver																									
Hepatocholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Mediastinum, hepatocellular carcinoma, metastatic, liver																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	7 6 5 1	7 7 2 1	7 7 4 1	7 7 5 1	7 7 8 1	**Total Tissues/ Tumors**
Hematopoietic System (continued)						
Lymph node	+	+	+	+	+	80
Inguinal, histiocytic sarcoma						1
Mediastinal, hepatocholangiocarcinoma, metastatic, liver						1
Mediastinal, histiocytic sarcoma						2
Lymph node, mandibular	+	+	+	+	+	79
Histiocytic sarcoma						3
Lymph node, mesenteric	+	+	+	+	+	77
Hemangioma						1
Histiocytic sarcoma						3
Spleen	+	+	+	+	+	80
Histiocytic sarcoma						2
Thymus	M	+	+	+	+	73
Histiocytic sarcoma						2
Integumentary System						
Mammary gland	+	+	+	+	+	80
Adenoma						1
Skin	+	+	+	+	+	80
Subcutaneous tissue, fibrosarcoma			X			5
Subcutaneous tissue, neurofibrosarcoma						1
Musculoskeletal System						
Bone	+	+	+	+	+	80
Skeletal muscle						1
Fibrosarcoma, metastatic, skin						1
Nervous System						
Brain	+	+	+	+	+	80
Histiocytic sarcoma						1
Peripheral nerve						1
Spinal cord						1
Respiratory System						
Lung	+	+	+	+	+	80
Alveolar/bronchiolar adenoma	X					4
Alveolar/bronchiolar carcinoma				X		3
Fibrosarcoma, metastatic, skin						1
Hepatoblastoma, metastatic, liver						1
Hepatocellular carcinoma, metastatic, liver						2
Hepatocholangiocarcinoma, metastatic, liver						1
Histiocytic sarcoma						3
Mediastinum, hepatocellular carcinoma, metastatic, liver						1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	135	179	241	278	286	314	349	361	433	477	500	566	568	573	579	584	606	610	619	632	666	684	688	705	707
Carcass ID Number	7031	6911	7191	7591	7601	7731	7711	7401	6981	7351	7361	7321	7611	7521	7671	7181	7481	6971	7201	7331	7261	7511	7211	7681	7081
Respiratory System (continued)																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear									I				+												
Harderian gland	M	+	M	+	+	+	+	+	+	+	+	M	+	M	+	M	M	M	M	+	+	M	M	M	M
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X	X	X	X						
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																			X						
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X	X	X	X						
Lymphoma malignant lymphocytic														X								X	X		
Lymphoma malignant mixed			X																						
Lymphoma malignant undifferentiated cell type																									

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	709	712	715	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	732	732
Carcass ID Number	6851	7101	7761	7011	7051	7071	7151	7231	7281	7301	7371	7451	7791	6811	6831	6861	6891	6901	6931	6941	6951	6961	7661	7021	7061
Respiratory System (continued)																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Harderian gland	+	+	+	M	M	M	+	M	M	M	M	+	M	M	M	+	+	+	I	+	M	M	M	M	+
Adenoma		X																		X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant lymphocytic			X																				X		
Lymphoma malignant mixed							X	X				X													
Lymphoma malignant undifferentiated cell type														X							X				

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	3	3	3	3	3	3	3	3	6	6	6	6	6	6	6	6	6	7	7
Carcass ID Number	7	7	7	7	7	7	7	7	7	7	7	7	7	7	6	7	7	7	7	7	7	7	7	7	7
	0	1	1	1	1	1	2	2	2	2	2	3	3	3	8	4	4	4	4	4	5	5	5	6	6
	9	2	3	4	6	7	2	4	5	7	9	1	8	9	8	1	2	3	7	9	0	4	8	2	3
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Respiratory System (continued)																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Harderian gland	M	+	M	M	M	M	M	M	M	+	M	M	M	+	M	M	M	M	+	M	M	M	+	+	+
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed											X			X					X				X		
Lymphoma malignant undifferentiated cell type	X		X							X															

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride: 175 ppm (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	7 6 5 1	7 7 2 1	7 7 4 1	7 7 5 1	7 7 8 1	**Total Tissues/ Tumors**
Respiratory System (continued)						
Nose	+	+	+	+	+	80
Trachea	+	+	+	+	+	80
Special Senses System						
Ear						1
Harderian gland	+	+	M	+	+	34
Adenoma						2
Urinary System						
Kidney	+	+	+	+	+	80
Histiocytic sarcoma						4
Urinary bladder	+	+	+	+	+	78
Histiocytic sarcoma						1
Systemic Lesions						
Multiple organs	+	+	+	+	+	80
Histiocytic sarcoma						5
Lymphoma malignant lymphocytic						5
Lymphoma malignant mixed						8
Lymphoma malignant undifferentiated cell type	X					6

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

	Control	25 ppm	100 ppm	175 ppm
Harderian Gland: Adenoma				
Overall rates[a]	4/80 (5%)	2/52 (4%)	6/50 (12%)	2/80 (3%)
Adjusted rates[b]	6.4%	5.3%	16.8%	3.7%
Terminal rates[c]	2/53 (4%)	2/38 (5%)	5/34 (15%)	1/52 (2%)
First incidence (days)	420	729 (T)	634	712
Life table tests[d]	P=0.471N	P=0.518N	P=0.137	P=0.368N
Logistic regression tests[d]	P=0.456N	P=0.528N	P=0.137	P=0.315N
Cochran-Armitage test[d]	P=0.430N			
Fisher exact test[d]		P=0.557N	P=0.132	P=0.341N
Harderian Gland: Adenoma or Adenocarcinoma				
Overall rates	5/80 (6%)	3/52 (6%)	6/50 (12%)	2/80 (3%)
Adjusted rates	8.2%	7.5%	16.8%	3.7%
Terminal rates	3/53 (6%)	2/38 (5%)	5/34 (15%)	1/52 (2%)
First incidence (days)	420	648	634	712
Life table tests	P=0.305N	P=0.570N	P=0.212	P=0.245N
Logistic regression tests	P=0.288N	P=0.588N	P=0.209	P=0.211N
Cochran-Armitage test	P=0.267N			
Fisher exact test		P=0.610N	P=0.204	P=0.221N
Liver: Hepatocellular Adenoma				
Overall rates	49/80 (61%)	28/52 (54%)	23/50 (46%)	34/80 (43%)
Adjusted rates	80.0%	68.2%	60.4%	60.6%
Terminal rates	41/53 (77%)	25/38 (66%)	19/34 (56%)	30/52 (58%)
First incidence (days)	358	587	634	632
Life table tests	P=0.018N	P=0.101N	P=0.046N	P=0.016N
Logistic regression tests	P=0.027N	P=0.253N	P=0.081N	P=0.036N
Cochran-Armitage test	P=0.009N			
Fisher exact test		P=0.254N	P=0.064N	P=0.013N
Liver: Hepatocellular Carcinoma				
Overall rates	14/80 (18%)	11/52 (21%)	8/50 (16%)	12/80 (15%)
Adjusted rates	23.3%	27.5%	20.7%	22.0%
Terminal rates	9/53 (17%)	9/38 (24%)	5/34 (15%)	10/52 (19%)
First incidence (days)	602	678	527	632
Life table tests	P=0.334N	P=0.462	P=0.498N	P=0.458N
Logistic regression tests	P=0.353N	P=0.377	P=0.524N	P=0.505N
Cochran-Armitage test	P=0.270N			
Fisher exact test		P=0.380	P=0.512N	P=0.415N
Liver: Hepatoblastoma or Hepatocellular Carcinoma				
Overall rates	14/80 (18%)	12/52 (23%)	8/50 (16%)	14/80 (18%)
Adjusted rates	23.3%	30.0%	20.7%	24.5%
Terminal rates	9/53 (17%)	10/38 (26%)	5/34 (15%)	10/52 (19%)
First incidence (days)	602	678	527	477
Life table tests	P=0.461N	P=0.365	P=0.498N	P=0.533
Logistic regression tests	P=0.476N	P=0.280	P=0.524N	P=0.501
Cochran-Armitage test	P=0.387N			
Fisher exact test		P=0.285	P=0.512N	P=0.582N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
Liver: Hepatocellular Adenoma, Hepatoblastoma, or Hepatocellular Carcinoma				
Overall rates	55/80 (69%)	33/52 (63%)	26/50 (52%)	42/80 (53%)
Adjusted rates	84.4%	78.5%	64.8%	72.3%
Terminal rates	43/53 (81%)	29/38 (76%)	20/34 (59%)	36/52 (69%)
First incidence (days)	358	587	527	477
Life table tests	P=0.040N	P=0.147N	P=0.042N	P=0.044N
Logistic regression tests	P=0.052N	P=0.339N	P=0.056N	P=0.084N
Cochran-Armitage test	P=0.014N			
Fisher exact test		P=0.328N	P=0.042N	P=0.026N
Liver: Hepatocellular Adenoma, Hepatoblastoma, Hepatocellular Carcinoma, or Hepatocholangiocarcinoma				
Overall rates	55/80 (69%)	33/52 (63%)	26/50 (52%)	43/80 (54%)
Adjusted rates	84.4%	78.5%	64.8%	72.6%
Terminal rates	43/53 (81%)	29/38 (76%)	20/34 (59%)	36/52 (69%)
First incidence (days)	358	587	527	361
Life table tests	P=0.059N	P=0.147N	P=0.042N	P=0.065N
Logistic regression tests	P=0.077N	P=0.339N	P=0.056N	P=0.116N
Cochran-Armitage test	P=0.022N			
Fisher exact test		P=0.328N	P=0.042N	P=0.037N
Liver: Hepatocellular Adenoma, Hepatoblastoma, Hepatocellular Carcinoma, or Hepatocholangiocarcinoma[e]				
Overall rates	69/142 (49%)	37/62 (60%)	29/63 (46%)	46/99 (46%)
Adjusted rates	86.6%	80.0%	66.7%	73.7%
Interim sacrifice 1[f]	0/10 (0%)	0/2 (0%)	0/3 (0%)	0/10 (0%)
Interim sacrifice 2[f]	3/10 (30%)	4/8 (50%)	3/10 (30%)	3/9 (33%)
Terminal rates	43/53 (81%)	29/38 (76%)	20/34 (59%)	36/52 (69%)
First incidence (days)	358	458 (I)	458 (I)	361
Life table tests	P=0.006N	P=0.047N	P=0.007N	P=0.001N
Logistic regression tests	P=0.121N	P=0.493	P=0.134N	P=0.215N
Cochran-Armitage test	P=0.222N			
Fisher exact test		P=0.096	P=0.426N	P=0.423N
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	5/80 (6%)	4/52 (8%)	2/50 (4%)	4/80 (5%)
Adjusted rates	8.6%	9.6%	5.9%	7.7%
Terminal rates	3/53 (6%)	2/38 (5%)	2/34 (6%)	4/52 (8%)
First incidence (days)	592	617	729 (T)	729 (T)
Life table tests	P=0.363N	P=0.546	P=0.433N	P=0.524N
Logistic regression tests	P=0.371N	P=0.511	P=0.453N	P=0.550N
Cochran-Armitage test	P=0.326N			
Fisher exact test		P=0.504	P=0.451N	P=0.500N
Lung: Alveolar/bronchiolar Adenoma or Alveolar/bronchiolar Carcinoma				
Overall rates	8/80 (10%)	6/52 (12%)	4/50 (8%)	7/80 (9%)
Adjusted rates	13.4%	14.7%	11.4%	13.5%
Terminal rates	4/53 (8%)	4/38 (11%)	3/34 (9%)	7/52 (13%)
First incidence (days)	592	617	724	729 (T)
Life table tests	P=0.409N	P=0.546	P=0.462N	P=0.531N
Logistic regression tests	P=0.428N	P=0.499	P=0.492N	P=0.567N
Cochran-Armitage test	P=0.361N			
Fisher exact test		P=0.497	P=0.480N	P=0.500N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	25/80 (31%)	7/51 (14%)	8/50 (16%)	13/79 (16%)
Adjusted rates	40.5%	17.4%	23.5%	24.3%
Terminal rates	18/53 (34%)	5/37 (14%)	8/34 (24%)	12/52 (23%)
First incidence (days)	528	534	729 (T)	606
Life table tests	P=0.060N	P=0.015N	P=0.041N	P=0.029N
Logistic regression tests	P=0.067N	P=0.020N	P=0.048N	P=0.037N
Cochran-Armitage test	P=0.045N			
Fisher exact test		P=0.018N	P=0.039N	P=0.022N
Pituitary Gland (Pars Distalis): Adenoma[e]				
Overall rates	28/141 (20%)	7/61 (11%)	8/63 (13%)	13/98 (13%)
Adjusted rates	42.3%	17.4%	23.5%	24.3%
Interim sacrifice 1	0/10 (0%)	0/2 (0%)	0/3 (0%)	0/10 (0%)
Interim sacrifice 2	0/10 (0%)	0/8 (0%)	0/10 (0%)	0/9 (0%)
Terminal rates	18/53 (34%)	5/37 (14%)	8/34 (24%)	12/52 (23%)
First incidence (days)	528	534	729 (T)	606
Life table tests	P=0.030N	P=0.008N	P=0.023N	P=0.014N
Logistic regression tests	P=0.066N	P=0.026N	P=0.051N	P=0.045N
Cochran-Armitage test	P=0.131N			
Fisher exact test		P=0.105N	P=0.149N	P=0.123N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rates	2/80 (3%)	2/52 (4%)	0/50 (0%)	5/80 (6%)
Adjusted rates	3.4%	4.5%	0.0%	9.3%
Terminal rates	1/53 (2%)	1/38 (3%)	0/34 (0%)	4/52 (8%)
First incidence (days)	670	395	---	705
Life table tests	P=0.171	P=0.549	P=0.349N	P=0.211
Logistic regression tests	P=0.182	P=0.573	P=0.351N	P=0.188
Cochran-Armitage test	P=0.190			
Fisher exact test		P=0.516	P=0.377N	P=0.221
Skin (Subcutaneous Tissue): Fibrosarcoma, Neurofibrosarcoma, or Hemangiosarcoma				
Overall rates	2/80 (3%)	2/52 (4%)	0/50 (0%)	6/80 (8%)
Adjusted rates	3.4%	4.5%	0.0%	10.6%
Terminal rates	1/53 (2%)	1/38 (3%)	0/34 (0%)	4/52 (8%)
First incidence (days)	670	395	---	566
Life table tests	P=0.091	P=0.549	P=0.349N	P=0.131
Logistic regression tests	P=0.106	P=0.573	P=0.351N	P=0.119
Cochran-Armitage test	P=0.103			
Fisher exact test		P=0.516	P=0.377N	P=0.138
Stomach (Forestomach): Squamous Papilloma				
Overall rates	3/80 (4%)	4/52 (8%)	2/50 (4%)	4/80 (5%)
Adjusted rates	5.2%	10.5%	5.9%	6.6%
Terminal rates	2/53 (4%)	4/38 (11%)	2/34 (6%)	2/52 (4%)
First incidence (days)	644	729 (T)	729 (T)	477
Life table tests	P=0.533	P=0.317	P=0.658	P=0.472
Logistic regression tests	P=0.547	P=0.276	P=0.643	P=0.526
Cochran-Armitage test	P=0.547N			
Fisher exact test		P=0.273	P=0.640	P=0.500

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
Thyroid Gland (Follicular Cell): Adenoma				
Overall rates	4/80 (5%)	0/52 (0%)	0/50 (0%)	2/80 (3%)
Adjusted rates	6.7%	0.0%	0.0%	3.6%
Terminal rates	2/53 (4%)	0/38 (0%)	0/34 (0%)	0/52 (0%)
First incidence (days)	644	---	---	707
Life table tests	P=0.358N	P=0.126N	P=0.144N	P=0.368N
Logistic regression tests	P=0.352N	P=0.132N	P=0.140N	P=0.366N
Cochran-Armitage test	P=0.332N			
Fisher exact test		P=0.131N	P=0.139N	P=0.341N
All Organs: Hemangioma				
Overall rates	4/80 (5%)	2/52 (4%)	0/50 (0%)	2/80 (3%)
Adjusted rates	6.8%	5.3%	0.0%	3.7%
Terminal rates	2/53 (4%)	2/38 (5%)	0/34 (0%)	1/52 (2%)
First incidence (days)	592	729 (T)	---	709
Life table tests	P=0.208N	P=0.514N	P=0.142N	P=0.367N
Logistic regression tests	P=0.209N	P=0.550N	P=0.140N	P=0.369N
Cochran-Armitage test	P=0.186N			
Fisher exact test		P=0.557N	P=0.139N	P=0.341N
All Organs: Hemangiosarcoma				
Overall rates	3/80 (4%)	3/52 (6%)	4/50 (8%)	1/80 (1%)
Adjusted rates	5.0%	7.7%	11.4%	1.9%
Terminal rates	2/53 (4%)	2/38 (5%)	3/34 (9%)	1/52 (2%)
First incidence (days)	518	698	724	729 (T)
Life table tests	P=0.269N	P=0.486	P=0.273	P=0.322N
Logistic regression tests	P=0.276N	P=0.455	P=0.252	P=0.306N
Cochran-Armitage test	P=0.244N			
Fisher exact test		P=0.443	P=0.255	P=0.310N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rates	7/80 (9%)	5/52 (10%)	4/50 (8%)	3/80 (4%)
Adjusted rates	11.6%	12.8%	11.4%	5.6%
Terminal rates	4/53 (8%)	4/38 (11%)	3/34 (9%)	2/52 (4%)
First incidence (days)	518	698	724	709
Life table tests	P=0.129N	P=0.599	P=0.557N	P=0.189N
Logistic regression tests	P=0.131N	P=0.553	P=0.578N	P=0.181N
Cochran-Armitage test	P=0.106N			
Fisher exact test		P=0.548	P=0.577N	P=0.164N
All Organs: Histiocytic Sarcoma				
Overall rates	5/80 (6%)	3/52 (6%)	2/50 (4%)	5/80 (6%)
Adjusted rates	7.9%	7.2%	4.9%	8.0%
Terminal rates	2/53 (4%)	2/38 (5%)	0/34 (0%)	1/52 (2%)
First incidence (days)	562	584	587	584
Life table tests	P=0.515	P=0.577N	P=0.452N	P=0.577
Logistic regression tests	P=0.481N	P=0.590N	P=0.405N	P=0.580N
Cochran-Armitage test	P=0.537N			
Fisher exact test		P=0.610N	P=0.451N	P=0.627N

Table D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rates	11/80 (14%)	5/52 (10%)	11/50 (22%)	19/80 (24%)
Adjusted rates	19.3%	12.4%	30.0%	32.6%
Terminal rates	8/53 (15%)	4/38 (11%)	9/34 (26%)	14/52 (27%)
First incidence (days)	652	587	379	241
Life table tests	P=0.012	P=0.282N	P=0.181	P=0.069
Logistic regression tests	P=0.010	P=0.333N	P=0.145	P=0.051
Cochran-Armitage test	P=0.018			
Fisher exact test		P=0.336N	P=0.163	P=0.078
All Organs: Malignant Lymphoma and Histiocytic Sarcoma				
Overall rates	16/80 (20%)	8/52 (15%)	13/50 (26%)	24/80 (30%)
Adjusted rates	26.2%	19.3%	33.4%	38.4%
Terminal rates	10/53 (19%)	6/38 (16%)	9/34 (26%)	15/52 (29%)
First incidence (days)	562	584	379	241
Life table tests	P=0.022	P=0.282N	P=0.301	P=0.089
Logistic regression tests	P=0.023	P=0.335N	P=0.267	P=0.077
Cochran-Armitage test	P=0.031			
Fisher exact test		P=0.333N	P=0.278	P=0.100
All Organs: Malignant Lymphoma and Histiocytic Sarcoma[e]				
Overall rates	17/142 (12%)	8/62 (13%)	13/63 (21%)	24/99 (24%)
Adjusted rates	26.8%	19.3%	33.2%	38.4%
Interim sacrifice 1	0/10 (0%)	0/2 (0%)	0/3 (0%)	0/10 (0%)
Interim sacrifice 2	0/10 (0%)	0/8 (0%)	0/10 (0%)	0/9 (0%)
Terminal rates	10/53 (19%)	6/38 (16%)	9/34 (26%)	15/52 (29%)
First incidence (days)	562	584	379	241
Life table tests	P=0.024	P=0.261N	P=0.322	P=0.092
Logistic regression tests	P=0.005	P=0.434N	P=0.160	P=0.017
Cochran-Armitage test	P=0.004			
Fisher exact test		P=0.509	P=0.082	P=0.011
All Organs: Benign Tumors				
Overall rates	65/80 (81%)	34/52 (65%)	29/50 (58%)	45/80 (56%)
Adjusted rates	92.7%	77.1%	72.3%	73.5%
Terminal rates	48/53 (91%)	28/38 (74%)	23/34 (68%)	36/52 (69%)
First incidence (days)	358	534	527	349
Life table tests	P=0.009N	P=0.016N	P=0.008N	P=0.005N
Logistic regression tests	P=0.006N	P=0.034N	P=0.005N	P=0.003N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.033N	P=0.004N	P<0.001N
All Organs: Malignant Tumors				
Overall rates	34/80 (43%)	25/52 (48%)	25/50 (50%)	44/80 (55%)
Adjusted rates	50.5%	56.4%	59.1%	63.5%
Terminal rates	21/53 (40%)	19/38 (50%)	17/34 (50%)	27/52 (52%)
First incidence (days)	420	395	379	241
Life table tests	P=0.052	P=0.457	P=0.300	P=0.076
Logistic regression tests	P=0.044	P=0.322	P=0.245	P=0.053
Cochran-Armitage test	P=0.071			
Fisher exact test		P=0.326	P=0.256	P=0.077

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	25 ppm	100 ppm	175 ppm
All Organs: Benign and Malignant Tumors				
Overall rates	72/80 (90%)	41/52 (79%)	37/50 (74%)	61/80 (76%)
Adjusted rates	96.0%	87.1%	84.0%	85.8%
Terminal rates	50/53 (94%)	32/38 (84%)	27/34 (79%)	42/52 (81%)
First incidence (days)	358	395	379	241
Life table tests	P=0.211N	P=0.054N	P=0.064N	P=0.155N
Logistic regression tests	P=0.105N	P=0.073N	P=0.024N	P=0.067N
Cochran-Armitage test	P=0.026N			
Fisher exact test		P=0.064N	P=0.016N	P=0.017N

(I)Interim sacrifice
(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals necropsied or examined microscopically for this tumor type
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly to the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Includes paired controls and animals examined at interim sacrifices
[f] Observed incidence at interim sacrifice (interim 1: 165 days; interim 2: 458 days)

TABLE D4a
Historical Incidence of Malignant Lymphoma in Untreated Female $B6C3F_1$ Mice

Study	Incidence of Malignant Lymphoma in Controls
Historical Incidence at Battelle Columbus Laboratory[a]	
Chlorobenzene	17/50
N-phenyl-2-naphthylamine	24/50
Rotenone	9/49
l-ascorbic acid	11/50
2,4-Dichlorophenol	12/50
Diphenylhydantoin	22/50
Dowicide EC-7 pentachlorophenol	15/35
Ethylenethiourea	21/50
Technical grade pentachlorophenol	14/35
Total	145/419 (34.6%)
Standard deviation	10.8%
Range	18%-48%
Overall Historical Incidence	
Total	693/2209 (31.4%)
Standard deviation	14.0%
Range	10%-74%

[a] Data as of 1 January 1990

TABLE D4b
Historical Incidence of Hepatocellular Neoplasms in Untreated Female $B6C3F_1$ Mice

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratory[a]			
Chlorobenzene	4/48	4/48	8/48
N-phenyl-2-naphthylamine	3/50	1/50	4/50
Rotenone	3/49	1/49	4/49
l-ascorbic acid	2/50	1/50	3/50
2,4-Dichlorophenol	0/50	2/50	2/50
Diphenylhydantoin	5/50	0/50	5/50
Dowicide EC-7 pentachlorophenol	1/35	0/35	1/35
Ethylenethiourea	2/50	2/50	4/50
Technical grade pentachlorophenol	3/35	0/35	3/35
Total	23/417 (5.5%)	11/417 (2.6%)	34/417 (8.2%)
Standard deviation	3.2%	2.6%	4.0%
Range	0%-10%	0%-8%	3%-17%
Overall Historical Incidence			
Total	131/2202 (5.9%)	78/2202 (3.5%)	204/2202 (9.3%)
Standard deviation	3.7%	2.4%	4.2%
Range	0%-16%	0%-8%	3%-20%

[a] Data as of 1 January 1990

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

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Disposition Summary					
Animals initially in study	100	50	70	70	99
Early deaths					
Natural death	13	7	5	7	16
Moribund sacrifice	14	6	9	9	12
Survivors					
Terminal sacrifice	53	8	38	32	51
Natural death				2	1
Paired control		29			
Animals examined microscopically	80	42	52	50	80
Alimentary System					
Esophagus	(79)	(42)	(52)	(50)	(80)
Inflammation, chronic active		1 (2%)			
Gallbladder	(79)	(40)	(51)	(48)	(79)
Mineralization	1 (1%)				
Artery, necrosis, fibrinoid				1 (2%)	
Intestine small, duodenum	(80)	(42)	(52)	(48)	(79)
Inflammation, chronic active				2 (4%)	2 (3%)
Intestine small, ileum	(78)	(42)	(52)	(49)	(78)
Lymphoid tissue, hyperplasia		1 (2%)			
Intestine small, jejunum	(80)	(42)	(52)	(49)	(78)
Inflammation, chronic active	1 (1%)				
Lymphoid tissue, hyperplasia	3 (4%)				
Liver	(80)	(42)	(52)	(50)	(80)
Angiectasis				1 (2%)	
Basophilic focus	2 (3%)	6 (14%)	1 (2%)	3 (6%)	
Clear cell focus	3 (4%)	2 (5%)	2 (4%)	2 (4%)	3 (4%)
Eosinophilic focus	22 (28%)	4 (10%)	21 (40%)	8 (16%)	10 (13%)
Hematopoietic cell proliferation	6 (8%)	2 (5%)	3 (6%)	3 (6%)	6 (8%)
Hepatodiaphragmatic nodule		1 (2%)	1 (2%)		1 (1%)
Inflammation, chronic active	2 (3%)			1 (2%)	3 (4%)
Leukocytosis		2 (5%)			
Mineralization				1 (2%)	
Necrosis, coagulative	7 (9%)	4 (10%)	4 (8%)	9 (18%)	3 (4%)
Pigmentation, hemosiderin		1 (2%)		1 (2%)	
Vacuolization cytoplasmic	4 (5%)	5 (12%)	3 (6%)	4 (8%)	3 (4%)
Artery, necrosis, fibrinoid				1 (2%)	
Bile duct, cyst	1 (1%)	1 (2%)	1 (2%)		
Mesentery	(28)	(6)	(15)	(15)	(28)
Hemorrhage	1 (4%)				
Inflammation, chronic active		1 (17%)			1 (4%)
Inflammation, necrotizing	24 (86%)	3 (50%)	12 (80%)	12 (80%)	15 (54%)
Mineralization	11 (39%)		7 (47%)	5 (33%)	4 (14%)
Artery, necrosis, fibrinoid				1 (7%)	
Pancreas	(80)	(42)	(52)	(49)	(79)
Infiltration cellular, lymphocytic			1 (2%)		
Inflammation, chronic active	1 (1%)	1 (2%)			
Acinus, atrophy	3 (4%)			4 (8%)	2 (3%)
Acinus, hyperplasia					2 (3%)
Duct, ectasia				1 (2%)	3 (4%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Alimentary System (continued)					
Salivary glands	(79)	(41)	(52)	(50)	(80)
Duct, ectasia					1 (1%)
Stomach, forestomach	(80)	(42)	(52)	(49)	(79)
Acanthosis	5 (6%)		6 (12%)	5 (10%)	3 (4%)
Diverticulum	1 (1%)	1 (2%)	1 (2%)		
Inflammation, chronic active	3 (4%)	1 (2%)	5 (10%)	3 (6%)	5 (6%)
Stomach, glandular	(80)	(42)	(52)	(49)	(79)
Cyst			1 (2%)		
Erosion	1 (1%)	2 (5%)			3 (4%)
Hyperplasia	2 (3%)				
Inflammation, chronic active			1 (2%)		
Mineralization			1 (2%)		4 (5%)
Tooth	(80)	(42)	(52)	(50)	(80)
Dentine, incisor, dysplasia	33 (41%)	1 (2%)	19 (37%)	22 (44%)	23 (29%)
Dentine, incisor, necrosis				2 (4%)	2 (3%)
Incisor, lower, dysplasia		1 (2%)			
Incisor, ameloblast, atrophy	1 (1%)			1 (2%)	3 (4%)
Incisor, ameloblast, degeneration				1 (2%)	
Peridontal tissue, incisor, inflammation, suppurative				1 (2%)	
Peridontal tissue, incisor, necrosis					1 (1%)
Cardiovascular System					
Blood vessel	(1)			(1)	
Artery, necrosis, fibrinoid				1 (100%)	
Heart	(79)	(41)	(52)	(50)	(80)
Cardiomyopathy, chronic	1 (1%)		1 (2%)	1 (2%)	
Inflammation, chronic active	1 (1%)				
Artery, necrosis, fibrinoid				1 (2%)	
Endocrine System					
Adrenal gland	(79)	(42)	(52)	(50)	(80)
Accessory adrenal cortical nodule	3 (4%)				1 (1%)
Adrenal gland, cortex	(79)	(42)	(52)	(50)	(80)
Cyst				1 (2%)	1 (1%)
Cytoplasmic alteration					1 (1%)
Degeneration, fatty	2 (3%)		3 (6%)	1 (2%)	
Fibrosis			1 (2%)		
Hematopoietic cell proliferation	1 (1%)			1 (2%)	2 (3%)
Hyperplasia	2 (3%)	1 (2%)	1 (2%)		2 (3%)
Hypertrophy	6 (8%)		1 (2%)	4 (8%)	
Capsule, spindle cell, hyperplasia	1 (1%)		1 (2%)	3 (6%)	1 (1%)
Adrenal gland, medulla	(78)	(42)	(52)	(50)	(80)
Hyperplasia	1 (1%)		1 (2%)		
Hypertrophy	1 (1%)				

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Endocrine System (continued)					
Parathyroid gland	(73)	(37)	(51)	(47)	(75)
Cyst	1 (1%)		1 (2%)		1 (1%)
Hyperplasia		1 (3%)			
Pituitary gland	(80)	(41)	(51)	(50)	(79)
Craniopharyngeal duct, pars distalis, cyst				1 (2%)	
Craniopharyngeal duct, pars distalis, inflammation, suppurative				1 (2%)	
Pars distalis, cyst	5 (6%)	1 (2%)		4 (8%)	2 (3%)
Pars distalis, hyperplasia	15 (19%)	1 (2%)	20 (39%)	16 (32%)	25 (32%)
Thyroid gland	(80)	(42)	(52)	(50)	(80)
Inflammation, chronic active	1 (1%)	1 (2%)	1 (2%)	2 (4%)	2 (3%)
Ultimobranchial cyst	1 (1%)		1 (2%)		3 (4%)
Follicle, cyst					1 (1%)
Follicular cell, hyperplasia	30 (38%)	8 (19%)	27 (52%)	24 (48%)	33 (41%)
General Body System					
None					
Genital System					
Clitoral gland	(2)		(2)		(3)
Pigmentation, melanin	1 (50%)				
Duct, dilatation	1 (50%)		1 (50%)		
Ovary	(78)	(41)	(50)	(50)	(80)
Atrophy	63 (81%)	14 (34%)	38 (76%)	39 (78%)	59 (74%)
Cyst	24 (31%)	12 (29%)	22 (44%)	16 (32%)	23 (29%)
Inflammation, chronic active		1 (2%)			
Mineralization	1 (1%)		1 (2%)		
Necrosis, coagulative		1 (2%)			1 (1%)
Thrombus			2 (4%)		1 (1%)
Uterus	(80)	(42)	(52)	(50)	(80)
Angiectasis	1 (1%)				1 (1%)
Dilatation	13 (16%)	11 (26%)	13 (25%)	6 (12%)	13 (16%)
Hyperplasia, cystic, glandular	71 (89%)	34 (81%)	46 (88%)	47 (94%)	72 (90%)
Inflammation, necrotizing	1 (1%)				
Inflammation, suppurative					1 (1%)
Hematopoietic System					
Bone marrow	(80)	(42)	(52)	(50)	(80)
Femoral, hyperplasia, mast cell	1 (1%)				
Femoral, myelofibrosis	32 (40%)	5 (12%)	32 (62%)	31 (62%)	45 (56%)
Humerus, myelofibrosis	26 (33%)	7 (17%)	26 (50%)	20 (40%)	40 (50%)
Mandible, myelofibrosis	1 (1%)				1 (1%)
Maxilla, hyperplasia, mast cell	1 (1%)				
Maxilla, myelofibrosis	18 (23%)	3 (7%)	19 (37%)	21 (42%)	42 (53%)
Thoracic, vertebra, myelofibrosis	55 (69%)	20 (48%)	43 (83%)	41 (82%)	65 (81%)
Tibia, myelofibrosis	13 (16%)	3 (7%)	15 (29%)	9 (18%)	23 (29%)

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Hematopoietic System (continued)					
Lymph node	(80)	(42)	(52)	(50)	(80)
Mediastinal, hyperplasia, plasma cell		1 (2%)			
Renal, sinus, ectasia				1 (2%)	
Lymph node, mandibular	(76)	(42)	(52)	(47)	(79)
Hyperplasia, lymphoid					2 (3%)
Lymph node, mesenteric	(79)	(40)	(49)	(49)	(77)
Hyperplasia, plasma cell	1 (1%)				
Sinus, ectasia	1 (1%)		1 (2%)	1 (2%)	
Spleen	(79)	(42)	(52)	(50)	(80)
Depletion lymphoid				1 (2%)	
Fibrosis				1 (2%)	
Hematopoietic cell proliferation	20 (25%)	10 (24%)	15 (29%)	15 (30%)	20 (25%)
Hemorrhage					1 (1%)
Hyperplasia, lymphoid	10 (13%)	3 (7%)	7 (13%)	7 (14%)	11 (14%)
Thymus	(76)	(42)	(48)	(45)	(73)
Cyst	3 (4%)	3 (7%)	6 (13%)	1 (2%)	4 (5%)
Ectopic parathyroid gland		1 (2%)			
Hyperplasia, lymphoid			3 (6%)		2 (3%)
Artery, necrosis, fibrinoid				1 (2%)	
Thymocyte, necrosis		1 (2%)			
Integumentary System					
Mammary gland	(78)	(41)	(51)	(50)	(80)
Hyperplasia, cystic	8 (10%)	7 (17%)	8 (16%)	8 (16%)	7 (9%)
Inflammation, chronic active		1 (2%)			
Skin	(80)	(42)	(52)	(50)	(80)
Acanthosis	1 (1%)				
Alopecia				1 (2%)	
Cyst epithelial inclusion			1 (2%)		
Hyperkeratosis	1 (1%)				
Inflammation, chronic active	2 (3%)		2 (4%)	1 (2%)	2 (3%)
Mineralization	1 (1%)				
Artery, necrosis, fibrinoid				1 (2%)	
Hair follicle, cyst	1 (1%)				
Musculoskeletal System					
Bone	(80)	(42)	(52)	(50)	(80)
Femur, osteosclerosis					1 (1%)
Humerus, osteosclerosis	2 (3%)				2 (3%)
Humerus, periosteum, proliferation, focal			1 (2%)		
Intervertebral disc, degeneration	14 (18%)	2 (5%)	13 (25%)	8 (16%)	16 (20%)
Mandible, inflammation, suppurative		1 (2%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Musculoskeletal System					
Bone (continued)					
Periosteum, tibia, proliferation, focal	1 (1%)				
Periosteum, maxilla, proliferation, focal			1 (2%)		
Rib, cartilage, degeneration			1 (2%)	1 (2%)	1 (1%)
Rib, cartilage, necrosis	1 (1%)				
Thoracic, vertebra, osteosclerosis	1 (1%)		1 (2%)		3 (4%)
Tibia, osteosclerosis		1 (2%)			2 (3%)
Skeletal muscle	(2)	(1)		(1)	(1)
Inflammation, chronic active		1 (100%)			
Nervous System					
Brain	(80)	(42)	(52)	(50)	(80)
Compression	3 (4%)		2 (4%)	2 (4%)	1 (1%)
Hydrocephalus	3 (4%)		1 (2%)	1 (2%)	
Inflammation, chronic active					1 (1%)
Artery, necrosis, fibrinoid				1 (2%)	
Neuron, necrosis			1 (2%)		
White matter, degeneration			1 (2%)		
Peripheral nerve	(1)		(1)	(3)	(1)
Sciatic, degeneration			1 (100%)	1 (33%)	
Spinal, degeneration				1 (33%)	
Spinal cord	(1)		(1)	(3)	(1)
White matter, degeneration				1 (33%)	1 (100%)
Respiratory System					
Lung	(80)	(42)	(52)	(50)	(80)
Inflammation, chronic active	3 (4%)	1 (2%)	4 (8%)	1 (2%)	2 (3%)
Leukocytosis		2 (5%)		1 (2%)	
Mineralization			1 (2%)	1 (2%)	
Pigmentation, hemosiderin			1 (2%)		
Alveolar epithelium, hyperplasia	2 (3%)	2 (5%)	3 (6%)	1 (2%)	
Nose	(80)	(42)	(52)	(50)	(80)
Inflammation, chronic active		1 (2%)		1 (2%)	
Nasolacrimal duct, inflammation, suppurative	1 (1%)		1 (2%)	3 (6%)	1 (1%)
Special Senses System					
Ear			(1)	(1)	(1)
Middle ear, inflammation, suppurative				1 (100%)	
Eye	(1)	(1)	(2)	(2)	
Inflammation, chronic active	1 (100%)				
Phthisis bulbi			1 (50%)		
Cornea, inflammation, chronic active				2 (100%)	
Lens, cataract			1 (50%)		
Retina, atrophy			1 (50%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Special Senses System (continued)					
Harderian gland	(49)	(36)	(42)	(37)	(34)
Hyperplasia		1 (3%)	1 (2%)		
Inflammation, chronic active		1 (3%)			
Urinary System					
Kidney	(80)	(42)	(52)	(50)	(80)
Atypical cells					1 (1%)
Cyst		1 (2%)	2 (4%)		1 (1%)
Hydronephrosis	1 (1%)			1 (2%)	
Hypertrophy	1 (1%)				
Metaplasia, osseous			1 (2%)	1 (2%)	1 (1%)
Mineralization	63 (79%)	22 (52%)	34 (65%)	26 (52%)	28 (35%)
Necrosis, coagulative		1 (2%)			
Nephropathy, chronic	50 (63%)	12 (29%)	38 (73%)	27 (54%)	25 (31%)
Artery, necrosis, fibrinoid				1 (2%)	
Perivascular, hyperplasia, lymphoid					2 (3%)
Renal tubule, necrosis					3 (4%)
Urinary bladder	(80)	(42)	(52)	(50)	(78)
Inflammation, necrotizing	1 (1%)				

APPENDIX E
SUMMARY OF LESIONS IN MALE AND FEMALE RATS AND MICE AT THE FIRST INTERIM EVALUATION

TABLE E1
Summary of the Incidence of Neoplasms and Nonneoplastic Lesions in Male Rats Sacrificed at 27 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Animals sacrificed	10		10	10	9
Animals examined microscopically	10		10	10	9
Neoplasms					
None					
Nonneoplastic Lesions					
Alimentary System					
Intestine large, rectum	(10)				(9)
Parasite metazoan	1 (10%)				1 (11%)
Liver	(10)				(9)
Clear cell focus					1 (11%)
Inflammation, chronic active	2 (20%)				
Centrilobular, vacuolization cytoplasmic	1 (10%)				
Pancreas	(10)				(9)
Acinus, atrophy	4 (40%)				1 (11%)
Cardiovascular System					
Heart	(10)				(9)
Degeneration, chronic	9 (90%)				7 (78%)
Endocrine System					
Pituitary gland	(10)				(9)
Pars distalis, cyst	1 (10%)				
Integumentary System					
Mammary gland	(9)				(9)
Hemorrhage					1 (11%)
Hyperplasia, cystic	9 (100%)				7 (78%)
Respiratory System					
Nose	(10)				(9)
Mucosa, inflammation, acute					1 (11%)
Sinus, foreign body					1 (11%)
Urinary System					
Kidney	(10)				(9)
Nephropathy, chronic	9 (90%)				9 (100%)

[a] Only those systems in which lesions were found are presented here. A complete list of tissues examined is presented in Table 1 in Materials and Methods.

TABLE E2
Summary of the Incidence of Neoplasms and Nonneoplastic Lesions in Female Rats Sacrificed at 27 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Animals sacrificed	10		10	10	10
Animals examined microscopically	10		10	10	10
Neoplasms					
None					
Nonneoplastic Lesions					
Alimentary System					
Liver	(10)				(10)
Hepatodiaphragmatic nodule					1 (10%)
Mesentery	(1)				
Inflammation, chronic active	1 (100%)				
Pancreas	(10)				(10)
Acinus, atrophy	1 (10%)				
Stomach, forestomach	(10)				(10)
Acanthosis	1 (10%)				
Cardiovascular System					
Heart	(10)				(10)
Degeneration, chronic					2 (20%)
Endocrine System					
Pituitary gland	(9)				(10)
Pars distalis, hyperplasia	1 (11%)				
Genital System					
Ovary	(10)				(10)
Periovarian tissue, cyst					1 (10%)
Integumentary System					
Mammary gland	(10)				(9)
Hyperplasia, cystic	3 (30%)				1 (11%)
Musculoskeletal System					
Bone	(10)		(10)	(10)	(10)
Thoracic, vertebra, fibrous osteodystrophy	1 (10%)				
Tibia, fibrous osteodystrophy	1 (10%)				

TABLE E2
Summary of the Incidence of Neoplasms and Nonneoplastic Lesions in Female Rats Sacrificed at 27 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a] (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Urinary System					
Kidney	(10)				(10)
Nephropathy, chronic	3 (30%)				
Renal tubule, mineralization	9 (90%)				2 (20%)

[a] Only those systems in which lesions were found are presented here. A complete list of tissues examined is presented in Table 1 in Materials and Methods.

TABLE E3
Summary of the Incidence of Neoplasms and Nonneoplastic Lesions in Male Mice Sacrificed at 24 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Animals sacrificed	10		10	10	10
Animals examined microscopically	10			2	10
Neoplasms					
None					
Nonneoplastic Lesions					
Alimentary System					
Mesentery				(1)	
Inflammation, chronic active				1 (100%)	
Tooth	(1)				
Dentine, incisor, dysplasia	1 (100%)				
Special Senses System					
Eye	(1)				
Cornea, mineralization	1 (100%)				
Lens, cataract	1 (100%)				
Retina, atrophy	1 (100%)				

[a] Only those systems in which lesions were found are presented here. A complete list of tissues examined is presented in Table 1 in Materials and Methods.

TABLE E4
Summary of the Incidence of Neoplasms and Nonneoplastic Lesions in Female Mice Sacrificed at 24 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Animals sacrificed	10		10	10	10
Animals examined microscopically	10		2	3	10
Neoplasms					
None					
Nonneoplastic Lesions					
Hematopoietic System					
Bone marrow	(10)		(2)	(1)	(10)
Femoral, myelofibrosis				1 (100%)	
Humerus, myelofibrosis	1 (10%)				2 (20%)
Thoracic, vertebra, myelofibrosis			2 (100%)		
Tibia, myelofibrosis					1 (10%)

[a] Only those systems in which lesions were found are presented here. A complete list of tissues examined is presented in Table 1 in Materials and Methods.

APPENDIX F
SUMMARY OF LESIONS IN MALE AND FEMALE RATS AND MICE AT THE SECOND INTERIM EVALUATION

TABLE F1
Summary of the Incidence of Neoplasms in Male Rats Sacrificed at 66 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Animals sacrificed	9		9	10	10
Animals examined microscopically	9		9	10	10
Alimentary System					
Liver	(9)		(9)	(10)	(10)
Leukemia mononuclear	3 (33%)			2 (20%)	
Endocrine System					
Adrenal gland, medulla	(9)		(9)	(10)	(10)
Pheochromocytoma benign			1 (11%)	1 (10%)	
Pituitary gland	(9)		(9)	(10)	(10)
Pars distalis, adenoma	1 (11%)				2 (20%)
Thyroid gland	(9)		(9)	(10)	(10)
C-cell, adenoma				1 (10%)	1 (10%)
Follicular cell, carcinoma					1 (10%)
Genital System					
Preputial gland	(9)		(9)	(10)	(10)
Adenoma			1 (11%)		1 (10%)
Testes	(9)		(9)	(10)	(10)
Bilateral, interstitial cell, adenoma	1 (11%)		1 (11%)	1 (10%)	1 (10%)
Interstitial cell, adenoma	1 (11%)		5 (56%)	5 (50%)	3 (30%)
Hematopoietic System					
Lymph node, mandibular	(9)		(9)	(10)	(10)
Leukemia mononuclear	2 (22%)			2 (20%)	
Lymph node, mesenteric	(9)		(9)	(10)	(10)
Leukemia mononuclear	2 (22%)			1 (10%)	
Spleen	(9)		(9)	(10)	(10)
Leukemia mononuclear	3 (33%)			2 (20%)	
Integumentary System					
Skin	(9)		(9)	(10)	(10)
Keratoacanthoma				1 (10%)	
Respiratory System					
Lung	(9)		(9)	(10)	(10)
Alveolar/bronchiolar adenoma				1 (10%)	1 (10%)

TABLE F1
Summary of the Incidence of Neoplasms in Male Rats Sacrificed at 66 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a] (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Special Senses System					
Ear			(1)		
Pinna, fibroma			1 (100%)		
Urinary System					
Kidney	(9)		(9)	(10)	(10)
Renal tubule, adenoma			1 (11%)		
Systemic Lesions					
Multiple organs[b]	(9)		(9)	(10)	(10)
Leukemia mononuclear	3 (33%)			3 (30%)	
Tumor Summary					
Total animals with primary neoplasms[c]	4		7	8	8
Total primary neoplasms	6		10	13	10
Total animals with benign neoplasms	3		7	7	7
Total benign neoplasms	3		10	10	9
Total animals with malignant neoplasms	3			3	1
Total malignant neoplasms	3			3	1

[a] Only those systems in which lesions were found are presented here. A complete list of tissues examined is presented in Table 1 in Materials and Methods.
[b] The number in parentheses is the number of animals with any tissue examined microscopically.
[c] Primary tumors: all tumors except metastatic tumors

TABLE F2
Summary of the Incidence of Nonneoplastic Lesions in Male Rats Sacrificed at 66 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Animals sacrificed	9		9	10	10
Animals examined microscopically	9		9	10	10
Alimentary System					
Liver	(9)		(9)	(10)	(10)
Basophilic focus	3 (33%)		1 (11%)		2 (20%)
Clear cell focus	1 (11%)			2 (20%)	1 (10%)
Degeneration, cystic				1 (10%)	
Hepatodiaphragmatic nodule			1 (11%)	1 (10%)	
Inflammation, chronic active	8 (89%)		9 (100%)	7 (70%)	8 (80%)
Vacuolization cytoplasmic	8 (89%)		7 (78%)	8 (80%)	9 (90%)
Bile duct, hyperplasia	8 (89%)		9 (100%)	10 (100%)	6 (60%)
Mesentery					(2)
Fat, inflammation, chronic active					2 (100%)
Pancreas	(9)		(9)	(10)	(10)
Acinus, atrophy	5 (56%)		3 (33%)	4 (40%)	1 (10%)
Tooth	(9)		(9)	(10)	(10)
Dentine, incisor, dysplasia					1 (10%)
Incisor, ameloblast, degeneration					1 (10%)
Periodontal tissue, inflammation, chronic					1 (10%)
Periodontal tissue, molar, inflammation, suppurative	4 (44%)			1 (10%)	2 (20%)
Cardiovascular System					
Heart	(9)		(9)	(10)	(10)
Degeneration, chronic	9 (100%)		8 (89%)	9 (90%)	9 (90%)
Endocrine System					
Adrenal gland, medulla	(9)		(9)	(10)	(10)
Hyperplasia				1 (10%)	
Pituitary gland	(9)		(9)	(10)	(10)
Pars distalis, cyst	1 (11%)		1 (11%)	1 (10%)	
Pars distalis, hyperplasia	3 (33%)		4 (44%)	3 (30%)	2 (20%)
Thyroid gland	(9)		(9)	(10)	(10)
C-cell, hyperplasia			1 (11%)	2 (20%)	2 (20%)
Genital System					
Preputial gland	(9)		(9)	(10)	(10)
Hyperplasia	1 (11%)		1 (11%)	1 (10%)	1 (10%)
Inflammation, chronic active	6 (67%)		5 (56%)	7 (70%)	5 (50%)
Testes	(9)		(9)	(10)	(10)
Interstitial cell, hyperplasia	9 (100%)		9 (100%)	10 (100%)	9 (90%)

TABLE F2
Summary of the Incidence of Nonneoplastic Lesions in Male Rats Sacrificed at 66 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a] (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Hematopoietic System					
Spleen	(9)		(9)	(10)	(10)
Fibrosis			1 (11%)		
Integumentary System					
Mammary gland	(8)		(9)	(10)	(10)
Hyperplasia, cystic	8 (100%)		8 (89%)	10 (100%)	10 (100%)
Musculoskeletal System					
Bone	(9)		(9)	(10)	(10)
Humerus, ligament, metaplasia, cartilaginous, focal	1 (11%)				
Respiratory System					
Lung	(9)		(9)	(10)	(10)
Inflammation, chronic active, focal				1 (10%)	
Alveolar epithelium, hyperplasia	1 (11%)				
Nose	(9)		(9)	(10)	(10)
Inflammation, chronic active	4 (44%)		1 (11%)	3 (30%)	3 (30%)
Metaplasia, squamous	2 (22%)			1 (10%)	3 (30%)
Special Senses System					
Eye	(1)				
Lens, cataract	1 (100%)				
Retina, atrophy	1 (100%)				
Urinary System					
Kidney	(9)		(9)	(10)	(10)
Nephropathy, chronic	9 (100%)		9 (100%)	10 (100%)	10 (100%)

[a] Only those systems in which lesions were found are presented here. A complete list of tissues examined is presented in Table 1 in Materials and Methods.

TABLE F3
Summary of the Incidence of Neoplasms in Female Rats Sacrificed at 66 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Animals sacrificed	10		10	10	9
Animals examined microscopically	10		10	10	9
Alimentary System					
Liver	(10)		(10)	(10)	(9)
Leukemia mononuclear			1 (10%)		2 (22%)
Endocrine System					
Pituitary gland	(10)		(10)	(10)	(9)
Pars distalis, adenoma			3 (30%)	2 (20%)	1 (11%)
Thyroid gland	(10)		(10)	(10)	(9)
C-cell, adenoma			1 (10%)		
Genital System					
Uterus	(10)		(10)	(10)	(9)
Polyp stromal				1 (10%)	
Hematopoietic System					
Lymph node, mandibular	(10)		(10)	(9)	(9)
Leukemia mononuclear					1 (11%)
Spleen	(10)		(10)	(10)	(9)
Leukemia mononuclear			1 (10%)		2 (22%)
Integumentary System					
Skin	(10)		(10)	(10)	(9)
Subcutaneous tissue, fibroma					1 (11%)
Subcutaneous tissue, fibrous histiocytoma					1 (11%)
Respiratory System					
Lung	(10)		(10)	(10)	(9)
Alveolar/bronchiolar carcinoma				1 (10%)	
Systemic Lesions					
Multiple organs[b]	(10)		(10)	(10)	(9)
Leukemia mononuclear			1 (10%)		2 (22%)

TABLE F3
Summary of the Incidence of Neoplasms in Female Rats Sacrificed at 66 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a] (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Tumor Summary					
Total animals with primary neoplasms[c]			4	3	3
Total primary neoplasms			5	4	5
Total animals with benign neoplasms			3	3	2
Total benign neoplasms			4	3	2
Total animals with malignant neoplasms			1	1	2
Total malignant neoplasms			1	1	3

[a] Only those systems in which lesions were found are presented here. A complete list of tissues examined is presented in Table 1 in Materials and Methods.
[b] The number in parentheses is the number of animals with any tissue examined microscopically.
[c] Primary tumors: all tumors except metastatic tumors

TABLE F4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats Sacrificed at 66 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Animals sacrificed	10		10	10	9
Animals examined microscopically	10		10	10	9
Alimentary System					
Liver	(10)		(10)	(10)	(9)
Basophilic focus	3 (30%)		6 (60%)	1 (10%)	3 (33%)
Hepatodiaphragmatic nodule	1 (10%)		1 (10%)	2 (20%)	1 (11%)
Inflammation, chronic active	5 (50%)		4 (40%)	5 (50%)	5 (56%)
Bile duct, hyperplasia	1 (10%)		4 (40%)	4 (40%)	1 (11%)
Pancreas	(10)		(10)	(10)	(9)
Acinus, atrophy	1 (10%)		3 (30%)		2 (22%)
Tooth	(10)		(10)	(10)	(9)
Periodontal tissue, molar, inflammation, suppurative	1 (10%)		2 (20%)		3 (33%)
Cardiovascular System					
Heart	(10)		(10)	(10)	(9)
Degeneration, chronic	6 (60%)		4 (40%)	5 (50%)	4 (44%)
Endocrine System					
Adrenal gland, cortex	(10)		(10)	(10)	(9)
Angiectasis			1 (10%)		
Hyperplasia			1 (10%)		
Hypertrophy	1 (10%)				1 (11%)
Adrenal gland, medulla	(10)		(10)	(10)	(9)
Angiectasis			1 (10%)		
Pituitary gland	(10)		(10)	(10)	(9)
Pars distalis, cyst	3 (30%)		4 (40%)	2 (20%)	1 (11%)
Pars distalis, hyperplasia	5 (50%)		2 (20%)	3 (30%)	2 (22%)
Thyroid gland	(10)		(10)	(10)	(9)
C-cell, hyperplasia	1 (10%)				1 (11%)
Genital System					
Clitoral gland	(10)		(10)	(10)	(9)
Hyperplasia					1 (11%)
Inflammation, chronic active	1 (10%)		2 (20%)		1 (11%)
Duct, cyst				1 (10%)	
Ovary	(10)		(10)	(10)	(9)
Periovarian tissue, cyst				1 (10%)	
Uterus	(10)		(10)	(10)	(9)
Endometrium, hyperplasia, cystic, glandular	4 (40%)		3 (30%)	4 (40%)	3 (33%)

Table F4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats Sacrificed at 66 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a] (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Hematopoietic System					
Thymus	(10)		(10)	(9)	(9)
Depletion lymphoid				1 (11%)	
Integumentary System					
Mammary gland	(10)		(10)	(10)	(9)
Hyperplasia, cystic	4 (40%)		5 (50%)	5 (50%)	2 (22%)
Musculoskeletal System					
Bone	(10)		(10)	(10)	(9)
Femur, osteosclerosis				1 (10%)	
Humerus, osteosclerosis				1 (10%)	
Mandible, fibrous osteodystrophy	1 (10%)				
Maxilla, osteosclerosis				1 (10%)	
Thoracic, vertebra, osteosclerosis				1 (10%)	
Tibia, osteosclerosis			1 (10%)	2 (20%)	
Vertebra, osteosclerosis			1 (10%)		
Respiratory System					
Lung	(10)		(10)	(10)	(9)
Alveolar epithelium, hyperplasia, focal				1 (10%)	
Nose	(10)		(10)	(10)	(9)
Inflammation, chronic active	1 (10%)		1 (10%)	1 (10%)	1 (11%)
Metaplasia, squamous			1 (10%)	1 (10%)	
Special Senses System					
Eye	(1)		(1)	(1)	
Lens, cataract			1 (100%)	1 (100%)	
Retina, atrophy			1 (100%)	1 (100%)	
Urinary System					
Kidney	(10)		(10)	(10)	(9)
Nephropathy, chronic	9 (90%)		10 (100%)	9 (90%)	6 (67%)

[a] Only those systems in which lesions were found are presented here. A complete list of tissues examined is presented in Table 1 in Materials and Methods.

Table F5
Summary of the Incidence of Neoplasms in Male Mice Sacrificed at 66 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Animals sacrificed	10		10	9	10
Animals examined microscopically	10		10	9	10
Alimentary System					
Liver	(10)		(10)	(9)	(10)
Hemangiosarcoma	1 (10%)				
Hemangiosarcoma, multiple	1 (10%)				
Hepatocellular carcinoma				1 (11%)	
Hepatocellular adenoma	2 (20%)		3 (30%)	2 (22%)	5 (50%)
Hepatocellular adenoma, multiple	2 (20%)		2 (20%)		
Cardiovascular System					
Heart	(10)		(10)	(9)	(10)
Hemangiosarcoma, metastatic, liver	1 (10%)				
Musculoskeletal System					
Bone	(10)		(10)	(9)	(10)
Femur, osteosarcoma			1 (10%)		
Respiratory System					
Lung	(10)		(10)	(9)	(10)
Alveolar/bronchiolar adenoma	1 (10%)			1 (11%)	
Special Senses System					
Harderian gland	(10)		(7)	(9)	(8)
Adenoma					1 (13%)
Tumor Summary					
Total animals with primary neoplasms[b]	6		6	4	5
Total primary neoplasms	7		6	4	6
Total animals with benign neoplasms	5		5	3	5
Total benign neoplasms	5		5	3	6
Total animals with malignant neoplasms	2		1	1	
Total malignant neoplasms	2		1	1	
Total animals with secondary neoplasms[c]	1				
Total secondary neoplasms	1				

[a] Only those systems in which lesions were found are presented here. A complete list of tissues examined is presented in Table 1 in Materials and Methods.
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE F6
Summary of the Incidence of Nonneoplastic Lesions in Male Mice Sacrificed at 66 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Animals sacrificed	10		10	9	10
Animals examined microscopically	10		10	9	10
Alimentary System					
Intestine small, jejunum	(10)		(10)	(9)	(10)
Peyer's patch, hyperplasia, lymphoid			2 (20%)		
Liver	(10)		(10)	(9)	(10)
Clear cell focus	6 (60%)		7 (70%)	2 (22%)	6 (60%)
Eosinophilic focus	2 (20%)		2 (20%)	1 (11%)	
Mixed cell focus					2 (20%)
Necrosis, coagulative	1 (10%)				1 (10%)
Vacuolization cytoplasmic	8 (80%)		9 (90%)	9 (100%)	9 (90%)
Mesentery	(2)		(1)		
Inflammation, necrotizing	2 (100%)		1 (100%)		
Pancreas	(10)		(10)	(9)	(10)
Inflammation, chronic active	1 (10%)				
Acinus, atrophy	2 (20%)				1 (10%)
Stomach, glandular	(10)		(10)	(9)	(10)
Mineralization				1 (11%)	
Tooth	(10)		(10)	(9)	(10)
Dentine, incisor, dysplasia	6 (60%)		8 (80%)	5 (56%)	9 (90%)
Endocrine System					
Adrenal gland, cortex	(10)		(10)	(9)	(10)
Hypertrophy				1 (11%)	
Bilateral, capsule, spindle cell, Hyperplasia	1 (10%)				
Capsule, spindle cell, hyperplasia			2 (20%)	2 (22%)	3 (30%)
Islets, pancreatic	(10)		(10)	(9)	(10)
Hyperplasia				1 (11%)	1 (10%)
Genital System					
Preputial gland	(2)		(2)	(2)	(2)
Duct, dilatation	2 (100%)		2 (100%)	2 (100%)	2 (100%)
Seminal vesicle	(10)		(10)	(9)	(10)
Inflammation, chronic active					1 (10%)
Hematopoietic System					
Bone marrow	(10)		(10)	(9)	(10)
Femoral, myelofibrosis					1 (10%)
Lymph node, mesenteric	(10)		(10)	(9)	(10)
Hyperplasia, lymphoid			2 (20%)		
Thymus	(10)		(10)	(8)	(9)
Cyst	1 (10%)		5 (50%)		

Table F6
Summary of the Incidence of Nonneoplastic Lesions in Male Mice Sacrificed at 66 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a] (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Respiratory System					
Lung	(10)		(10)	(9)	(10)
Inflammation, chronic active	1 (10%)				
Alveolar epithelium, hyperplasia	1 (10%)		1 (10%)	1 (11%)	
Nose	(10)		(10)	(9)	(10)
Nasolacrimal duct, inflammation, suppurative			1 (10%)		
Urinary System					
Kidney	(10)		(10)	(9)	(10)
Cyst			1 (10%)		
Nephropathy, chronic	10 (100%)		10 (100%)	8 (89%)	9 (90%)

[a] Only those systems in which lesions were found are presented here. A complete list of tissues examined is presented in Table 1 in Materials and Methods.

TABLE F7
Summary of the Incidence of Neoplasms in Female Mice Sacrificed at 66 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Animals sacrificed	10		8	10	9
Animals examined microscopically	10		8	10	9
Alimentary System					
Liver	(10)		(8)	(10)	(9)
Hepatocellular carcinoma					1 (11%)
Hepatocellular adenoma	3 (30%)		2 (25%)	2 (20%)	2 (22%)
Hepatocellular adenoma, multiple			2 (25%)	1 (10%)	
Endocrine System					
Thyroid gland	(10)		(8)	(10)	(9)
Follicular cell, adenocarcinoma			1 (13%)		
Genital System					
Ovary	(10)		(7)	(8)	(8)
Cystadenoma					1 (13%)
Uterus	(10)		(8)	(10)	(9)
Polyp stromal	1 (10%)				
Hematopoietic System					
Spleen	(10)		(8)	(9)	(9)
Hemangiosarcoma	1 (10%)				
Special Senses System					
Harderian gland	(9)		(6)	(8)	(8)
Adenoma				1 (13%)	
Tumor Summary					
Total animals with primary neoplasms[b]	5		4	3	4
Total primary neoplasms	5		5	4	4
Total animals with benign neoplasms	4		4	3	3
Total benign neoplasms	4		4	4	3
Total animals with malignant neoplasms	1		1		1
Total malignant neoplasms	1		1		1

[a] Only those systems in which lesions were found are presented here. A complete list of tissues examined is presented in Table 1 in Materials and Methods.
[b] Primary tumors: all tumors except metastatic tumors

TABLE F8
Summary of the Incidence of Nonneoplastic Lesions in Female Mice Sacrificed at 66 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Animals sacrificed	10		8	10	9
Animals examined microscopically	10		8	10	9
Alimentary System					
Gallbladder	(10)		(8)	(10)	(9)
Cyst			1 (13%)		
Liver	(10)		(8)	(10)	(9)
Eosinophilic focus	1 (10%)		1 (13%)	3 (30%)	2 (22%)
Vacuolization cytoplasmic	2 (20%)		1 (13%)	3 (30%)	3 (33%)
Mesentery			(1)	(3)	
Inflammation, necrotizing			1 (100%)	2 (67%)	
Pancreas	(10)		(8)	(10)	(9)
Inflammation, chronic active			1 (13%)		
Tooth	(10)		(8)	(10)	(9)
Dentine, incisor, dysplasia	1 (10%)		2 (25%)	1 (10%)	1 (11%)
Endocrine System					
Adrenal gland, cortex	(10)		(8)	(10)	(9)
Hyperplasia	1 (10%)				
Pituitary gland	(10)		(8)	(10)	(9)
Pars distalis, hyperplasia	1 (10%)				
Thyroid gland	(10)		(8)	(10)	(9)
Ultimobranchial cyst				1 (10%)	
Genital System					
Ovary	(10)		(7)	(8)	(8)
Cyst			3 (43%)		2 (25%)
Uterus	(10)		(8)	(10)	(9)
Dilatation			1 (13%)		1 (11%)
Hyperplasia, cystic, glandular	10 (100%)		8 (100%)	9 (90%)	9 (100%)
Hematopoietic System					
Bone marrow	(10)		(8)	(10)	(9)
Femoral, myelofibrosis	2 (20%)		2 (25%)	2 (20%)	8 (89%)
Humerus, myelofibrosis	1 (10%)		1 (13%)	6 (60%)	5 (56%)
Maxilla, myelofibrosis	1 (10%)		1 (13%)		2 (22%)
Thoracic, vertebra, myelofibrosis	6 (60%)		5 (63%)	8 (80%)	9 (100%)
Tibia, myelofibrosis	1 (10%)		1 (13%)		2 (22%)
Thymus	(10)		(8)	(10)	(9)
Cyst	1 (10%)			3 (30%)	2 (22%)

TABLE F8
Summary of the Incidence of Nonneoplastic Lesions in Female Mice Sacrificed at 66 Weeks in the 2-Year Drinking Water Studies of Sodium Fluoride[a] (continued)

	Control	Paired Control	25 ppm	100 ppm	175 ppm
Respiratory System					
Lung	(10)		(8)	(10)	(9)
Inflammation, chronic active					1 (11%)
Special Senses System					
Harderian gland	(9)		(6)	(8)	(8)
Hyperplasia			1 (17%)		
Urinary System					
Kidney	(10)		(8)	(10)	(9)
Nephropathy, chronic	2 (20%)		5 (63%)	2 (20%)	1 (11%)

[a] Only those systems in which lesions were found are presented here. A complete list of tissues examined is presented in Table 1 in Materials and Methods.

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

TABLE G1
Organ Weights for Rats at the 27-Week Interim Evaluation in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

Organ	Control	25 ppm	100 ppm	175 ppm
Male				
n	10	10	10	9
Necropsy body wt (g)	399 ± 6	408 ± 8	415 ± 5	413 ± 6
Liver	14.11 ± 0.41	15.42 ± 0.54	15.71 ± 0.44*	15.18 ± 0.40
R. kidney	1.32 ± 0.03	1.28 ± 0.04	1.44 ± 0.02*	1.37 ± 0.02
L. kidney	1.37 ± 0.04	1.33 ± 0.06	1.44 ± 0.02	1.38 ± 0.03
Brain	2.03 ± 0.02	2.02 ± 0.03	2.07 ± 0.02	2.01 ± 0.02
Female				
n	10	10	10	10
Necropsy body wt (g)	229 ± 2	225 ± 5	235 ± 5	221 ± 4
Liver	7.69 ± 0.29	7.32 ± 0.43	7.54 ± 0.25	6.90 ± 0.17
R. kidney	0.78 ± 0.02	0.77 ± 0.02	0.84 ± 0.02	0.76 ± 0.02
L. kidney	0.80 ± 0.02	0.78 ± 0.02	0.86 ± 0.02	0.77 ± 0.02
Brain	1.90 ± 0.03	1.86 ± 0.02	1.89 ± 0.03	1.87 ± 0.02

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
a Organ and body weights are reported in grams. Mean ± standard error

TABLE G2
Organ-Weight-to-Body-Weight Ratios for Rats at the 27-Week Interim Evaluation in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

Organ	Control	25 ppm	100 ppm	175 ppm
Male				
n	10	10	10	9
Necropsy body wt (g)	399 ± 6	408 ± 8	415 ± 5	413 ± 6
Liver	35.3 ± 0.72	37.8 ± 1.12	37.9 ± 0.84	36.9 ± 1.08
R. kidney	3.32 ± 0.04	3.14 ± 0.07	3.47 ± 0.04	3.32 ± 0.05
L. kidney	3.43 ± 0.06	3.25 ± 0.11	3.47 ± 0.04	3.35 ± 0.07
Brain	5.09 ± 0.09	4.95 ± 0.10	5.00 ± 0.07	4.89 ± 0.07
Female				
n	10	10	10	10
Necropsy body wt (g)	229 ± 2	225 ± 5	235 ± 5	221 ± 4
Liver	33.6 ± 1.35	32.7 ± 2.00	32.1 ± 0.86	31.2 ± 0.63
R. kidney	3.40 ± 0.10	3.41 ± 0.09	3.57 ± 0.09	3.43 ± 0.08
L. kidney	3.49 ± 0.11	3.49 ± 0.09	3.65 ± 0.08	3.47 ± 0.04
Brain	8.29 ± 0.12	8.29 ± 0.22	8.08 ± 0.22	8.46 ± 0.15

[a] Organ-weight-to-body-weight ratios are expressed as milligrams of organ weight/gram of body weight. Mean ± standard error; differences from the control group are not significant by Dunn's or Shirley's test.

TABLE G3
Organ Weights for Rats at the 66-Week Interim Evaluation in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

Organ	Control	25 ppm	100 ppm	175 ppm
Male				
n	9	9	10	10
Necropsy body wt (g)	481 ± 9	475 ± 11	469 ± 8	453 ± 11
Liver	17.21 ± 0.48	16.69 ± 0.66	17.17 ± 0.41	15.38 ± 0.72*
R. kidney	1.63 ± 0.05	1.63 ± 0.05	1.63 ± 0.03	1.49 ± 0.07
L. kidney	1.63 ± 0.04	1.63 ± 0.05	1.68 ± 0.03	1.55 ± 0.07
Brain	2.16 ± 0.02	2.13 ± 0.02	2.13 ± 0.03	2.11 ± 0.01
Female				
n	10	10	10	9
Necropsy body wt (g)	289 ± 8	291 ± 7	285 ± 8	265 ± 5*
Liver	8.70 ± 0.23	8.69 ± 0.17	8.90 ± 0.27	7.91 ± 0.18
R. kidney	0.95 ± 0.02	0.98 ± 0.02	0.95 ± 0.02	0.88 ± 0.01*
L. kidney	0.96 ± 0.02	0.98 ± 0.01	0.94 ± 0.03	0.91 ± 0.02
Brain	1.92 ± 0.02	1.89 ± 0.02	1.89 ± 0.02	1.90 ± 0.03

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Organ and body weights are reported in grams. Mean ± standard error

TABLE G4
Organ-Weight-to-Body-Weight Ratios for Rats at the 66-Week Interim Evaluation in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

Organ	Control	25 ppm	100 ppm	175 ppm
Male				
n	9	9	10	10
Necropsy body wt (g)	481 ± 9	475 ± 11	469 ± 8	453 ± 11
Liver	35.8 ± 0.76	35.1 ± 1.26	36.7 ± 0.96	33.8 ± 1.08
R. kidney	3.39 ± 0.09	3.43 ± 0.08	3.48 ± 0.06	3.29 ± 0.10
L. kidney	3.40 ± 0.07	3.42 ± 0.07	3.59 ± 0.06	3.40 ± 0.09
Brain	4.49 ± 0.09	4.51 ± 0.11	4.55 ± 0.10	4.69 ± 0.14
Female				
n	10	10	10	9
Necropsy body wt (g)	289 ± 8	291 ± 7	285 ± 8	265 ± 5*
Liver	30.2 ± 0.58	29.9 ± 0.53	31.2 ± 0.63	29.9 ± 0.72
R. kidney	3.31 ± 0.07	3.37 ± 0.07	3.35 ± 0.06	3.35 ± 0.07
L. kidney	3.33 ± 0.08	3.37 ± 0.07	3.31 ± 0.08	3.44 ± 0.11
Brain	6.67 ± 0.17	6.51 ± 0.15	6.66 ± 0.15	7.17 ± 0.14*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Organ-weight-to-body-weight ratios are expressed as milligrams of organ weight/gram of body weight. Mean ± standard error

TABLE G5
Organ Weights for Mice at the 24-Week Interim Evaluation in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

Organ	Control	25 ppm	100 ppm	175 ppm
Male				
n	10	10	10	10
Necropsy body wt (g)	43.5 ± 1.4	45.3 ± 0.9	45.1 ± 1.0	44.1 ± 1.0
Liver	2.08 ± 0.16	2.34 ± 0.14	2.21 ± 0.16	2.00 ± 0.09
R. kidney	0.33 ± 0.01	0.35 ± 0.01	0.34 ± 0.01	0.33 ± 0.01
L. kidney	0.32 ± 0.01	0.35 ± 0.01	0.33 ± 0.01	0.31 ± 0.01
Brain	0.45 ± 0.01	0.46 ± 0.01	0.46 ± 0.01	0.45 ± 0.01
Female				
n	10	10	10	10
Necropsy body wt (g)	37.2 ± 1.6	42.6 ± 0.9*	40.8 ± 1.4	36.5 ± 1.5
Liver	1.63 ± 0.08	1.56 ± 0.04	1.64 ± 0.04	1.53 ± 0.06
R. kidney	0.23 ± 0.01	0.21 ± 0.01	0.23 ± 0.00	0.21 ± 0.01
L. kidney	0.22 ± 0.01	0.21 ± 0.01	0.21 ± 0.00	0.21 ± 0.01
Brain	0.49 ± 0.01	0.46 ± 0.00**	0.48 ± 0.01	0.48 ± 0.01

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Organ and body weights are reported in grams. Mean ± standard error

TABLE G6
Organ-Weight-to-Body-Weight Ratios for Mice at the 24-Week Interim Evaluation in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

Organ	Control	25 ppm	100 ppm	175 ppm
Male				
n	10	10	10	10
Necropsy body wt (g)	43.5 ± 1.4	45.3 ± 0.9	45.1 ± 1.0	44.1 ± 1.0
Liver	47.3 ± 2.12	51.3 ± 2.18	48.6 ± 2.40	45.1 ± 1.15
R. kidney	7.66 ± 0.14	7.81 ± 0.17	7.43 ± 0.12	7.54 ± 0.14
L. kidney	7.28 ± 0.16	7.63 ± 0.18	7.25 ± 0.20	7.10 ± 0.14
Brain	10.4 ± 0.30	10.3 ± 0.23	10.1 ± 0.22	10.2 ± 0.25
Female				
n	10	10	10	10
Necropsy body wt (g)	37.2 ± 1.6	42.6 ± 0.9*	40.8 ± 1.4	36.5 ± 1.5
Liver	44.0 ± 1.75	36.7 ± 0.89**	40.3 ± 0.91	42.1 ± 1.14
R. kidney	6.20 ± 0.32	5.00 ± 0.16**	5.58 ± 0.16	5.89 ± 0.20
L. kidney	5.98 ± 0.28	4.85 ± 0.12**	5.11 ± 0.14	5.69 ± 0.20
Brain	13.5 ± 0.66	10.9 ± 0.24**	12.0 ± 0.44	13.4 ± 0.49

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Organ-weight-to-body-weight ratios are expressed as milligrams of organ weight/gram of body weight. Mean ± standard error

TABLE G7
Organ Weights for Mice at the 66-Week Interim Evaluation in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

Organ	Control	25 ppm	100 ppm	175 ppm
Male				
n	10	10	9	10
Necropsy body wt (g)	49.7 ± 0.9	51.1 ± 0.7	50.2 ± 0.6	49.8 ± 1.0
Liver	2.56 ± 0.10	2.73 ± 0.15	2.63 ± 0.08	2.49 ± 0.12
R. kidney	0.41 ± 0.02	0.44 ± 0.02	0.41 ± 0.01	0.40 ± 0.01
L. kidney	0.40 ± 0.02	0.41 ± 0.02	0.40 ± 0.01	0.38 ± 0.01
Brain	0.45 ± 0.01	0.47 ± 0.01	0.47 ± 0.01	0.46 ± 0.01
Female				
n	10	8	10	9
Necropsy body wt (g)	52.3 ± 2.3	55.4 ± 1.8	59.0 ± 1.9	51.8 ± 2.7
Liver	1.97 ± 0.06	2.09 ± 0.15	2.22 ± 0.13	1.89 ± 0.11
R. kidney	0.27 ± 0.01	0.27 ± 0.01	0.27 ± 0.01	0.27 ± 0.01
L. kidney	0.25 ± 0.01	0.26 ± 0.01	0.25 ± 0.01	0.25 ± 0.01
Brain	0.48 ± 0.00	0.48 ± 0.01	0.47 ± 0.01	0.48 ± 0.01

[a] Organ and body weights are reported in grams. Mean ± standard error; differences from the control group are not significant by Dunn's or Shirley's test.

TABLE G8
Organ-Weight-to-Body-Weight Ratios for Mice at the 66-Week Interim Evaluation in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

Organ	Control	25 ppm	100 ppm	175 ppm
Male				
n	10	10	9	10
Necropsy body wt (g)	49.7 ± 0.9	51.1 ± 0.7	50.2 ± 0.6	49.8 ± 1.0
Liver	51.5 ± 1.62	53.3 ± 2.44	52.4 ± 1.41	49.9 ± 1.45
R. kidney	8.17 ± 0.35	8.51 ± 0.33	8.23 ± 0.17	7.96 ± 0.20
L. kidney	7.95 ± 0.30	8.02 ± 0.34	7.94 ± 0.14	7.55 ± 0.15
Brain	9.10 ± 0.16	9.16 ± 0.16	9.28 ± 0.13	9.30 ± 0.29
Female				
n	10	8	10	9
Necropsy body wt (g)	52.3 ± 2.3	55.4 ± 1.8	59.0 ± 1.9	51.8 ± 2.7
Liver	38.1 ± 1.23	37.6 ± 1.55	37.4 ± 1.45	36.6 ± 1.45
R. kidney	5.26 ± 0.22	4.82 ± 0.16	4.59 ± 0.06*	5.20 ± 0.24
L. kidney	4.79 ± 0.23	4.65 ± 0.12	4.23 ± 0.09	4.61 ± 0.19
Brain	9.27 ± 0.45	8.80 ± 0.41	8.04 ± 0.31	9.41 ± 0.51

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Organ-weight-to-body-weight ratios are expressed as milligrams of organ weight/gram of body weight. Mean ± standard error

APPENDIX H
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA PROTOCOL

Testing was performed as reported by Ames *et al.* (1975) with modifications as listed below and described in greater detail by Haworth *et al.* (1983). Sodium fluoride, sent to the laboratory coded from Radian Corporation (Austin, TX), was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C prior to the addition of soft agar supplemented with *l*-histidine and *d*-biotin, and subsequent plating on minimal glucose agar plates. Incubation continued for an additional 48 hours.

Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of test chemical. High dose was limited to 10 mg/plate. All trials were repeated.

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

MOUSE LYMPHOMA PROTOCOL

Testing was performed as reported by Myhr *et al.* (1985) and Clive *et al.* (1979) and is presented briefly below. All study chemicals were supplied as coded aliquots by Radian Corporation (Austin, TX). The highest dose of the study compound was determined by solubility or toxicity, and did not exceed 5 mg/mL. Mouse lymphoma L5178Y cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM *l*-glutamine, 110 μg/mL sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (TFT) resistant cells, subcultures were exposed once to medium containing THMG (thymidine, hypoxanthine, methotrexate, glycine) for one day, to THG for one day, and to normal medium for 3 to 5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 for metabolic activation was obtained from the livers of either Aroclor 1254-induced or noninduced Fischer 344 male rats.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in a 10 mL volume of medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with study chemical continued for 4 hours, at which time the medium plus chemical was removed and the cells were resuspended in 20 ml of fresh medium and incubated for an additional 2 days to allow expression of the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of TFT-resistant cells ($TK^{-/-}$), and 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% carbon dioxide for 10 to 12 days. All data were evaluated statistically for both trend and peak response. Both responses had to be significant ($P<0.05$) for a chemical to be considered positive; a significant response at only one dose led to a "questionable" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr *et al.* (1985). This assay is initially performed without S9; if a clearly positive response is not obtained, the experiment is repeated with induced S9.

CHINESE HAMSTER OVARY CYTOGENETICS ASSAY

Testing was performed as reported by Galloway *et al.* (1985, 1987) and is presented briefly below. Sodium fluoride was sent to the laboratories in coded aliquots from Radian Corporation (Austin, TX). It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCE) and chromosomal aberrations (Abs) both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of test chemical; the high dose was limited by toxicity.

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

In the Abs test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 10 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

For the SCE test, if significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test: if cell cycle delay was anticipated, the incubation period was extended approximately 5 hours.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, usually 50 second-division metaphase cells were scored for frequency of SCE per cell from each dose level; 100 first-division metaphase cells were scored at each dose level for the Abs test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. If one dose point was positive, the chemical was termed "weak positive"; if two or more doses were positive, the chemical was judged "positive." Abs data is presented as percentage of cells with aberrations. As with SCE, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P<0.003$) effect on the slope of the curve or on at least two dose points ($P<0.05$) was sufficient for a conclusion of positive for a test; a single positive dose point resulted in a conclusion of weak positive. In both the SCE and Abs tests, the term "weak positive" refers to the strength of the evidence for a positive response, rather than to the magnitude of the response.

RESULTS

Sodium fluoride did not induce gene mutations in *Salmonella typhimurium* when tested with a preincubation protocol at doses of 100 to 10,000 μg/plate in strains TA100, TA1535, TA1537, and TA98; all strains were tested with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Haworth *et al.*, 1983).

Sodium fluoride was tested in two laboratories for induction of trifluorothymidine resistance in mouse L5178Y lymphoma cells. In the first laboratory, sodium fluoride was positive both with and without Aroclor 1254-induced male Fischer 344 rat liver S9; the effective doses, with and without S9, ranged from 300 to 600 μg/mL (Caspary *et al.*, 1987). In the second laboratory, sodium fluoride was tested without S9 only, and test results were positive in the first trial at 62.5, 125, and 1,000 μg/mL and in the second trial at 800 and 900 μg/mL. The mutant colonies obtained after sodium fluoride treatment of L5178Y cells were primarily small colonies, suggesting that chromosomal abnormalities may be involved.

Sodium fluoride was tested for the induction of cytogenetic effects in CHO cells in two laboratories with different results. SCEs were induced in one laboratory at doses of 66.7 and 75 μg/mL without S9 and at doses of 1,200 μg/mL and higher with S9. In two of the five cases, the positive results were seen following delayed harvest to allow cells, whose division time was inhibited by the higher doses of sodium fluoride, to progress to the second metaphase division to the point where the cells could be scored. The laboratory reporting negative SCE results did not employ extended harvest times and was able to test up to only 50 μg/mL sodium fluoride without S9 and 500 μg/mL with S9.

In the tests for the induction of Abs, positive results were reported in one laboratory at doses of 400 μg/mL sodium fluoride and greater without S9. The second laboratory reported negative results without S9, but the highest dose tested was 200 μg/mL. Neither laboratory showed a reproducible increase in Abs in the presence of S9.

TABLE H1
Mutagenicity of Sodium Fluoride in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	70 ± 5.4	92 ± 5.9	85 ± 7.5	91 ± 6.0	100 ± 4.4	75 ± 7.4
	100	119 ± 3.6	92 ± 6.7	94 ± 2.1	95 ± 6.8	111 ± 6.9	108 ± 13.4
	333	125 ± 6.6	103 ± 11.0	86 ± 12.1	94 ± 4.7	109 ± 6.6	104 ± 4.5
	1,000	106 ± 10.1	84 ± 3.3	89 ± 7.1	89 ± 7.8	100 ± 2.2	94 ± 5.9
	3,333	116 ± 8.0	89 ± 6.2	91 ± 6.4	92 ± 8.2	100 ± 5.5	94 ± 5.0
	10,000	114 ± 1.2	94 ± 3.3	85 ± 7.8	85 ± 7.2	97 ± 8.1	96 ± 5.4
Trial Summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		318 ± 21.4	394 ± 5.7	428 ± 22.9	1492 ± 34.2	234 ± 10.5	684 ± 44.0
TA1535	0	19 ± 2.3	8 ± 0.6	5 ± 0.6	6 ± 0.7	12 ± 1.8	7 ± 0.9
	100	24 ± 3.8	10 ± 2.1	11 ± 3.2	9 ± 2.3	13 ± 1.8	7 ± 1.0
	333	20 ± 5.2	7 ± 0.9	10 ± 0.3	8 ± 2.6	12 ± 2.1	7 ± 1.5
	1,000	21 ± 3.5	9 ± 2.3	11 ± 1.7	8 ± 3.2	9 ± 1.3	8 ± 0.0
	3,333	24 ± 2.6	8 ± 2.8	9 ± 1.7	8 ± 0.9	12 ± 2.1	7 ± 1.0
	10,000	24 ± 0.0	8 ± 1.3	7 ± 0.7	4 ± 0.7	12 ± 3.2	10 ± 2.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		216 ± 8.2	244 ± 5.8	293 ± 11.9	274 ± 6.9	155 ± 7.6	189 ± 7.5
TA1537	0	6 ± 1.3	7 ± 1.5	5 ± 0.6	6 ± 1.0	16 ± 1.2	6 ± 0.9
	100	5 ± 1.5	6 ± 0.3	21 ± 2.9	7 ± 1.9	16 ± 0.9	11 ± 3.0
	333	8 ± 1.5	4 ± 0.9	15 ± 1.5	6 ± 0.6	15 ± 3.2	9 ± 2.5
	1,000	7 ± 0.9	6 ± 1.9	15 ± 2.0	7 ± 0.7	17 ± 4.3	5 ± 1.5
	3,333	6 ± 1.2	4 ± 1.8	15 ± 2.1	7 ± 1.2	15 ± 1.5	6 ± 1.5
	10,000	8 ± 0.6	4 ± 0.6	14 ± 2.8	4 ± 0.3	15 ± 1.2	7 ± 0.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		59 ± 2.0	107 ± 41.0	113 ± 6.2	464 ± 28.0	239 ± 35.2	251 ± 18.4
TA98	0	17 ± 1.2	14 ± 2.1	40 ± 12.5	22 ± 3.4	25 ± 2.2	26 ± 3.2
	100	20 ± 3.8	13 ± 3.2	34 ± 2.7	19 ± 0.9	43 ± 3.8	32 ± 3.2
	333	18 ± 0.3	14 ± 3.2	38 ± 4.0	21 ± 4.6	38 ± 3.8	23 ± 2.2
	1,000	16 ± 0.3	11 ± 2.8	30 ± 1.7	16 ± 3.2	35 ± 1.8	21 ± 2.0
	3,333	23 ± 2.2	10 ± 2.5	33 ± 2.3	25 ± 2.9	27 ± 0.9	15 ± 1.5
	10,000	19 ± 2.6	12 ± 1.3	29 ± 7.0	17 ± 0.3	32 ± 2.1	18 ± 1.0
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		504 ± 20.3	684 ± 9.8	265 ± 3.8	638 ± 104.1	146 ± 5.2	180 ± 10.4

[a] Study performed at SRI. The detailed protocol and these data are presented in Haworth *et al.* (1983). Cells and study compound or solvent (dimethylsulfoxide) were incubated in the absence of exogenous metabolic activation (-S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague-Dawley rat liver. High dose was limited to 10 mg/plate; 0 μg/plate dose is the solvent control.

[b] Revertants are presented as mean ± the standard error from 3 plates.

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

Table H2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Cells by Sodium Fluoride

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Tft-Resistant Cells	Mutant Fraction[a]
Study performed at Litton Bionetics, Inc.[b]					
-S9					
Trial 1					
Distilled water		75.8 ± 3.8[c,d]	99.8 ± 4.8	67.0 ± 5.9	29.5 ± 1.9
Sodium fluoride	200	85.5 ± 18.5[e]	81.5 ± 8.5	80.5 ± 13.5	32.0 ± 2.0
	300	85.3 ± 4.7	72.0 ± 5.2	133.3 ± 22.3	52.7 ± 9.4*
	400	78.7 ± 0.9	41.0 ± 4.0	107.7 ± 4.9	45.7 ± 1.9*
	500	75.0 ± 3.8	16.7 ± 2.7	125.0 ± 16.7	55.3 ± 4.8*
	600	79.5 ± 3.5[e]	10.0 ± 1.0	196.0 ± 3.0	83.0 ± 5.0*
	800	Lethal			
Methyl methanesulfonate	5	66.7 ± 2.4	70.7 ± 5.2	489.0 ± 43.7	244.3 ± 13.2*
-S9					
Trial 2					
Distilled water		105.7 ± 9.1	100.0 ± 9.1	77.0 ± 2.5	24.3 ± 1.9
Sodium fluoride	50	91.0 ± 7.0	86.3 ± 2.0	59.0 ± 9.3	22.0 ± 3.1
	100	92.0 ± 4.0[e]	71.5 ± 8.5	75.5 ± 3.5	27.0 ± 0
	200	88.0 ± 4.6	57.0 ± 2.3	72.7 ± 11.1	27.3 ± 3.0
	300	89.3 ± 10.2	49.3 ± 3.7	58.3 ± 8.7	22.0 ± 2.7
	400	104.0 ± 12.0[e]	40.0 ± 0.0	112.0 ± 25.0	35.5 ± 4.5
	500	94.3 ± 7.6	17.3 ± 3.0	119.0 ± 28.4	41.3 ± 8.5*
	600	Lethal			
Methyl methanesulfonate	5	80.7 ± 11.3	61.3 ± 3.4	315.7 ± 32.1	140.0 ± 36.5*
+S9[f]					
Trial 1					
Distilled water		107.5 ± 1.3[d]	100.0 ± 6.8	83.8 ± 6.9	25.8 ± 2.1
Sodium fluoride	100	85[g]	75	66	26
	200	99.7 ± 7.8	70.7 ± 4.9	59.7 ± 9.9	20.7 ± 4.4
	300	94.5 ± 5.5[e]	52.0 ± 9.0	110.5 ± 5.5	39.5 ± 4.5
	400	106.7 ± 7.0	41.3 ± 2.3	121 ± 14.1	39.0 ± 7.6*
	500	72.3 ± 9.2	13.3 ± 3.8	177.7 ± 45.1	81.0 ± 19.3*
	600	77.5 ± 13.5[e]	7.5 ± 0.5	206.5 ± 24.5	94.0 ± 27.0*
Methycholanthrene	2.5	61.3 ± 5.2	28.0 ± 2.1	615.0 ± 43.3	334.7 ± 11.9*
+S9					
Trial 2					
Distilled water		82.3 ± 3.0[d]	100.0 ± 9.3	81.5 ± 8.7	33.0 ± 2.4
Sodium fluoride	50	78.0 ± 2.9	100.0 ± 7.8	63.7 ± 4.2	27.0 ± 1.2
	100	79.3 ± 6.0	86.7 ± 21.1	88.7 ± 14.0	37.7 ± 6.8
	200	85.0 ± 13.1	83.3 ± 6.4	98.0 ± 18.6	38.0 ± 2.0
	300	76.3 ± 0.3	49.7 ± 3.3	119.0 ± 11.8	51.7 ± 5.2*
	400	77.3 ± 3.8	29.0 ± 1.5	144.7 ± 10.3	62.3 ± 2.3*
	500	74.3 ± 3.4	21.0 ± 3.1	167.7 ± 27.9	75.7 ± 14.3*
	600	Lethal			
Methylcholanthrene	2.5	47.7 ± 2.7	21.0 ± 2.7	731.7 ± 22.9	573.7 ± 34.6*

Table H2
Induction of Trifluorothymidine Resistance in Mouse L5178Y/TK$^{+/-}$ Cells by Sodium Fluoride (continued)

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Tft-Resistant Cells	Mutant Fraction[a]
Study performed by Inveresk Research International[b]					
-S9					
Trial 1					
Fischer's medium without serum		58.8 ± 3.0[d]	100.0 ± 10.3	101 ± 14.0	58.0 ± 9.7
Sodium fluoride	62.5	52.5 ± 5.5	88.5 ± 12.5	162.0 ± 0.0	104.5 ± 11.5*
	125	52.5 ± 8.5	78.0 ± 4.0	144.0 ± 24.0	97.5 ± 31.5*
	250	59.0 ± 4.0	70.0 ± 9.0	130.0 ± 9.0	73.5 ± 0.5
	500	70.0 ± 15.0	36.0 ± 1.0	161.5 ± 18.5	82.5 ± 26.5
	1000	40.0 ± 4.0	8.0 ± 3.0	155.5 ± 13.5	134.0 ± 25.0*
Methyl methanesulfonate	15	16.5 ± 1.5	13.0 ± 2.0	172.0 ± 3.0	342.5 ± 24.5*
-S9					
Trial 2					
Fischer's medium without serum		90.5 ± 5.72[d]	100.0 ± 5.3	138.3 ± 12.8	51.0 ± 4.1
Sodium fluoride	500	82.0 ± 3.0	33.0 ± 0.0	145.0 ± 20.0	58.5 ± 5.5
	600	87.0 ± 10.0	28.0 ± 3.0	148.5 ± 0.5	58.0 ± 7.0
	700	90.5 ± 3.5	25.0 ± 0.0	177.0 ± 25.0	66.0 ± 12.0
	800	78.5 ± 0.5	20.0 ± 1.0	215.5 ± 22.5	91.5 ± 9.5*
	900	78.0 ± 2.0	13.0 ± 1.0	445.0 ± 22.0	195.5 ± 3.5*
	1000	Lethal			
Methyl methanesulfonate	15	52.0 ± 4.0	35.0 ± 1.0	77.0 ± 14.0	49.0 ± 5.0

* Significant positive response ($P<0.05$); occurs when the relative mutant fraction (average mutant fraction of treated culture/average mutant fraction of solvent control) is greater than or equal to approximately 1.6.
[a] Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by the number of replicates to arrive at mutant fraction/1×10^6 cells treated.
[b] The experimental protocol is presented in detail by Myhr *et al.* (1985) and follows the basic format of Clive *et al.* (1979); data from the Litton Bionetics study is presented in Caspary *et al.* (1987). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/mL. All doses are tested in triplicate in the Litton Bionetics study and in duplicate in the Inveresk Research International study unless otherwise noted; the average of the replicates is presented in the table. Cells (6×10^6) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.
[c] Mean ± standard error from replicate plates of approximately (3×10^6) cells each.
[d] Number of replicates = 4
[e] Number of replicates = 2
[f] Tests conducted with metabolic activation were performed as described in [b] except that S9, prepared from the livers of Aroclor 1254-induced Fischer 344/N rats, was added at the same time as the test chemical and/or solvent.
[g] Number of replicates = 1

TABLE H3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Sodium Fluoride[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Increase over Solvent (%)[b]
Study performed by Environmental Health Research and Testing, Inc.								
-S9								
Trial 1--Summary: Negative								
Medium		50	1049	402	0.38	8.0	26.5	
Sodium fluoride	1.6	50	1047	384	0.36	7.7	26.5	-4.30
	5.0	50	1046	473	0.45	9.5	26.5	18.00
	16.0	50	1048	387	0.36	7.7	26.5	-3.64
	50.0	50	1049	416	0.39	8.3	26.5	3.48
	160.0	Toxic						
Mitomycin-C	0.0010	50	1050	602	0.57	12.0	26.5	49.61
	0.0050	10	209	277	1.32	27.7	26.5	245.85
	P=0.320							
-S9								
Trial 2--Summary: Negative								
Medium		50	1046	378	0.36	7.6	26.5	
Sodium fluoride	5.0	50	1038	360	0.34	7.2	26.5	-4.03
	25.0	50	1048	402	0.38	8.0	26.5	6.15
	50.0	50	1036	415	0.40	8.3	26.5	10.85
	75.0	Toxic						
	100.0	Toxic						
Mitomycin-C	0.0010	50	1044	592	0.56	11.8	26.5	56.91
	0.0050	10	209	288	1.37	28.8	26.5	281.32
	P=0.034							
+S9								
Trial 1--Summary: Negative								
Medium		50	1047	521	0.49	10.4	26.0	
Sodium fluoride	16.0	50	1049	426	0.40	8.5	26.0	-18.39
	50.0	50	1050	444	0.42	8.9	26.0	-15.02
	160.0	50	1050	474	0.45	9.5	26.0	-9.28
	500.0	50	1045	529	0.50	10.6	26.0	1.73
	1600.0	Toxic						
Cyclophosphamide	0.3	50	1046	829	0.79	16.6	26.0	59.27
	0.6	10	208	261	1.25	26.1	26.0	152.17
	P=0.172							

Table H3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Sodium Fluoride[a] (continued)

Compound	Dose (μg/mL)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hours in BrdU	Increase over Solvent (%)[b]
Study performed at Litton Bionetics, Inc.								
-S9								
Trial 1--Summary: Weak positive								
Medium		50	1032	423	0.40	8.5	26.8	
Sodium fluoride	6.7	50	1012	379	0.37	7.6	26.8	-8.63
	20.0	50	1032	413	0.40	8.3	26.8	-2.37
	66.7	50	1035	523	0.50	10.5	31.3[e]	23.28*
	200.0	Toxic						
Mitomycin-C	0.0010	50	1034	560	0.54	11.2	26.8	32.13
	0.0100	5	100	172	1.72	34.4	26.8	319.64
	$P<0.001$							
-S9								
Trial 2--Summary: Weak positive								
Medium		50	1039	462	0.44	9.2	26.0	
Sodium fluoride	50.0	50	1021	534	0.52	10.7	26.0	17.62
	75.0	50	1037	565	0.54	11.3	26.0	22.53*
	100.5	50	1024	532	0.51	10.6	32.5[e]	16.84
	125.0	Toxic						
Mitomycin-C	0.0010	50	1030	588	0.57	11.8	26.0	28.39
	0.0100	5	104	262	2.51	52.4	26.0	466.56
	$P=0.005$							
+S9								
Trial 1--Summary: Questionable								
Medium		50	1037	476	0.45	9.5	26.0	
Sodium fluoride	330	50	1035	515	0.49	10.3	26.0	8.40
	350	50	1032	495	0.47	9.9	26.0	4.50
	400	50	1027	559	0.54	11.2	26.0	18.58
Cyclophosphamide	0.300	50	1022	655	0.65	13.3	26.0	41.76
	2.000	5	105	222	2.11	44.4	26.0	360.62
	$P=0.004$							

TABLE H3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Sodium Fluoride[a]
(continued)

Compound	Dose (μg/mL)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hours in BrdU	Increase over Solvent (%)[b]
+S9								
Trial 3--Summary: Positive								
Medium		50	1035	448	0.43	9.0	25.6	
Sodium fluoride	1200	50	1030	579	0.56	11.6	25.6	29.87*
	1400	50	1020	577	0.56	11.5	30.7[c]	30.69*
	1600	50	1020	587	0.57	11.7	30.7[c]	32.95*
Cyclophosphamide	0.3	50	1034	673	0.65	13.5	25.6	50.37
	2.0	5	107	226	2.11	45.2	25.6	387.96
	P<0.001							

*Statistically significant effect on slope of dose-response curve (P<0.003) or on a dose point (P<0.05)

[a] SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (medium) and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air dried, and stained. In the absence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and Colcemid was added, and incubation was continued for 2 to 3 hours. In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. The cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with Colcemid present for the final 2 to 3 hours. Harvest times are occasionally extended to maximize the proportion of second division cells available for analysis, because some chemicals induce a delay in the cell division cycle. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

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

TABLE H4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Sodium Fluoride[a]

Study performed at Environmental Health Research and Testing

-S9

Dose (µg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1--Harvest time: 12.0 hours				
Medium	100	3	0.03	3.0
Sodium fluoride				
16	100	3	0.03	1.0
50	100	1	0.01	1.0
160	100	1	0.01	1.0
500	100	3	0.03	3.0
	Summary: Negative			
Mitomycin-C				
0.1250	100	18	0.18	18.0
0.2500	50	16	0.32	30.0
		P=0.500		
Trial 2--Harvest Time: 13.0 Hours				
Medium	100	0	0.00	0.0
Sodium fluoride				
300	100	3	0.03	3.0
400	100	19	0.19	19.0*
500	100	39	0.39	39.0*
600	100	34	0.34	33.0*
	Summary: Positive			
Mitomycin-C				
0.1250	100	17	0.17	16.0
0.2500	50	13	0.26	24.0
		P<0.001		
Trial 3--Harvest Time: 13.0 hours				
Medium	100	0	0.00	0.0
Sodium fluoride				
300	100	3	0.03	2.0
400	100	23	0.23	21.0*
500	100	19	0.19	16.0*
600	100	27	0.27	27.0*
800	0			
	Summary: Positive			
Mitomycin-C				
0.1250	100	17	0.17	16.0
0.2500	50	13	0.26	24.0
		P<0.001		

+S9

Dose (µg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1--Harvest time: 13.0 hours				
Medium	100	0	0.00	0.0
Sodium fluoride				
50	100	1	0.01	1.0
160	100	0	0.00	0.0
500	100	9	0.09	8.0*
1000	100	6	0.06	2.0
	Summary: Weak Positive			
Cyclophosphamide				
15	100	78	0.78	47.0
		P=0.259		
Trial 2--Harvest Time: 13.0 Hours				
Medium	100	0	0.00	0.0
Sodium fluoride				
400	100	3	0.03	3.0
600	100	3	0.03	3.0
800	100	2	0.02	2.0
1000	100	5	0.05	4.0
	Summary: Negative			
Cyclophosphamide				
10	100	43	0.43	35.0
15	50	55	1.10	52.0
		P=0.078		

TABLE H4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Sodium Fluoride[a] (continued)

-S9					+S9				
Dose (µg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Study performed at Litton Bionetics, Inc.									
Trial 1--Harvest Time: 20.5 Hours[b]					**Trial 1**--Harvest Time: 22.0 Hours				
Medium	100	0	0.00	0.0	Medium	100	0	0.00	0.0
Sodium fluoride					Sodium fluoride				
150	100	3	0.03	2.0	1200	100	4	0.04	2.0
176	100	1	0.01	1.0	1400	100	5	0.05	4.0
200	100	4	0.04	3.0	1600	100	4	0.04	4.0
		Summary: Negative					Summary: Negative		
Mitomycin-C					Cyclophosphamide				
0.0500	50	12	0.24	22.0	10	50	17	0.34	20.0
		P=0.076					P=0.022		

* Statistically significant effect on slope of dose-response curve ($P<0.003$) or on a dose point ($P<0.05$)

a Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (medium). Cells were arrested in the first metaphase by addition of Colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa. In the absence of S9, cells were incubated with study compound or solvent for 8 to 10 hours at 37° C. Cells were then washed and fresh medium containing Colcemid was added for an additional 2 to 3 hours followed by harvest. In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8 to 10 hours. Colcemid was added for the last 2 to 3 hours of incubation before harvest. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

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

APPENDIX I
SUPPLEMENTAL STUDIES

SUPPLEMENTAL STUDIES

6-Month Studies

Fluoride Concentrations in Bone, Plasma, and Urine

At termination of the 6-month studies, the fluoride concentrations in bone, plasma, and urine were determined from samples collected from five F344/N rats of each sex and from all surviving $B6C3F_1$ mice from all groups (except the control groups given sodium-chloride-supplemented deionized drinking water and a low fluoride, semisynthetic diet). Samples from the same animals were included in all three evaluations. Results are summarized in Tables I1 and I2.

Bone Preparation and Analysis

One humerus from each animal was collected at necropsy and stored frozen until it was analyzed for fluoride content. Prior to analysis, bones were cleaned of soft tissue by boiling in water for 1 hour and scraping with a razor blade. Individual bones were cleaned of fat by soaking in 10 to 15 mL anhydrous ether for 3 days; the ether was changed twice a day. The bones were dried by placing them in an oven at 110° C overnight; they were weighed and then pulverized into a fine powder. The bone ash was dissolved in acid, neutralized, and pH adjusted prior to fluoride determination with a fluoride ion electrode. The method of Singer and Armstrong (1968) was used for bone analysis with one modification.[1] Fluoride concentrations are expressed in μg/mg of ashed bone.

Plasma Preparation and Analysis

Animals were anesthetized with pentobarbital. From rats, 5 mL of blood was collected from the vena cava in tubes containing ethylenediaminetetraacetic acid (EDTA). From mice, as much blood as possible was collected via cardiac puncture in tubes containing EDTA; due to the low volume obtained from individual mice, blood was pooled so that two analyses were conducted for each group. The plasma was separated and stored frozen until it was analyzed (Singer and Ophaug, 1977). Plasma fluoride was fixed with low fluoride calcium phosphate, ashed, and buffered to pH 5.0; concentration was determined with the fluoride ion electrode. A detection limit of 0.025 μg/sample was established for sample sizes between 0.5 to 3.0 mL plasma. For every five samples analyzed, a recovery check was performed as described by Singer and Ophaug (1977). Fluoride concentrations are reported in μg/mL plasma.

Urine Preparation and Analysis

Urine samples were collected 7 days prior to necropsy from the same animals used for bone and plasma fluoride analyses. During urine collection, animals received undosed deionized water and the appropriate diet. Individual 24-hour urine samples were collected from rats; however, due to the low volume of urine obtained from individual mice, urine samples from mice were pooled by dose group. Individual samples from rats and pooled collections from mice were stored frozen until analysis was performed 24 to 72 hours after collection. Urine fluoride concentrations were determined directly from the buffered urine samples using a fluoride ion electrode. Urine fluoride is expressed in total micrograms of fluoride excreted in a 24-hour period.

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[1]Singer and Armstrong's method requires nearly neutralizing the excess acid with 1.1 mL of 0.125 M NaOH and titrating to pH 4.7 with sodium acetate solution. When this procedure was followed, the final volume exceeded 5 mL. The method was modified by nearly neutralizing the excess acid with 0.8 mL of 0.2 M NaOH.

TABLE I1
Fluoride Concentrations in Bone, Plasma, and Urine of Rats in the 6-Month Drinking Water Studies of Sodium Fluoride[a]

Dose (ppm)	Bone		Plasma		Urine	
	n	μg F/mg ash	n	μg F/mL	n	μg F/24 hours
Male						
0[b]	5	0.091 ± 0.034	5	0.039[d]	5	4.42 ± 0.70
0[c]	5	0.922 ± 0.027**	5	0.067 ± 0.008**	5	53.94 ± 2.32**
10	5	0.248 ± 0.041*	5	0.031[d]	5	14.80 ± 3.29**
30	5	0.607 ± 0.026**	5	–[e]	5	23.32 ± 1.18**
100	5	2.636 ± 0.081**	5	0.050[d]	5	80.82 ± 5.54**
300	5	7.320 ± 0.158**	5	0.560 ± 0.125**	5	212.82 ± 38.54**
Female						
0[b]	5	0.057 ± 0.007	4	–[e]	5	2.84 ± 0.30
10	5	0.423 ± 0.013**	5	0.047[d]	5	9.50 ± 0.50**
30	5	0.833 ± 0.057**	5	0.051[d]	5	14.38 ± 1.60**
100	5	3.154 ± 0.180**	5	0.033[d]	5	49.26 ± 6.86**
300	5	8.028 ± 0.349**	5	0.199 ± 0.027**	5	162.54 ± 9.54**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
a Mean ± standard error
b Control group of male and female rats receiving a low fluoride, semisynthetic diet and deionized water
c Control group of male rats receiving a standard NIH-07 diet and deionized water
d Four of the five values were below the limit of detection
e All values were below the limit of detection

TABLE I2
Fluoride Concentrations in Bone, Plasma, and Urine of Mice in the 6-Month Drinking Water Studies of Sodium Fluoride

Dose (ppm)	Bone		Plasma			Urine		
	No. of animals	μg F/mg ash[a]	No. of samples	Samples pooled	μg F/mL pooled[b]	No. of samples	Samples pooled	μg F/24 hr pooled[b]
Male								
0[c]	9	0.188 ± 0.037	1	5[d]	0.024	2	9	0.8
0[e]	11	1.607 ± 0.076**	1	5[d]	0.021	2	10	12.4
10	9	0.667 ± 0.064**	1	5[d]	0.039	2	10	3.4
50	10	2.927 ± 0.242**	2	9	0.110	2	10	17.4
100	10	5.607 ± 0.571**	2	10	0.139	2	10	30.6
200	10	8.071 ± 0.569**	2	10	0.101	2	10	34.7
300	7	11.067 ± 0.725**	2	6	0.215	2	7	67.4
600	5	14.760 ± 0.839**	1	4	0.365	1	5	150.1
Female								
0[c]	11	0.258 ± 0.123	2	11	–[f]	2	11	1.3
0[e]	8	1.483 ± 0.183**	1	4[d]	0.060	2	9	15.3
10	11	0.811 ± 0.112**	1	5[d]	0.048	2	11	3.6
50	10	2.439 ± 0.134**	2	10	0.091	2	10	13.3
100	10	4.377 ± 0.219**	2	10	0.154	2	10	26.7
200	10	6.875 ± 0.328**	2	10	0.208	2	10	52.7
300	12	9.195 ± 0.264**	2	12	0.279	2	12	64.9
600	2	12.350 ± 1.250**	1	2	0.630	1	2	95.1

** Significantly different ($P \leq 0.01$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error
[b] No statistical analyses were performed.
[c] Control group of mice receiving a low fluoride, semisynthetic diet and deionized water
[d] Values of pooled sample from remaining animals in this group was below the detectable limit of 0.025 μg total fluoride per sample.
[e] Control group of mice receiving a standard NIH-07 diet and deionized water
[f] Values of all samples were below the detectable limit of 0.025 μg total fluoride per sample.

2-YEAR STUDIES

A number of supplemental studies were conducted during the 2-year studies of sodium fluoride. Details of studies to determine fluoride concentrations in bone, serum, and urine, hematology and clinical chemistry profiles, urinalysis and urine concentration ability, and bioavailability are presented on the following pages.

Fluoride Concentrations in Bone, Serum, and Urine

The left humerus was collected from designated animals at necropsy: all male and female F344/N rats scheduled for 27-week and 66-week interim sacrifice, all B6C3F$_1$ mice scheduled for 24-week and 66-week interim sacrifice, and ten randomly selected animals of each sex and species sacrificed at the end of the studies (105 weeks). Bone analysis was performed according to the method of Singer and Armstrong (1968). The bone was cleaned by boiling for approximately 1 hour, followed by the removal of any adhering tissue with a razor blade. The bone was then placed in anhydrous ether for approximately 72 hours; the ether was changed twice a day. The bone was dried overnight in an oven, ashed at 550° C, weighed, and then pulverized into a fine powder. The ash was dissolved overnight in 0.25 M HCl; then the excess acid was neutralized with NaOH. Deionized water was added after the addition of 1 mL 0.05 M sodium acetate and subsequent adjustment to a pH of 4.7. Bone fluoride concentrations were determined with an Orion 701A Digital Ionalyzer equipped with a fluoride specific ion electrode. Results are presented in Tables I3 and I4.

Blood samples were collected from the retro-orbital sinus in serum separator tubes (Microtainers®, Becton-Dickinson, Rutherford, NJ). Serum fluoride was measured by fixing with low fluoride calcium phosphate, ashing in a crucible at 500° C, followed by the direct determination of fluoride with a fluoride ion electrode in solution of ashed serum adjusted to a pH of 5.0. Recovery checks were performed as described by Singer and Ophaug (1977). Results are presented in Table I5.

Rats were individually housed in metabolism cages (Maryland Plastics, New York, NY) for 16-hour urine collection. Animals were fasted during urine collection, but sodium-fluoride-supplemented water was available *ad libitum*. Urine was analyzed for fluoride concentration by fixing with low fluoride calcium phosphate, ashing in a crucible at 500° C, followed by the direct determination of fluoride with a fluoride ion electrode in a solution of ashed urine adjusted to a pH of 5.0. Results are presented in Table I6.

TABLE I3
Bone Fluoride Concentrations in Rats at the 27-Week and 66-Week Interim Sacrifices and at the Terminal Sacrifice in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	25 ppm	100 ppm	175 ppm
Male				
27-Week Interim Sacrifice				
n	10	10	10	9
Bone fluoride (μg/mg ash)	0.253 ± 0.005	0.617 ± 0.020**	1.685 ± 0.027**	2.936 ± 0.051**
66-Week Interim Sacrifice				
n	9	9	10	10
Bone fluoride (μg/mg ash)	0.357 ± 0.011	0.871 ± 0.012**	2.563 ± 0.076**	4.020 ± 0.220**
105-Week Terminal Sacrifice				
n	10	10	10	10
Bone fluoride (μg/mg ash)	0.445 ± 0.007	0.978 ± 0.043**	3.648 ± 0.146**	5.263 ± 0.207**
Female				
27-Week Interim Sacrifice				
n	10	10	10	10
Bone fluoride (μg/mg ash)	0.320 ± 0.005	0.805 ± 0.029**	2.081 ± 0.075**	3.236 ± 0.078**
66-Week Interim Sacrifice				
n	10	10	10	9
Bone fluoride (μg/mg ash)	0.425 ± 0.024	1.045 ± 0.047**	3.115 ± 0.078**	4.622 ± 0.274**
105-Week Terminal Sacrifice				
n	9	10	10	9
Bone fluoride (μg/mg ash)	0.554 ± 0.007	1.348 ± 0.051**	3.726 ± 0.138**	5.554 ± 0.224**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test

** P≤0.01

[a] Mean ± standard error. Mean prestudy fluoride concentrations were 0.18 ± 0.03 μg fluoride per mg ash of the right humerus of male rats and 0.19 ± 0.04 μg fluoride per mg ash for female rats.

TABLE I4
Bone Fluoride Concentrations in Mice at the 24-Week and 66-Week Interim Sacrifices and at the Terminal Sacrifice in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	25 ppm	100 ppm	175 ppm
Male				
24-Week Interim Sacrifice				
n	10	10	10	10
Bone fluoride (μg/mg ash)	0.360 ± 0.019	0.728 ± 0.025**	1.884 ± 0.136**	2.796 ± 0.117**
66-Week Interim Sacrifice				
n	10	10	9	10
Bone fluoride (μg/mg ash)	0.558 ± 0.033	1.163 ± 0.036**	2.868 ± 0.162**	4.324 ± 0.397**
105-Week Terminal Sacrifice				
n	10	10	10	10
Bone fluoride (μg/mg ash)	0.719 ± 0.064	1.606 ± 0.063**	3.585 ± 0.109**	5.690 ± 0.227**
Female				
24-Week Interim Sacrifice				
n	10	10	10	10
Bone fluoride (μg/mg ash)	0.395 ± 0.012	0.731 ± 0.018**	1.880 ± 0.080**	2.837 ± 0.091**
66-Week Interim Sacrifice				
n	10	8	10	9
Bone fluoride (μg/mg ash)	0.595 ± 0.026	1.606 ± 0.409**	2.883 ± 0.084**	4.716 ± 0.234**
105-Week Terminal Sacrifice				
n	10	10	10	10
Bone fluoride (μg/mg ash)	0.917 ± 0.073	1.523 ± 0.082**	4.370 ± 0.155**	6.241 ± 0.279**

** Significantly different (P≤0.01) from the control group by Dunn's or Shirley's test

[a] Mean ± standard error. Mean prestudy fluoride concentrations were 0.32 ± 0.06 μg fluoride per mg ash of the right humerus of male mice and 0.35 ± 0.05 μg fluoride per mg ash for female mice.

TABLE I5
Serum Fluoride Concentrations in Rats at the 27-Week and 66-Week Interim Sacrifices in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	25 ppm	100 ppm	175 ppm
Male				
27-Week Interim Sacrifice				
n	10	10	10	10
Serum fluoride (μg/mL)	0.063 ± 0.008	0.041 ± 0.007	0.065 ± 0.008	0.102 ± 0.018
66-Week Interim Sacrifice				
n	9	9	10	10
Serum fluoride (μg/mL)	0.067 ± 0.005	0.090 ± 0.008*	0.111 ± 0.006**	0.156 ± 0.014**
Female				
27-Week Interim Sacrifice				
n	10	10	9	10
Serum fluoride (μg/mL)	0.051 ± 0.016	0.086 ± 0.017	0.099 ± 0.018*	0.112 ± 0.007**
66-Week Interim Sacrifice				
n	10	10	10	9
Serum fluoride (μg/mL)	0.071 ± 0.007	0.085 ± 0.005*	0.107 ± 0.010**	0.191 ± 0.021**

* 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

TABLE I6
Urine Fluoride Concentrations in Rats at the 27-Week and 66-Week Interim Sacrifices in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	25 ppm	100 ppm	175 ppm
Male				
27-Week Interim Sacrifice				
n	10	10	10	10
Urine fluoride (µg/mL)	0.919 ± 0.095	3.055 ± 0.364**	10.473 ± 0.935**	17.110 ± 1.835**
66-Week Interim Sacrifice				
n	9	9	10	10
Urine fluoride (µg/mL)	1.01 ± 0.08	3.41 ± 0.28**	10.66 ± 0.86**	20.29 ± 1.97**
Female				
27-Week Interim Sacrifice				
n	10	10	10	10
Urine fluoride (µg/mL)	1.09 ± 0.31	5.00 ± 0.27**	18.51 ± 1.72**	32.97 ± 3.73**
66-Week Interim Sacrifice				
n	10	10	10	9
Urine fluoride (µg/mL)	0.851 ± 0.105	3.748 ± 0.185**	13.500 ± 2.062**	26.778 ± 1.562**

** Significantly different ($P \leq 0.01$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error

Hematology and Clinical Chemistry

During the 2-year studies of sodium fluoride, hematology and clinical chemistry analyses were conducted on all male and female F344/N rats scheduled for 27-week and 66-week interim sacrifice and B6C3F$_1$ mice scheduled for 24-week and 66-week interim sacrifice. Animals were anesthetized with a mixture of carbon dioxide and oxygen. Results are presented in Tables I7 through I10.

Blood samples for hematology analyses were collected from the retro-orbital sinus in tubes (Microtainers®, Becton-Dickinson, Rutherford, NJ) containing sodium EDTA. The following hematology measures were determined with an Ortho ELT-8 Laser Hematology Counter (Ortho Instruments, Westwood, MA): red blood cell count (RBC), hemoglobin, hematocrit, white blood cell count (WBC) with differential, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), reticulocyte count, and erythrocyte morphology (nRBC or nucleated red blood cells).

Blood samples for clinical chemistry analyses were collected from the retro-orbital sinus in serum separator tubes (Microtainers®, Becton-Dickinson, Rutherford, NJ). The following clinical chemistry measures were determined with an Hitachi 704 Chemistry Analyzer (Boehringer-Mannheim, Indianapolis, IN): serum calcium concentration, inorganic phosphorus concentration, and alkaline phosphatase activity.

TABLE I7
Hematology and Serum Chemistry Data for Rats at the 27-Week Interim Sacrifice in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	25 ppm	100 ppm	175 ppm
Male				
n	10	9	9	9
Hematocrit (%)	50.10 ± 0.67	52.44 ± 1.37	52.56 ± 0.73	52.11 ± 0.45
Hemoglobin (g/dL)	14.92 ± 0.22	15.44 ± 0.48	15.49 ± 0.19	15.32 ± 0.19
RBC ($10^6/\mu L$)	10.16 ± 0.17	10.59 ± 0.31	10.73 ± 0.19	10.33 ± 0.12
WBC ($10^3/\mu L$)	9.94 ± 0.46	8.02 ± 0.47	9.69 ± 0.63	9.44 ± 0.45
Segmented neutrophils ($10^3/\mu L$)	2.18 ± 0.23	1.77 ± 0.24	2.28 ± 0.27	2.20 ± 0.25
Lymphocytes ($10^3/\mu L$)	7.50 ± 0.44	6.07 ± 0.46	7.30 ± 0.46	7.01 ± 0.35
Monocytes ($10^3/\mu L$)	0.149 ± 0.061	0.101 ± 0.037	0.038 ± 0.020	0.099 ± 0.041
Eosinophils ($10^3/\mu L$)	0.105 ± 0.035	0.079 ± 0.036	0.075 ± 0.030	0.136 ± 0.055
MCV (μm^3)	49.60 ± 0.31	49.44 ± 0.18	48.89 ± 0.26	50.33 ± 0.24
MCH (pg)	14.67 ± 0.09	14.58 ± 0.09	14.43 ± 0.12	14.84 ± 0.10
MCHC (g/dL)	29.73 ± 0.15	29.42 ± 0.19	29.42 ± 0.18	29.49 ± 0.28
Platelets ($10^3/\mu L$)	629.6 ± 14.8	638.7 ± 21.8	674.7 ± 20.1	635.1 ± 17.1
nRBC/100 WBC	0.100 ± 0.100	0.222 ± 0.222	0.222 ± 0.222	0.111 ± 0.111
Calcium (mg/dL)	11.42 ± 0.18	11.62 ± 0.15[b]	11.70 ± 0.12[b]	11.78 ± 0.13[b]
Phosphorus (mg/dL)	6.28 ± 0.41	6.87 ± 0.39[b]	7.59 ± 0.25*[b]	6.42 ± 0.36[b]
Alkaline phosphatase (IU/L)	507.1 ± 24.9	568.2 ± 26.4[b]	483.0 ± 17.1[b]	533.9 ± 18.1
Female				
n	9	9	10	9
Hematocrit (%)	49.78 ± 0.32	49.33 ± 0.67	49.90 ± 0.38	49.11 ± 0.48
Hemoglobin (g/dL)	15.20 ± 0.15	15.17 ± 0.17	15.19 ± 0.09	15.00 ± 0.23
RBC ($10^6/\mu L$)	9.47 ± 0.07	9.42 ± 0.11	9.50 ± 0.10	9.33 ± 0.14
WBC ($10^3/\mu L$)	7.60 ± 0.88	6.51 ± 0.32	7.69 ± 0.71	6.64 ± 0.56
Segmented neutrophils ($10^3/\mu L$)	1.93 ± 0.54	1.55 ± 0.27	1.87 ± 0.34	1.27 ± 0.25
Lymphocytes ($10^3/\mu L$)	5.50 ± 0.56	4.80 ± 0.36	5.70 ± 0.47	5.26 ± 0.42
Monocytes ($10^3/\mu L$)	0.079 ± 0.027	0.045 ± 0.025	0.038 ± 0.013	0.068 ± 0.016
Eosinophils ($10^3/\mu L$)	0.084 ± 0.025	0.108 ± 0.034	0.076 ± 0.025	0.041 ± 0.018
MCV (μm^3)	52.56 ± 0.18	52.22 ± 0.40	52.60 ± 0.37	52.56 ± 0.41
MCH (pg)	16.04 ± 0.10	16.11 ± 0.13	16.01 ± 0.12	16.07 ± 0.06
MCHC (g/dL)	30.59 ± 0.14	30.92 ± 0.26	30.46 ± 0.13	30.56 ± 0.23
Platelets ($10^3/\mu L$)	616.9 ± 12.3	643.9 ± 53.7	603.7 ± 9.9	599.2 ± 15.4
nRBC/100 WBC	0.556 ± 0.294	0.222 ± 0.147	0.300 ± 0.213	0.444 ± 0.242
Calcium (mg/dL)	11.54 ± 0.15[b]	11.36 ± 0.29[b]	11.44 ± 0.19	11.16 ± 0.18[b]
Phosphorus (mg/dL)	6.47 ± 0.41[b]	7.07 ± 0.29[b]	6.64 ± 0.33	6.55 ± 0.45[b]
Alkaline phosphatase (IU/L)	520.5 ± 28.8[b]	427.2 ± 38.3[b]	481.9 ± 24.3	481.8 ± 16.9[b]

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error
[b] n=10

TABLE I8
Hematology and Serum Chemistry Data for Rats at the 66-Week Interim Sacrifice in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	25 ppm	100 ppm	175 ppm
Male				
n	8	8	10	8
Hematocrit (%)	47.71 ± 0.58	47.44 ± 0.70	46.22 ± 0.61	45.95 ± 1.27
Hemoglobin (g/dL)	15.39 ± 0.14	15.20 ± 0.17	14.91 ± 0.20	14.80 ± 0.35*
RBC ($10^6/\mu L$)	9.57 ± 0.12	9.32 ± 0.15	9.20 ± 0.12	9.09 ± 0.26
WBC ($10^3/\mu L$)	6.28 ± 0.50	6.54 ± 0.70	6.75 ± 0.48	6.49 ± 0.54
Segmented neutrophils ($10^3/\mu L$)	1.74 ± 0.30	2.05 ± 0.23	2.09 ± 0.19	2.10 ± 0.18
Lymphocytes ($10^3/\mu L$)	4.25 ± 0.38	4.31 ± 0.51	4.51 ± 0.38	4.35 ± 0.45
Monocytes ($10^3/\mu L$)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils ($10^3/\mu L$)	0.093 ± 0.022	0.174 ± 0.034	0.148 ± 0.027	0.046 ± 0.015
MCV (μm^3)	49.88 ± 0.30	50.75 ± 0.45	50.30 ± 0.30	50.75 ± 0.41
MCH (pg)	16.09 ± 0.10	16.33 ± 0.14	16.21 ± 0.07	16.29 ± 0.15
MCHC (g/dL)	32.25 ± 0.14	32.06 ± 0.21	32.26 ± 0.12	32.23 ± 0.22
Platelets ($10^3/\mu L$)	480.5 ± 30.3	490.6 ± 35.0	500.6 ± 23.7	564.0 ± 44.1
nRBC/100 WBC	0.500 ± 0.267	0.875 ± 0.350	1.000 ± 0.394	1.000 ± 0.423
Calcium (mg/dL)	11.69 ± 0.16[b]	11.42 ± 0.13[b]	11.68 ± 0.10	11.44 ± 0.13[c]
Phosphorus (mg/dL)	6.38 ± 0.26[b]	6.07 ± 0.12[b]	6.42 ± 0.18	6.64 ± 0.34[c]
Alkaline phosphatase (IU/L)	314.8 ± 15.0[b]	327.1 ± 16.9[b]	343.3 ± 19.2	331.4 ± 16.8[c]
Female				
n	10	10	10	9
Hematocrit (%)	47.38 ± 0.73	46.33 ± 0.86	46.38 ± 0.68	47.71 ± 0.72
Hemoglobin (g/dL)	15.55 ± 0.21	15.11 ± 0.29	15.20 ± 0.21	15.60 ± 0.22
RBC ($10^6/\mu L$)	8.61 ± 0.13	8.45 ± 0.15	8.52 ± 0.13	8.74 ± 0.12
WBC ($10^3/\mu L$)	3.33 ± 0.39	3.25 ± 0.31	4.11 ± 0.49	3.32 ± 0.43
Segmented neutrophils ($10^3/\mu L$)	1.17 ± 0.17	1.08 ± 0.10	1.35 ± 0.21	1.35 ± 0.31
Lymphocytes ($10^3/\mu L$)	2.08 ± 0.32	2.11 ± 0.25	2.71 ± 0.41	1.92 ± 0.24
Monocytes ($10^3/\mu L$)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils ($10^3/\mu L$)	0.082 ± 0.019	0.061 ± 0.014	0.058 ± 0.013	0.054 ± 0.025
MCV (μm^3)	55.00 ± 0.21	54.80 ± 0.13	54.40 ± 0.31	54.56 ± 0.29
MCH (pg)	18.07 ± 0.15	17.89 ± 0.11	17.84 ± 0.10	17.87 ± 0.13
MCHC (g/dL)	32.84 ± 0.22	32.62 ± 0.15	32.76 ± 0.10	32.72 ± 0.16
Platelets ($10^3/\mu L$)	444.3 ± 19.8	428.2 ± 20.5	454.5 ± 23.4	454.6 ± 12.6
nRBC/100 WBC	2.10 ± 0.35	2.30 ± 0.62	1.80 ± 0.53	1.89 ± 0.48
Calcium (mg/dL)	11.36 ± 0.19	11.38 ± 0.15	11.40 ± 0.13	11.67 ± 0.12
Phosphorus (mg/dL)	6.17 ± 0.31	6.03 ± 0.25	6.17 ± 0.41	6.58 ± 0.15
Alkaline phosphatase (IU/L)	255.0 ± 8.5[b]	211.8 ± 13.0*	225.9 ± 12.0*	215.8 ± 16.2*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error
[b] n=9
[c] n=10

TABLE I9
Hematology and Serum Chemistry Data for Mice at the 24-Week Interim Sacrifice in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	25 ppm	100 ppm	175 ppm
Male				
n	10	10	10	9
Hematocrit (%)	52.70 ± 0.73	53.40 ± 0.82	52.60 ± 0.73	51.44 ± 0.65
Hemoglobin (g/dL)	16.02 ± 0.17	16.38 ± 0.27	15.94 ± 0.28	15.73 ± 0.19
RBC ($10^6/\mu L$)	11.52 ± 0.18	11.65 ± 0.15	11.38 ± 0.18	11.32 ± 0.16
WBC ($10^3/\mu L$)	3.18 ± 0.29	3.70 ± 0.20	3.96 ± 0.20	3.58 ± 0.22
Segmented neutrophils ($10^3/\mu L$)	0.539 ± 0.065	0.641 ± 0.108	0.726 ± 0.110	0.636 ± 0.066
Lymphocytes ($10^3/\mu L$)	2.62 ± 0.27	2.99 ± 0.15	3.19 ± 0.18	2.91 ± 0.22
Monocytes ($10^3/\mu L$)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils ($10^3/\mu L$)	0.019 ± 0.007	0.068 ± 0.022	0.035 ± 0.015	0.030 ± 0.022
MCV (μm^3)	45.70 ± 0.26	45.80 ± 0.25	46.10 ± 0.28	45.56 ± 0.24
MCH (pg)	13.94 ± 0.18	14.06 ± 0.13	14.00 ± 0.13	13.91 ± 0.08
MCHC (g/dL)	30.45 ± 0.35	30.65 ± 0.23	30.37 ± 0.27	30.51 ± 0.17
Platelets ($10^3/\mu L$)	1300 ± 33	1317 ± 27	1367 ± 27	1276 ± 39
nRBC/100 WBC	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Calcium (mg/dL)	9.60 ± 0.16	9.28 ± 0.14	9.40 ± 0.20	9.46 ± 0.18[b]
Phosphorus (mg/dL)	11.40 ± 0.45	11.25 ± 0.53	10.97 ± 0.37	11.62 ± 0.42[b]
Alkaline phosphatase (IU/L)	141.1 ± 5.4	164.3 ± 6.3*	147.0 ± 5.0	153.2 ± 2.8[b]
Female				
n	10	10	10	10
Hematocrit (%)	51.60 ± 0.87	51.10 ± 0.75	52.00 ± 0.63	50.00 ± 1.01
Hemoglobin (g/dL)	15.72 ± 0.20	14.86 ± 0.50	15.84 ± 0.20	15.28 ± 0.33
RBC ($10^6/\mu L$)	11.30 ± 0.21	11.03 ± 0.20	11.25 ± 0.13	10.89 ± 0.22
WBC ($10^3/\mu L$)	2.28 ± 0.16	2.58 ± 0.22	2.54 ± 0.13	2.18 ± 0.16
Segmented neutrophils ($10^3/\mu L$)	0.333 ± 0.045	0.329 ± 0.050	0.288 ± 0.049	0.299 ± 0.056
Lymphocytes ($10^3/\mu L$)	1.92 ± 0.14	2.23 ± 0.20	2.23 ± 0.12	1.86 ± 0.13
Monocytes ($10^3/\mu L$)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils ($10^3/\mu L$)	0.028 ± 0.010	0.024 ± 0.008	0.021 ± 0.011	0.019 ± 0.006
MCV (μm^3)	45.60 ± 0.22	46.30 ± 0.30	46.00 ± 0.15	45.90 ± 0.18
MCH (pg)	13.94 ± 0.18	13.93 ± 0.10	14.10 ± 0.14	14.04 ± 0.12
MCHC (g/dL)	30.53 ± 0.39	30.12 ± 0.21	29.64 ± 0.76	30.58 ± 0.19
Platelets ($10^3/\mu L$)	1209 ± 30	1118 ± 43	1110 ± 39	1175 ± 35
nRBC/100 WBC	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Calcium (mg/dL)	9.08 ± 0.28	9.48 ± 0.23	9.60 ± 0.16	9.24 ± 0.15
Phosphorus (mg/dL)	10.01 ± 0.22	10.20 ± 0.66	10.39 ± 0.58	9.86 ± 0.29
Alkaline phosphatase (IU/L)	200.1 ± 11.1	179.4 ± 11.7	214.4 ± 5.9	258.5 ± 10.7**

* 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
[b] n=10

TABLE I10
Hematology and Serum Chemistry Data for Mice at the 66-Week Interim Sacrifice in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	Control	25 ppm	100 ppm	175 ppm
Male				
n	10	10	9	10
Hematocrit (%)	48.53 ± 1.27	46.23 ± 0.48	49.19 ± 0.85	48.10 ± 0.72
Hemoglobin (g/dL)	15.56 ± 0.35	14.69 ± 0.15**	15.54 ± 0.29	15.19 ± 0.25
RBC ($10^6/\mu L$)	10.51 ± 0.21	9.81 ± 0.14*	10.36 ± 0.18	10.38 ± 0.18
WBC ($10^3/\mu L$)	4.61 ± 0.67	3.15 ± 0.35	4.34 ± 0.72	3.85 ± 0.44
Segmented neutrophils ($10^3/\mu L$)	0.788 ± 0.116	0.712 ± 0.093	0.923 ± 0.291	0.767 ± 0.132
Lymphocytes ($10^3/\mu L$)	3.75 ± 0.58	2.38 ± 0.38	3.34 ± 0.67	3.00 ± 0.33
Monocytes ($10^3/\mu L$)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils ($10^3/\mu L$)	0.062 ± 0.018	0.058 ± 0.011	0.073 ± 0.024	0.087 ± 0.020
MCV (μm^3)	46.00 ± 0.56	47.30 ± 0.47	47.44 ± 0.24	46.40 ± 0.27
MCH (pg)	14.81 ± 0.16	14.97 ± 0.18	15.01 ± 0.05	14.65 ± 0.05
MCHC (g/dL)	32.10 ± 0.18	31.80 ± 0.22	31.59 ± 0.14	31.58 ± 0.17
Platelets ($10^3/\mu L$)	780.7 ± 35.1	881.7 ± 38.8	865.7 ± 24.8	803.9 ± 57.5
nRBC/100 WBC	0.100 ± 0.100	0.100 ± 0.100	0.000 ± 0.000	0.000 ± 0.000
Calcium (mg/dL)	9.98 ± 0.19	10.12 ± 0.15	9.84 ± 0.10	9.78 ± 0.11
Phosphorus (mg/dL)	8.55 ± 0.21	8.72 ± 0.52	8.30 ± 0.43	7.48 ± 0.35*
Alkaline phosphatase (IU/L)	167.3 ± 7.2	164.5 ± 6.1	171.7 ± 9.0	185.7 ± 5.2*
Female				
n	10	8	10	9
Hematocrit (%)	49.62 ± 0.82	48.21 ± 0.77	48.55 ± 0.64	50.96 ± 0.82
Hemoglobin (g/dL)	15.67 ± 0.24	15.20 ± 0.30	15.26 ± 0.20	16.08 ± 0.29
RBC ($10^6/\mu L$)	10.38 ± 0.17	10.08 ± 0.21	10.14 ± 0.15	10.67 ± 0.18
WBC ($10^3/\mu L$)	2.99 ± 0.21	3.13 ± 0.22	2.79 ± 0.29	2.68 ± 0.20
Segmented neutrophils ($10^3/\mu L$)	0.638 ± 0.092	0.951 ± 0.119	0.669 ± 0.091	0.531 ± 0.066
Lymphocytes ($10^3/\mu L$)	2.29 ± 0.20	2.12 ± 0.17	2.07 ± 0.21	2.10 ± 0.16
Monocytes ($10^3/\mu L$)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils ($10^3/\mu L$)	0.062 ± 0.019	0.057 ± 0.017	0.049 ± 0.013	0.048 ± 0.012
MCV (μm^3)	47.80 ± 0.25	47.88 ± 0.48	48.00 ± 0.42	47.67 ± 0.33
MCH (pg)	15.12 ± 0.14	15.09 ± 0.10	15.08 ± 0.14	15.07 ± 0.07
MCHC (g/dL)	31.60 ± 0.29	31.53 ± 0.20	31.43 ± 0.22	31.57 ± 0.23
Platelets ($10^3/\mu L$)	668.8 ± 22.6	818.5 ± 45.4*	696.7 ± 35.1	603.7 ± 36.0
nRBC/100 WBC	0.000 ± 0.000	0.000 ± 0.000	0.300 ± 0.153	0.000 ± 0.000
Calcium (mg/dL)	9.93 ± 0.21[b]	9.93 ± 0.11	9.72 ± 0.13	10.00 ± 0.25
Phosphorus (mg/dL)	7.72 ± 0.50[b]	7.65 ± 0.50	6.98 ± 0.22	7.19 ± 0.23
Alkaline phosphatase (IU/L)	269.0 ± 15.3	310.9 ± 11.8	301.0 ± 19.7	506.7 ± 34.1**

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
a Mean ± standard error
b n=9

Urinalysis and Urine Concentration

During the 2-year studies of sodium fluoride, urinalysis and urine concentration studies were conducted on all male and female F344/N rats scheduled for 27-week and 66-week interim sacrifice. Results are presented in Tables I11 and I12.

For urinalysis studies, rats were individually housed in metabolism cages (Maryland Plastics, New York, NY) for 16-hour urine collection. Animals were fasted during urine collection, but sodium-fluoride-supplemented water was available *ad libitum*. Color and appearance of urine samples were recorded. Volume was measured to the nearest 100 μL. Specific gravity was determined by refractometer (American Optical, Buffalo, NY). Urine sediment was examined with a light microscope. The following additional parameters were measured with an Hitachi 704 Chemistry Analyzer (Boehringer-Mannheim, Indianapolis, IN): protein, glucose, calcium, inorganic phosphorus.

For urine concentration studies, rats were deprived of water for 16 hours, then each animal's urinary bladder was emptied by gently exerting manual pressure on the lower abdomen over the bladder. The animals were then individually housed in metabolism cages for 4-hour urine collection; drinking water was not available. Volume to the nearest 100 μL and specific gravity of each sample were measured.

TABLE I11
***Urinalysis Data for Rats at the 27-Week Interim Sacrifice in the 2-Year Drinking Water Studies of Sodium Fluoride*[a]**

	n	Control	25 ppm	100 ppm	175 ppm
Male					
Volume of concentrated urine (mL/4 hours)	10	0.180 ± 0.096	0.270 ± 0.096	0.260 ± 0.156	0.280 ± 0.103
Specific gravity of concentrated urine (g/mL)	3	1.055 ± 0.010	1.070 ± 0.011[b]	1.060 ± 0.018	1.061 ± 0.002[c]
Volume (mL/16 hours)	10	8.24 ± 0.88	7.67 ± 0.77	7.56 ± 1.18	8.42 ± 0.81
Specific gravity (g/mL)	10	1.029 ± 0.001	1.032 ± 0.003	1.030 ± 0.004	1.028 ± 0.003
Glucose (mg/dL)	10	5.90 ± 2.39	9.40 ± 3.75	7.50 ± 3.56	5.90 ± 3.32
Calcium (mg/L)	10	3.03 ± 0.23	2.93 ± 0.26	2.66 ± 0.27	3.93 ± 0.48
Phosphorus (mg/dL)	10	138.4 ± 10.5	159.2 ± 17.3	141.8 ± 15.0	149.0 ± 9.5
Protein (mg/dL)	10	130.6 ± 10.0	165.6 ± 19.5	156.8 ± 23.4	130.5 ± 16.2
WBC/HPF[d]	10	0 ± 1	0 ± 0	0 ± 1	0 ± 1
RBC/HPF	10	10 ± 11	10 ± 7	9 ± 10	12 ± 14
Casts/LPF[e]	10	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Epithelial cells/HPF	10	1 ± 1	1 ± 1	1 ± 0	0 ± 1
Mucous/HPF	10	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Sperm/HPF	10	7 ± 7	9 ± 12	2 ± 2	5 ± 7
Bacteria/HPF	10	3 ± 1	4 ± 1	3 ± 1	3 ± 1
Yeast/HPF	10	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Amorphous material/HPF	10	1 ± 1	1 ± 1	0 ± 1	1 ± 1
Crystals/HPF	10	6 ± 1	3 ± 1	3 ± 1	3 ± 1
Female					
Volume of concentrated urine (mL/4 hours)	10	0.025 ± 0.017	0.000 ± 0.000	0.045 ± 0.024	0.015 ± 0.015
Specific gravity of concentrated urine (g/mL)	3	1.068 ± 0.013[f]	–[g]	1.083 ± 0.012	1.051 ± [h]
Volume (mL/16 hours)	10	5.01 ± 1.03	6.68 ± 0.88	3.34 ± 0.55	2.80 ± 0.44
Specific gravity (g/mL)	10	1.027 ± 0.005	1.017 ± 0.002	1.029 ± 0.004	1.035 ± 0.005
Glucose (mg/dL)	10	8.10 ± 2.62	3.90 ± 1.33	11.50 ± 2.78	15.40 ± 2.83
Calcium (mg/L)	10	6.16 ± 1.11	4.44 ± 0.64	8.07 ± 0.48	9.20 ± 0.78*
Phosphorus (mg/dL)	10	109.60 ± 26.26	74.80 ± 16.16	92.80 ± 19.52	166.20 ± 35.22
Protein (mg/dL)	10	15.50 ± 3.15	8.60 ± 1.19	19.60 ± 3.02	19.80 ± 2.60
WBC/HPF	10	0 ± 0	0 ± 0	0 ± 0	0 ± 0
RBC/HPF	10	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Casts/LPF	10	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Epithelial cells/HPF	10	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Mucous/HPF	10	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Bacteria/HPF	10	1 ± 1	2 ± 1	1 ± 1	1 ± 1
Yeast/HPF	10	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Amorphous material/HPF	10	0 ± 0	0 ± 0	0 ± 0	0 ± 1
Crystals/HPF	10	1 ± 1	2 ± 1	1 ± 1	2 ± 1

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error
[b] n=5
[c] n=6
[d] HPF = high power field
[e] LPF = low power field
[f] n=2
[g] Analysis not done on this dose group
[h] n=1

TABLE I12
Urinalysis Data for Rats at the 66-Week Interim Sacrifice in the 2-Year Drinking Water Studies of Sodium Fluoride[a]

	n	Control	25 ppm	100 ppm	175 ppm
Male					
Volume of concentrated urine (mL/4 hours)	8	1.233 ± 0.356[b]	0.975 ± 0.291	1.340 ± 0.402[c]	1.200 ± 0.334
Specific gravity of concentrated urine (g/mL)	8	1.051 ± 0.010[b]	1.056 ± 0.004	1.040 ± 0.006[c]	1.045 ± 0.006
Volume (mL/16 hours)	10	7.98 ± 0.59[d]	6.93 ± 0.86[d]	8.02 ± 0.86	6.34 ± 0.79
Specific gravity (g/mL)	10	1.028 ± 0.002[d]	1.027 ± 0.001[d]	1.027 ± 0.002	1.027 ± 0.002
Glucose (mg/dL)	10	14.00 ± 1.71[d]	13.33 ± 1.08[d]	13.90 ± 1.52	15.10 ± 1.88
Calcium (mg/L)	10	1.467 ± 0.260[d]	1.500 ± 0.494[d]	0.790 ± 0.272	1.240 ± 0.393
Phosphorus (mg/dL)	10	100.74 ± 9.91[d]	97.70 ± 10.73[d]	102.65 ± 8.56	98.71 ± 13.83
Protein (mg/dL)	10	376.6 ± 40.0[d]	318.2 ± 29.1[d]	330.5 ± 27.2	295.1 ± 41.9
WBC/HPF[e]	10	0 ± 0[d]	0 ± 0[d]	0 ± 0	0 ± 0
RBC/HPF	10	2 ± 3[d]	12 ± 33[d]	5 ± 12	4 ± 9
Casts/LPF[f]	10	0 ± 0[d]	0 ± 0[d]	0 ± 0	0 ± 0
Epithelial cells/HPF	10	0 ± 0[d]	0 ± 0[d]	0 ± 0	0 ± 0
Mucous/HPF	10	0 ± 0[d]	0 ± 0[d]	0 ± 0	0 ± 0
Sperm/HPF	10	6 ± 13[d]	5 ± 7[d]	4 ± 4	4 ± 9
Bacteria/HPF	10	2 ± 1[d]	2 ± 1[d]	2 ± 1	2 ± 1
Yeast/HPF	10	0 ± 0[d]	0 ± 0[d]	0 ± 0	0 ± 0
Amorphous material/HPF	10	0 ± 0[d]	0 ± 0[d]	0 ± 0	0 ± 0
Crystals/HPF	10	2 ± 1[d]	1 ± 2[d]	2 ± 1	2 ± 2
Female					
Volume of concentrated urine (mL/4 hours)	10	0.430 ± 0.062	0.300 ± 0.093[g]	0.420 ± 0.068	0.356 ± 0.060[d]
Specific gravity of concentrated urine (g/mL)	10	1.053 ± 0.006	1.051 ± 0.006[d]	1.052 ± 0.005	1.054 ± 0.002[d]
Volume (mL/16 hours)	10	5.61 ± 0.71[d]	5.25 ± 0.61	5.22 ± 0.68	5.86 ± 0.55[d]
Specific gravity (g/mL)	10	1.020 ± 0.002	1.024 ± 0.002	1.022 ± 0.002	1.023 ± 0.001[d]
Glucose (mg/dL)	10	9.30 ± 1.24	10.40 ± 1.02	9.90 ± 0.97	9.00 ± 1.03[d]
Calcium (mg/L)	10	3.32 ± 0.96	5.40 ± 1.35	4.47 ± 0.84	6.67 ± 0.72[*,d]
Phosphorus (mg/dL)	10	81.99 ± 9.28	92.55 ± 9.45	82.79 ± 7.53	94.76 ± 8.85[d]
Protein (mg/dL)	10	104.10 ± 26.18	132.90 ± 35.78	164.80 ± 44.99	45.00 ± 8.29[d]
WBC/HPF	10	0 ± 0	0 ± 1	0 ± 0	0 ± 1[d]
RBC/HPF	10	1 ± 1	0 ± 1	0 ± 0	0 ± 0[d]
Casts/LPF	10	0 ± 0	0 ± 0	0 ± 0	0 ± 0[d]
Epithelial cells/HPF	10	0 ± 0	0 ± 0	0 ± 0	0 ± 0[d]
Mucous/HPF	10	0 ± 0	0 ± 0	0 ± 0	0 ± 0[d]
Bacteria/HPF	10	2 ± 1	2 ± 1	2 ± 1	2 ± 1[d]
Yeast/HPF	10	0 ± 0	0 ± 0	0 ± 0	0 ± 0[d]
Amorphous material/HPF	10	0 ± 0	0 ± 0	0 ± 0	0 ± 0[d]
Crystals/HPF	10	1 ± 0	1 ± 1	1 ± 0	1 ± 1[d]

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
a Mean ± standard error
b n=6
c n=10
d n=9
e HPF = high power field
f LPF = low power field
g n=8

Bioavailability

Methods

During the 2-year studies of sodium fluoride, studies were conducted on ten randomly selected control male rats after approximately 6, 12, and 18 months on study to obtain an estimate of the amount of fluoride contained in the NIH-07 diet that was available for absorption by the animals. This estimate was derived by determining the total amount of fluoride ingested, based on the fluoride content of the diet and water and measures of consumption, and the amount excreted in the feces. Under the assumptions that the primary route of excretion of bioavailable fluoride is via the urine and that excretion of fluoride in feces represents primarily fluoride not absorbed by the animal, an apparent fraction of the dietary fluoride that was bioavailable was obtained.

These rats were individually housed for 7 days in glass (Vanguard International, Neptune, NJ) or Nalgene® (Sybron Corporation, Rochester, NY) metabolism cages. During these 7-day periods, food and water intake were measured, as well as urine and feces output. During the 12-month and 18-month phases, the rats were acclimatized to these cages for 3 days before the 7-day test period. Urine was analyzed for fluoride concentration by fixing with low fluoride calcium phosphate, ashing in a crucible at 500° C, followed by the direct determination of fluoride with a fluoride ion electrode in a solution of ashed urine adjusted to a pH of 5.0. Fecal samples were dried, dissolved for 1 hour in 1 M HCl, diluted with deionized water, then mixed with a citrate buffer. Fluoride concentration was determined by ion selective electrode analysis.

Results

Results of these studies indicated that the bioavailable fraction of the dietary fluoride was 38% at 6 months, 64% at 12 months, and 63% at 18 months. Full results of these studies are on file at NIEHS.

APPENDIX J
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION

PROCUREMENT AND CHARACTERIZATION OF SODIUM FLUORIDE

Sodium fluoride was obtained from Apache Chemical, Inc, (Seward, IL) in two lots. Lot number A-06255 was used for the 14-day and 6-month drinking water studies. Lot number A022085 was used throughout the 2-year drinking water studies. Identity, purity, and stability analyses were conducted by Midwest Research Institute (Kansas City, MO). Reports of analyses performed in support of the sodium fluoride studies are on file at NIEHS.

Both lots of the study chemical, a white crystalline powder, were identified as sodium fluoride by elemental analysis. The elemental analyses were in agreement with the theoretical values for sodium and fluoride.

The purity of lot number A-06255 was determined by Karl Fischer water analysis and spark source mass spectrometry. Karl Fischer analysis indicated the presence of 0.17% water, while spark source mass spectrometry indicated less than 100 ppm total impurities. The cumulative analytical data indicated a purity of greater than 99%.

The purity of lot number A022085 was determined by elemental analysis, Karl Fischer water analysis, spark source mass spectrometry, weight loss upon drying, and potentiometrically monitored acid titration with 0.01 N sodium hydroxide. Elemental analysis indicated that hydrogen was present at less than 0.05%; Karl Fischer analysis indicated the presence of less than 0.002% water. Spark source mass spectrometry found chlorine to be present at a level of 180 ppm; all other impurities detected by spark source mass spectrometry totaled less than 57 ppm. Percent weight loss on drying at 170° C for 24 hours was 0.022%. Titration of acidic components with sodium hydroxide indicated less than 0.2% free acid (expressed as hydrofluoric acid). The cumulative analytical data indicated a purity of greater than 99%.

During the 6-month studies, Karl Fischer water analysis and elemental analysis (by titration for fluoride and atomic absorption analysis for sodium) were employed to reanalyze the bulk chemical. No significant differences between values for test and reference samples were found. During the 2-year studies, elemental analyses confirmed that sodium fluoride was stable as a bulk chemical, and no degradation of the study material was seen throughout the studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared weekly throughout the studies by mixing appropriate quantities of sodium fluoride with deionized water to obtain the required concentrations (Table J1). Stability studies were performed at Midwest Research Institute (MRI) by potentiometric titration of the fluoride ion with a fluoride ion electrode.

Sodium fluoride in deionized water at 25 ppm was found to be stable for up to 3 weeks under simulated animal dosing conditions when stored at room temperature (25° C) in sealed polypropylene containers protected from light.

No dose concentration analyses were performed during the 14-day studies of sodium fluoride. During the 6-month and 2-year studies, periodic analyses of the dose formulations of sodium fluoride were conducted at the study laboratory by potentiometric titration of the fluoride ion with a fluoride ion electrode. Results of analyses conducted during the 6-month studies are reported in Table J2, those during the 2-year studies in Tables J3 and J4. These analyses indicated that all dose formulations were within ±10% of target concentrations throughout the studies. Referee analyses were conducted by the analytical chemistry laboratory (MRI) once during the 6-month studies (Table J2) and five times throughout the 2-year studies (Table J5). Referee analyses during the 2-year studies indicated that dose formulations were within 10% of target concentrations.

TABLE J1
Preparation and Storage of Dose Formulations during the Drinking Water Studies of Sodium Fluoride

14-Day Studies	6-Month Studies	2-Year Studies
Preparation		
A premix was prepared by putting a weighed portion of sodium fluoride into a graduated mixing cylinder and mixing with 1,000 mL deionized water. The premix was placed in a 5 gallon container, diluted with deionized water to produce the proper volume of stock mixture for the high dose, and stirred for 5 to 10 minutes. Sequentially diluting this stock produced the remaining dose levels, which were placed in separate plastic containers and stored.	The highest dose concentration was prepared by grinding a weighed portion of sodium fluoride with a mortar and pestle, suspending the ground sodium fluoride in deionized water, then adding additional water to obtain the final volume. Lower concentrations were obtained by sequential dilution. Final solutions were stored in polypropylene jugs.	Sodium fluoride solutions were prepared weekly. A premix and a bulk mix were prepared for each formulation. The premix was prepared by grinding sodium fluoride with a mortar and pestle, placing a weighed amount into a polypropylene premix jar, and mixing with a specified volume of deionized water. The premix was placed into a polypropylene carboy and rinsed with additional deionized water. The bulk mix was completed by diluting the premix in the carboy with a specified final volume of deionized water. The carboy was sealed, placed in an opaque bag to protect the contents from light, and stored.
Maximum Storage Time for Dose Formulations		
1 week	Not specified	1 week
Storage Conditions for Dose Formulations		
Room temperature	Room temperature	Room temperature
Study Laboratory		
Battelle Columbus Laboratories (Columbus, OH)	Same as 14-day studies	Same as 14-day studies
Referee Laboratory		
None	Midwest Research Institute (Kansas City, MO)	Same as 6-month studies

TABLE J2
Results of Dose Formulation Analyses during the 6-Month Drinking Water Studies of Sodium Fluoride

Date Mixed	Theoretical Concentration (ppm)	Determined Concentration[a] (ppm)	Percent of Target
Rats			
24 September 1980	10	11	110
	30	33	110
	100	108	108
	300	320	107
Mice			
24 September 1980	50	54	108
	100	106	106
	200	217	109
	300	320	107
	600	608	101
Referee Analysis			
24 September 1980	300	320[b]	107

[a] Results are based on analysis by a fluoride selective electrode and multiplication of results by the factor 2.21 to convert the fluoride ion weight to the weight of the sodium fluoride molecule.
[b] Based on duplicate analyses

TABLE J3
Analyses of Dose Formulations Administered to Rats during the 2-Year Drinking Water Studies of Sodium Fluoride

Theoretical Dose Concentration (ppm)	Predosing Analyses[a]			Postdosing Analyses[b]		
	Samples (n)	Dose Concentration (ppm)[c]	Range	Samples (n)	Dose Concentration (ppm)[c]	Range
October 1985						
25	16	25.9 ± 0.3	23.2 - 27.5	3	26.8 ± 0.2	26.4 - 27.0
100	16	104.6 ± 1.0	99.1 - 109.0	2	107.3 ± 0.0	107.3 - 107.3
175	24	177.0 ± 1.1	168.9 - 189.9	2	186.5 ± 3.7	182.8 - 190.2
November 1985						
25	12	25.6 ± 0.2	24.5 - 26.6			
100	12	99.8 ± 1.0	95.7 - 104.6			
175	16	179.5 ± 1.1	172.2 - 185.0			
December 1985						
25	15	25.0 ± 0.2	24.1 - 26.3			
100	15	97.4 ± 0.6	94.3 - 102.9			
175	20	175.8 ± 1.2	169.0 - 183.6			
January 1986						
25	12	24.9 ± 0.2	23.4 - 25.3			
100	12	97.8 ± 0.9	91.6 - 101.9			
175	16	173.7 ± 1.8	162.1 - 185.0			
February 1986						
25	10	25.8 ± 0.2	24.7 - 27.0			
100	11	100.6 ± 1.2	94.7 - 107.6			
175	15	179.1 ± 1.2	175.6 - 187.7			
March 1986						
25	8	25.6 ± 0.1	25.2 - 26.2			
100	8	104.5 ± 1.1	100.8 - 108.7			
175	12	179.2 ± 1.4	172.6 - 188.2			
April 1986						
25	5	25.5 ± 0.4	24.6 - 27.0			
100	4	99.5 ± 1.1	97.7 - 102.3			
175	6	175.9 ± 1.7	171.7 - 182.5			
June 1986						
25	2	25.2 ± 0.0	25.2 - 25.2	2	26.5 ± 0.8	25.7 - 27.2
100	2	97.2 ± 0.9	96.3 - 98.1	2	101.0 ± 1.0	100.1 - 102.0
175	3	171.7 ± 1.0	169.7 - 172.8	3	176.6 ± 2.3	174.3 - 181.1
July 1986						
25	2	24.8 ± 0.0	24.8 - 24.8			
100	2	98.9 ± 1.0	97.9 - 99.9			
175	3	174.7 ± 2.4	172.3 - 179.4			

TABLE J3
Analyses of Dose Formulations Administered to Rats during the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

Theoretical Dose Concentration (ppm)	Predosing Analyses[a] Samples (n)	Dose Concentration (ppm)[c]	Range	Postdosing Analyses[b] Samples (n)	Dose Concentration (ppm)[c]	Range
September 1986						
25	2	25.0 ± 0.0	25.0 - 25.0	2	23.6 ± 0.0	23.6 - 23.6
100	2	96.5 ± 0.0	96.5 - 96.5	2	98.2 ± 0.0	98.2 - 98.2
175	3	172.2 ± 0.0	172.2 - 172.2	3	173.8 ± 0.0	173.8 - 173.8
November 1986						
25	2	22.6 ± 0.0	22.6 - 22.6			
100	2	95.3 ± 0.0	95.3 - 95.3			
175	3	172.5 ± 0.0	172.5 - 172.5			
January 1987						
25	2	27.4 ± 0.0	27.4 - 27.4			
100	2	97.9 ± 0.0	97.9 - 97.9			
175	3	172.4 ± 1.1	170.3 - 173.5			
March 1987						
25	2	24.2 ± 0.0	24.2 - 24.2	2	23.3 ± 0.2	23.1 - 23.5
100	2	101.8 ± 1.1	100.7 - 102.9	2	100.3 ± 0.0	100.3 - 100.3
175	3	184.7 ± 1.3	183.5 - 187.3	3	181.8 ± 3.4	176.7 - 188.2
May 1987						
25	2	25.2 ± 0.5	24.7 - 25.7			
100	2	96.5 ± 1.0	95.5 - 97.4			
175	3	175.7 ± 2.3	173.4 - 180.4			
July 1987						
25	2	26.4 ± 0.3	26.2 - 26.7			
100	2	102.2 ± 0.0	102.2 - 102.2			
175	3	177.7 ± 0.0	177.7 - 177.7			
August 1987						
25	2	23.8 ± 0.0	23.8 - 23.8	2	26.5 ± 0.2	26.3 - 26.7
100	2	98.9 ± 2.1	96.9 - 101.0	2	103.3 ± 0.7	102.6 - 104.0
175	3	181.5 ± 2.2	177.7 - 185.3	2	180.1 ± 0.7	179.4 - 180.8

[a] Analyses were performed using a potentiometric method with a fluoride ion electrode. All dose formulations prepared during the first 27 weeks of the studies were analyzed prior to use. During the remainder of the studies, analyses were performed once every 8 weeks.
[b] Analyses were performed using a potentiometric method with a fluoride ion electrode. Samples from the batches analyzed before dosing were retrieved from the animal room after dosing for the postdose analysis.
[c] Mean ± standard error

TABLE J4
Analyses of Dose Formulations Administered to Mice during the 2-Year Drinking Water Studies of Sodium Fluoride

Theoretical Dose Concentration (ppm)	Predosing Analyses[a] Samples (n)	Predosing Analyses[a] Dose Concentration (ppm)[c]	Predosing Analyses[a] Range	Postdosing Analyses[b] Samples (n)	Postdosing Analyses[b] Dose Concentration (ppm)[c]	Postdosing Analyses[b] Range
October 1985						
25	6	26.0 ± 0.3	25.1 – 27.5	3	25.5 ± 0.2	25.3 – 25.8
100	6	104.9 ± 1.1	100.8 – 108.4	3	100.0 ± 1.2	98.0 – 102.0
175	8	183.8 ± 1.7	177.9 – 189.7	3	184.6 ± 1.3	183.3 – 187.1
November 1985						
25	8	25.1 ± 0.2	24.5 – 25.8			
100	8	100.3 ± 0.7	95.7 – 101.9			
175	12	181.2 ± 1.9	167.7 – 190.7			
December 1985						
25	10	25.0 ± 0.2	24.1 – 25.9			
100	10	100.1 ± 1.1	94.7 – 106.6			
175	15	178.2 ± 1.2	169.0 – 187.9			
January 1986						
25	8	24.3 ± 0.5	23.4 – 25.2			
100	8	97.8 ± 1.4	91.6 – 101.9			
175	12	173.3 ± 1.8	162.1 – 183.6			
February 1986						
25	8	25.6 ± 0.3	24.7 – 26.7			
100	8	100.0 ± 1.3	92.9 – 104.3			
175	12	177.4 ± 1.2	169.2 – 182.7			
March 1986						
25	8	25.6 ± 0.1	24.7 – 26.2			
100	8	105.5 ± 1.0	100.8 – 108.7			
175	12	182.8 ± 1.2	176.6 – 188.2			
April 1986						
25	4	25.4 ± 0.2	25.0 – 26.0			
100	4	102.4 ± 1.1	99.6 – 104.3			
175	6	177.6 ± 1.3	175.1 – 182.5			
June 1986						
25	2	24.8 ± 0.5	24.3 – 25.2	1	25.69	25.69
100	2	96.3 ± 0.0	96.3 – 96.3	2	102.0 ± 0.0	102.0 – 102.0
175	3	163.4 ± 1.0	161.4 – 164.4	3	174.4 ± 3.9	167.8 – 181.1
July 1986						
25	2	24.1 ± 0.3	23.8 – 24.3			
100	2	99.9 ± 2.0	97.9 – 101.9			
175	3	172.3 ± 0.0	172.3 – 172.3			
September 1986						
25	2	25.0 ± 0.0	25.0 – 25.0	2	24.81 ± 0.26	24.55 – 25.06
100	2	98.4 ± 1.9	96.5 – 100.3	2	100.26 ± 2.05	98.21 –102.30
175	3	176.7 ± 2.3	172.2 – 179.0	2	177.43 ± 3.62	173.81 –181.04

TABLE J4
Analyses of Dose Formulations Administered to Mice during the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

Theoretical Dose Concentration (ppm)	Predosing Analyses[a] Samples (n)	Predosing Analyses[a] Dose Concentration (ppm)[c]	Predosing Analyses[a] Range	Postdosing Analyses[b] Samples (n)	Postdosing Analyses[b] Dose Concentration (ppm)[c]	Postdosing Analyses[b] Range
November 1986						
25	2	23.1 ± 0.5	22.6 – 23.6			
100	2	95.3 ± 0.0	95.3 – 95.3			
175	3	172.5 ± 0.0	172.5 – 172.5			
January 1987						
25	2	26.9 ± 0.5	26.4 – 27.4			
100	2	100.7 ± 0.9	99.7 – 101.6			
175	3	174.6 ± 1.1	173.5 – 176.7			
March 1987						
25	2	23.0 ± 0.2	22.7 – 23.2	2	22.6 ± 0.0	22.6 – 22.6
100	2	97.7 ± 0.9	96.6 – 98.7	2	101.3 ± 1.1	100.3 – 102.4
175	3	183.5 ± 2.2	179.7 – 187.3	3	183.0 ± 1.3	180.5 – 184.3
May 1987						
25	2	25.2 ± 0.5	24.7 – 25.7			
100	2	99.4 ± 0.0	99.4 – 99.4			
175	3	171.1 ± 2.3	166.6 – 173.4			
July 1987						
25	2	26.4 ± 0.8	25.6 – 27.2			
100	2	102.2 ± 0.0	102.2 – 102.2			
175	3	180.1 ± 2.4	177.7 – 184.9			
August 1987						
25	2	24.3 ± 0.0	24.3 – 24.3	2	26.1 ± 0.2	26.0 – 26.3
100	2	100.0 ± 1.1	98.9 - 101.0	2	103.3 ± 0.3	103.0 – 103.6
175	3	184.1 ± 1.3	181.5 - 185.3	3	179.7 ± 1.2	178.0 – 182.1
October 1987						
25	2	26.6 ± 0.4	26.2 – 26.9			
100	2	101.5 ± 0.9	100.7 – 102.4			
175	3	172.8 ± 0.3	172.5 – 173.5			

[a] Analyses were performed using a potentiometric method with a fluoride ion electrode. All dose formulations prepared during the first 27 weeks of the studies were analyzed prior to use. During the remainder of the studies, analyses were performed once every 8 weeks.
[b] Analyses were performed using a potentiometric method with a fluoride ion electrode. Samples from the batches analyzed before dosing were retrieved from the animal room after dosing for the postdose analysis.
[c] Mean ± standard error

TABLE J5
Referee Analyses of Dose Formulations Administered to Rats and Mice during the 2-year Drinking Water Studies of Sodium Fluoride

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm)		
		Study Laboratory		Referee Laboratory[b]
		Predosing Analyses[a]	Postdosing Analyses[a]	
Rats				
3 October 1985	25	26.8 ± 0.7	27.0 ± 0.0	25.4 ± 0.1
	25	26.3 ± 0.0	27.0 ± 0.0	
	25	26.8 ± 0.7	26.4 ± 0.7	
3 June 1986	175	169.7 ± 4.4	174.3 ± 0.0	177 ± 2.0
	175	172.8 ± 0.0	174.3 ± 0.0	
	175	172.8 ± 0.0	181.1 ± 0.0	
Mice				
13 January 1987	100	99.7 ± 0.0		99 ± 2
	100	101.6 ± 2.7		
30 June 1987	25	27.2 ± 0.8		24.6 ± 0.0
	25	25.6 ± 0.0		
6 October 1987	175	172.5 ± 0.0		193 ± 1
	175	172.5 ± 0.0		
	175	173.5 ± 0.5		

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

APPENDIX K
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN THE LOW FLUORIDE NIH-07 RAT AND MOUSE RATION

Table K1
Ingredients, Vitamins, and Minerals in 50 Kilograms of the Low Fluoride, Semisynthetic NIH-07 Rat and Mouse Ration for the 14-Day Drinking Water Studies of Sodium Fluoride

	Amount
Ingredients	
Casein	10.0 kg
Sucrose	6.0 kg
Cornstarch	24.3 kg
Mineral mix	2.0 kg
Gelatin	2.0 kg
Wesson corn oil	2.5 kg
Methionine	0.1 kg
Vitamin mix	0.5 kg
Cellulose	2.5 kg
Vitamins	
A	1,000,000 IU
D_2	25,000 IU
K_1	50 mg
d-α-Tocopheryl acetate	31.25 IU
Choline bitartrate	15.0 g
Folic acid	200 mg
d-Calcium pantothenate	1.5 g
Riboflavin	450 mg
Thiamine	300 mg
B_{12}	1.5 mg
Pyridoxine	300 mg
Biotin	15.0 mg
Nicotinic acid	3.0 g
Inositol	12.5 g
Minerals	
Calcium carbonate	420 g
Ferric phosphate	29.4 g
Manganese sulfate	448 mg
Magnesium sulfate	368.8 g
Zinc chloride	1.5 g
Potassium chloride	240 g
Aluminum potassium sulfate	180 mg
Copper sulfate	780 mg
Potassium iodide	100 mg
Potassium dihydrogen phosphate	620 g
Sodium chloride	210 g
Tricalcium phosphate	298 g

TABLE K2
Nutrient Composition of the Low Fluoride, Semisynthetic NIH-07 Rat and Mouse Ration for the 6-Month Drinking Water Studies of Sodium Fluoride

Nutrient	Amount
Protein (% by weight)	22.4
Crude fat (% by weight)	4.6
Crude fiber (% by weight)	3.1
Ash (% by weight)	3.69
Vitamins	
Vitamin A (IU/100 g)	1,100
Carotene (μg/100 g)	<50
Thiamine (mg/100 g)	0.52
Minerals	
Calcium (% by weight)	0.60
Phosphorus (% by weight)	0.53

TABLE K3
Contaminant Levels in the Low Fluoride, Semisynthetic NIH-07 Rat and Mouse Ration for the 6-Month Drinking Water Studies of Sodium Fluoride

	Mean
Contaminants	
Fluorine (ppm)	2.10
Arsenic (ppm)	<0.05
Cadmium (ppm)	<0.05
Lead (ppm)	<0.05
Mercury (ppm)	<0.05
Selenium (ppm)	0.7
Aflatoxins (ppb)	<10
Nitrate nitrogen (ppm)	13.8
Nitrite nitrogen (ppm)	1.00
BHA (ppm)	3.9
BHT (ppm)	2.0
Aerobic plate count (CFU/g)	660
Coliform (MPN/g)	<3.0
E. coli (MPN/g)	<3.0
N-Nitrosomorpholine (ppb)	<1.0
N-Nitrosodimethylamine (ppb)	<0.5
N-Nitrosopyrrolidine (ppb)	<1.0
Pesticides (ppm)	
α-BHC	<0.01
β-BHC	<0.02
-BHC	<0.01
δ-BHC	<0.01
Heptachlor	<0.01
Aldrin	<0.01
Heptachlor epoxide	<0.01
DDE	<0.01
DDD	<0.01
DDT	<0.01
HCB	<0.01
Mirex	<0.01
Methoxychlor	<0.01
Dieldrin	<0.01
Endrin	<0.01
Telodrin	<0.01
Chlordane	<0.1
Toxaphene	<0.1
Estimated PCBs	<0.2
Ronnel	<0.01
Ethion	<0.02
Trithion	<0.02
Diazinon	<0.1
Methyl parathion	<0.02
Ethyl parathion	<0.02
Malathion	<0.05

TABLE K4
Ingredients in the Low Fluoride NIH-07 Rat and Mouse Ration for the 2-Year Drinking Water Studies of Sodium Fluoride[a]

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

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

TABLE K5
Vitamins and Minerals in the Low Fluoride NIH-07 Rat and Mouse Ration for the 2-Year Drinking Water Studies of Sodium Fluoride

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

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

TABLE K6
Nutrient Composition of Low Fluoride NIH-07 Rat and Mouse Ration for the 2-Year Drinking Water Studies of Sodium Fluoride

	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.27 ± 0.79	21.10-24.10	10
Crude fat (% by weight)	5.46 ± 0.30	5.10–5.90	10
Crude fiber (% by weight)	3.49 ± 0.33	3.00–4.10	10
Ash (% by weight)	6.82 ± 0.31	6.27–7.37	10
Amino Acids (% of total diet)			
Arginine	1.050		
Cystine	0.261		
Glycine	1.040		
Histidine	0.521		
Isoleucine	0.833		
Leucine	1.890		
Lysine	1.210		
Methionine	0.379		
Phenylalanine	1.020		
Threonine	0.847		
Tryptophan	0.201		
Tyrosine	0.583		
Valine	1.000		
Essential Fatty Acids (% of total diet)			
Linoleic	2.26		
Linolenic	0.28		
Vitamins			
Vitamin A (IU/kg)	7,995 ± 3,105	5,000-15,000	10
α–Tocopherol (ppm)	45.90		
Thiamine (ppm)	27.70 ± 7.30	17.0-38.0	10
Riboflavin (ppm)	7.70		
Niacin (ppm)	120.00		
Pantothenic acid (ppm)	47.00		
Pyridoxine (ppm)	7.40		
Folic acid (ppm)	2.50		
Biotin (ppm)	0.30		
Vitamin B_{12} (ppb)	17.00		
Choline (ppm)	3,200		
Minerals			
Calcium (%)	1.28 ± 0.12	1.06-1.54	10
Phosphorus (%)	0.97 ± 0.10	0.80–1.10	10
Chloride (%)	0.880		
Sodium (%)	0.494		
Magnesium (%)	0.169		
Sulfur (%)	0.230		
Iron (ppm)	301.00		
Manganese (ppm)	115.0		
Zinc (ppm)	49.90		
Copper (ppm)	10.80		

Table K7
Contaminant Levels in Low Fluoride NIH-07 Rat and Mouse Ration for the 2-Year Drinking Water Studies of Sodium Fluoride

	Mean ± Standard Deviation	Range	Number of Samples
Contaminants			
Fluorine (ppm)[a]	8.66 ± 2.33	6.87-14.7	10
Arsenic (ppm)	0.51 ± 0.14	0.29–0.77	10
Cadmium (ppm)[b]	<0.10		10
Lead (ppm)	0.36 ± 0.21	0.16–0.76	10
Mercury (ppm)[b]	<0.05		10
Selenium (ppm)	0.35 ± 0.07	0.29–0.50	10
Aflatoxins (ppb)[b]	<5.0		10
Nitrate nitrogen (ppm)[c]	19.90 ± 8.66	12.00–42.0	10
Nitrite nitrogen (ppm)[c]	0.14 ± 0.07	0.10-0.30	10
BHA (ppm)[d]	2.30 ± 0.95	2.00–5.00	10
BHT (ppm)[d]	1.20 ± 0.63	1.00–3.00	10
Aerobic plate count (CFU/g)[e]	22,410 ± 15,494	6,100–48,000	10
Coliform (MPN/g)[f,g]	8.11 ± 13.23	3.00–43.00	9
Coliform (MPN/g)[f,h]	31.30 ± 74.38	3.00-240.0	10
E. coli (MPN/g)[f]	3.00		10
Total nitrosamines (ppb)[j]	8.21 ± 3.73	2.00–15.80	10
N-Nitrosodimethylamine (ppb)[j]	7.03 ± 3.34	1.00–13.00	10
N-Nitrosopyrrolidine (ppb)[j]	1.18 ± 0.57	1.00–2.80	10
Pesticides[b] (ppm)			
α-BHC[i]	<0.01		10
β-BHC	<0.02		10
-BHC	<0.01		10
δ-BHC	<0.01		10
Heptachlor	<0.01		10
Aldrin	<0.01		10
Heptachlor epoxide	<0.01		10
DDE	<0.01		10
DDD	<0.01		10
DDT	<0.01		10
HCB	<0.01		10
Mirex	<0.01		10
Methoxychlor	<0.05		10
Dieldrin	<0.01		10
Endrin	<0.01		10
Telodrin	<0.01		10
Chlordane	<0.05		10
Toxaphene	<0.1		10
Estimated PCBs	<0.2		10
Ronnel	<0.01		10
Ethion	<0.02		10
Trithion	<0.05		10
Diazinon	<0.1		10
Methyl parathion	<0.02		10
Ethyl parathion	<0.02		10
Malathion[k]	0.35 ± 0.58	0.05–1.78	10
Endosulfan I	<0.01		10
Endosulfan II	<0.01		10
Endosulfan sulfate	<0.03		10

Table K7
Contaminant Levels in Low Fluoride NIH-07 Rat and Mouse Ration for the 2-Year Drinking Water Studies of Sodium Fluoride (continued)

[a] Fish meal and mineral supplements are sources of contamination.
[b] All values were less than the detection limit, given in the table as the mean.
[c] Alfalfa, grains, and fish meal are sources of contamination.
[d] Soy oil and fish meal are sources of contamination.
[e] CFU = colony forming unit
[f] MPN = most probable number
[g] Mean, standard deviation, and range exclude one high value of 240 MPN obtained in the lot milled on 4 February 1987.
[h] Includes the high value of 240 MPN obtained in the lot milled on 4 February 1987.
[i] BHC = hexachlorocyclohexane or benzene hexachloride
[j] All values were corrected for percent recovery.
[k] Four lots contained more than 0.05 ppm.

APPENDIX L
WATER AND COMPOUND CONSUMPTION

TABLE L1
Water and Compound Consumption by Male Rats in the 2-Year Drinking Water Studies of Sodium Fluoride

	Control		25 ppm			100 ppm			175 ppm		
Week	Water (g/day)[a]	Body Weight (g)	Water (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Water (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Water (g/day)[a]	Body Weight (g)	Dose/ Day[b]
3	20.0	208	20.0	207	2.4	20.3	208	9.8	19.5	205	16.7
4	19.1	236	20.1	237	2.1	19.9	236	8.4	18.9	233	14.2
7	18.1	287	19.4	296	1.6	18.6	292	6.4	18.3	290	11.0
8	17.4	302	18.0	310	1.5	17.5	308	5.7	16.9	304	9.7
11	16.2	330	16.1	335	1.2	17.2	329	5.2	16.6	331	8.8
12	16.0	342	15.9	341	1.2	15.9	340	4.7	15.8	341	8.1
17	18.2	367	19.1	368	1.3	18.5	365	5.1	17.3	367	8.3
21	18.1	392	18.6	396	1.2	18.3	393	4.7	18.0	393	8.0
25	17.6	411	18.4	417	1.1	18.2	413	4.4	17.5	409	7.5
29	18.5	430	19.4	435	1.1	19.2	433	4.4	18.6	429	7.6
33	17.0	438	17.6	444	1.0	17.6	441	4.0	16.6	439	6.6
37	16.8	450	17.6	460	1.0	17.2	456	3.8	16.8	452	6.5
41	18.5	461	19.7	471	1.0	19.2	468	4.1	18.3	462	6.9
45	18.3	470	19.1	477	1.0	18.9	473	4.0	17.7	470	6.6
49	18.3	473	19.1	483	1.0	19.0	479	4.0	18.1	474	6.7
53	20.2	476	21.1	491	1.1	21.0	484	4.3	20.0	476	7.4
57	21.7	480	21.5	487	1.1	21.0	484	4.3	20.5	481	7.5
61	20.3	485	19.9	487	1.0	20.5	488	4.2	19.4	485	7.0
65	20.0	486	19.5	487	1.0	21.1	487	4.3	19.2	482	7.0
69	18.4	487	18.0	497	0.9	19.5	492	4.0	17.7	489	6.3
73	20.5	483	20.7	490	1.1	21.4	487	4.4	19.5	483	7.1
77	22.0	476	21.4	493	1.1	22.6	483	4.7	20.7	479	7.5
81	22.4	477	22.6	495	1.1	23.0	482	4.8	22.5	479	8.2
85	23.2	483	23.4	490	1.2	23.4	482	4.9	22.9	481	8.3
89	23.5	478	24.3	479	1.3	25.5	476	5.4	23.8	471	8.8
93	21.3	459	22.1	469	1.2	23.6	462	5.1	22.0	458	8.4
97	24.5	455	24.6	468	1.3	25.9	440	5.9	24.0	446	9.4
101	29.5	446	30.7	454	1.7	34.8	441	7.9	28.1	435	11.3
104	32.6	436	35.1	448	2.0	37.3	437	8.5	29.4	417	12.3
Mean for weeks											
1-13	17.8	284	18.3	288	1.7	18.2	286	6.7	17.7	284	11.4
14-52	17.9	432	18.7	439	1.1	18.5	436	4.3	17.7	433	7.2
52-104	22.9	472	23.2	481	1.2	24.3	473	5.2	22.1	469	8.3
1-104	20.3	421	20.8	428	1.3	21.2	423	5.2	19.8	419	8.6

a Grams of water consumed per animal per day; not corrected for waste
b Milligrams of compound consumed per day per kilogram body weight

TABLE L2
Water and Compound Consumption by Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride

	Control		25 ppm			100 ppm			175 ppm		
Week	Water (g/day)[a]	Body Weight (g)	Water (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Water (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Water (g/day)[a]	Body Weight (g)	Dose/ Day[b]
3	15.9	141	15.9	141	2.8	16.1	142	11.4	15.6	141	19.3
4	14.7	153	15.5	153	2.5	15.2	152	10.0	14.4	153	16.5
7	13.7	180	14.0	180	1.9	13.9	180	7.7	13.6	180	13.1
8	12.6	187	13.0	187	1.7	12.8	187	6.8	12.4	187	11.6
11	10.8	195	11.4	196	1.4	11.3	194	5.8	11.2	195	10.0
12	10.5	198	11.1	198	1.4	10.7	198	5.4	11.1	196	9.9
17	12.7	208	12.8	210	1.5	12.5	208	6.0	12.6	207	10.6
21	12.0	220	12.2	219	1.4	12.1	220	5.5	12.1	219	9.7
25	11.7	227	12.1	230	1.3	11.8	229	5.2	11.9	227	9.2
29	12.0	236	12.5	238	1.3	12.4	236	5.3	12.1	235	9.0
33	9.9	237	10.1	240	1.1	10.5	237	4.4	10.3	236	7.6
37	9.3	239	9.6	243	1.0	9.5	241	3.9	9.8	241	7.1
41	12.0	256	12.2	258	1.2	11.9	256	4.7	12.0	256	8.2
45	11.3	264	11.8	268	1.1	11.6	267	4.4	11.3	262	7.5
49	11.4	269	11.6	273	1.1	11.7	269	4.4	11.4	264	7.6
53	12.9	277	12.9	283	1.1	13.3	278	4.8	13.5	273	8.7
57	13.1	284	13.7	290	1.2	14.0	284	4.9	13.5	279	8.5
61	12.7	294	12.8	296	1.1	13.3	294	4.5	13.1	288	8.0
65	12.5	297	12.7	302	1.0	13.1	297	4.4	12.9	292	7.7
69	12.1	301	12.0	305	1.0	12.5	301	4.1	12.3	299	7.2
73	13.4	306	13.5	310	1.1	14.5	305	4.7	14.0	302	8.1
77	14.7	316	15.7	320	1.2	15.4	313	4.9	15.4	310	8.7
81	15.0	323	14.9	326	1.1	15.6	314	5.0	14.6	316	8.1
85	15.4	327	15.6	327	1.2	16.2	327	4.9	15.4	322	8.4
89	14.9	328	15.7	327	1.2	16.5	331	5.0	15.8	324	8.5
93	11.9	323	11.8	321	0.9	12.6	320	3.9	13.4	320	7.3
97	14.0	323	14.3	318	1.1	15.1	317	4.8	15.6	321	8.5
101	18.0	333	18.7	334	1.4	19.8	316	6.3	18.6	321	10.1
104	18.5	336	18.5	338	1.4	19.6	324	6.0	18.9	325	10.2
Mean for weeks											
1-13	13.0	176	13.5	176	2.0	13.3	176	7.9	13.0	176	13.4
14-52	11.4	240	11.6	242	1.2	11.6	240	4.9	11.5	238	8.5
52-104	14.2	312	14.5	314	1.2	15.1	309	4.9	14.8	307	8.4
1-104	13.1	261	13.4	263	1.3	13.6	260	5.5	13.4	258	9.5

[a] Grams of water consumed per animal per day; not corrected for waste
[b] Milligrams of compound consumed per day per kilogram body weight

TABLE L3
Water and Compound Consumption by Male Mice in the 2-Year Drinking Water Studies of Sodium Fluoride

	Control		25 ppm			100 ppm			175 ppm		
Week	Water (g/day)[a]	Body Weight (g)	Water (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Water (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Water (g/day)[a]	Body Weight (g)	Dose/ Day[b]
3	3.4	27.1	3.4	26.2	3.3	3.4	27.0	12.6	3.5	26.6	22.9
4	4.4	28.2	3.7	27.1	3.4	3.8	28.1	13.6	3.9	27.6	24.5
7	3.9	31.8	4.1	30.8	3.3	4.1	31.9	12.7	3.9	31.1	21.9
8	4.2	33.5	4.1	32.4	3.2	3.9	33.5	11.7	4.3	32.9	22.7
11	3.7	35.4	3.8	34.3	2.8	4.0	35.7	11.2	3.9	34.4	20.0
12	4.0	36.8	4.2	35.4	3.0	4.2	36.9	11.3	4.0	35.5	19.7
17	3.6	41.6	3.7	40.6	2.3	3.6	41.9	8.5	3.8	40.1	16.7
21	3.5	44.6	3.4	43.9	2.0	3.5	44.5	7.8	3.6	42.8	14.7
25	3.6	46.8	3.8	45.8	2.1	3.6	46.1	7.8	3.8	45.0	14.8
29	3.6	48.1	3.7	47.3	1.9	4.0	47.3	8.4	3.8	46.6	14.2
33	3.6	48.6	3.8	48.0	2.0	3.9	48.2	8.0	3.8	47.6	13.8
37	3.8	49.6	3.6	48.7	1.9	3.9	49.5	8.0	3.9	48.6	14.1
41	4.1	50.7	3.9	49.9	1.9	4.1	50.9	8.0	3.9	49.8	13.8
45	3.7	49.9	3.7	48.7	1.9	3.8	49.9	7.6	3.7	49.0	13.4
49	4.3	50.3	4.2	49.7	2.1	4.4	50.8	8.6	4.2	49.5	14.8
53	4.4	50.3	4.4	49.7	2.2	4.5	50.7	8.9	4.3	49.5	15.3
57	4.5	51.4	4.5	51.2	2.2	4.7	51.4	9.2	4.5	50.4	15.5
61	4.4	50.5	4.4	50.5	2.2	4.3	50.8	8.5	4.2	50.1	14.5
65	4.5	50.7	4.4	50.1	2.2	4.5	50.4	8.9	4.3	49.3	15.3
69	4.6	49.6	4.5	49.6	2.3	4.6	48.8	9.4	4.5	47.7	16.6
73	4.6	50.1	4.4	50.0	2.2	4.5	49.1	9.2	4.4	48.3	16.1
77	4.7	48.9	4.6	49.2	2.3	4.7	48.3	9.7	4.5	48.1	16.3
81	4.5	49.2	4.6	49.4	2.3	4.5	48.2	9.3	4.2	49.1	15.0
85	4.7	49.0	4.6	49.3	2.3	4.8	48.7	9.9	4.3	48.9	15.4
89	4.4	48.2	4.4	48.8	2.3	4.4	48.7	8.9	4.0	48.8	14.5
93	4.5	46.9	4.1	46.4	2.2	4.2	48.3	8.7	4.1	47.7	15.0
97	4.5	46.1	4.8	46.1	2.6	4.5	47.7	9.3	4.2	47.1	15.7
101	5.0	45.5	5.1	44.9	2.9	4.9	45.6	10.7	4.7	45.6	18.0
104	5.1	43.8	5.7	44.0	3.2	5.2	44.5	11.6	4.7	45.3	18.3
Mean for weeks											
1-13	3.9	32.1	3.9	31.0	3.2	3.9	32.2	12.2	3.9	31.4	21.9
14-52	3.7	47.8	3.7	47.0	2.0	3.9	47.7	8.1	3.8	46.6	14.5
52-104	4.6	48.6	4.6	48.5	2.4	4.6	48.7	9.4	4.4	48.3	15.8
1-104	4.2	44.9	4.2	44.4	2.4	4.2	44.9	9.6	4.1	44.2	16.7

[a] Grams of water consumed per animal per day; not corrected for waste
[b] Milligrams of compound consumed per day per kilogram body weight

TABLE L4
Water and Compound Consumption by Female Mice in the 2-Year Drinking Water Studies of Sodium Fluoride

	Control		25 ppm			100 ppm			175 ppm		
Week	Water (g/day)[a]	Body Weight (g)	Water (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Water (g/day)[a]	Body Weight (g)	Dose/ Day[b]	Water (g/day)[a]	Body Weight (g)	Dose/ Day[b]
3	4.2	22.1	3.8	22.3	4.2	3.9	22.2	17.4	4.1	22.4	31.7
4	5.6	23.2	5.2	23.2	5.6	5.5	22.8	24.1	4.3	23.0	32.5
7	4.9	25.9	5.5	25.8	5.3	4.5	25.4	17.8	4.8	25.7	33.0
8	5.7	26.7	4.9	26.6	4.6	5.4	25.9	20.9	4.8	26.5	31.7
11	4.8	29.7	6.1	28.8	5.3	5.2	29.0	18.0	4.5	29.2	26.8
12	4.7	30.3	5.0	29.7	4.2	4.9	29.6	16.6	5.2	29.5	31.1
17	4.8	36.0	6.1	34.9	4.4	4.9	34.5	14.2	4.3	34.7	21.9
21	4.5	39.6	4.8	38.4	3.2	4.8	38.3	12.6	4.5	38.0	20.9
25	4.4	42.5	5.1	42.2	3.0	5.0	41.4	12.1	4.5	40.6	19.3
29	4.2	44.2	4.3	44.0	2.4	4.6	43.4	10.6	4.3	42.3	17.8
33	4.2	45.3	4.2	45.8	2.3	4.5	44.9	10.0	4.4	43.9	17.4
37	4.2	48.2	4.2	47.9	2.2	4.2	47.0	9.0	4.1	46.4	15.3
41	4.3	49.5	4.2	49.7	2.1	4.4	48.6	9.0	4.3	48.5	15.4
45	4.1	50.4	4.3	50.1	2.1	4.2	49.2	8.5	4.1	48.8	14.7
49	4.4	52.9	4.4	52.8	2.1	4.6	52.6	8.8	4.3	51.1	14.8
53	4.4	54.0	4.4	54.0	2.0	4.5	53.1	8.4	4.4	52.9	14.4
57	4.4	55.2	4.4	55.6	2.0	4.6	54.9	8.3	4.5	54.8	14.2
61	4.3	55.6	4.1	56.3	1.8	4.2	55.3	7.6	4.3	55.2	13.6
65	4.3	56.1	4.2	56.2	1.9	4.3	55.1	7.8	4.2	55.0	13.3
69	4.4	55.5	4.4	56.0	2.0	4.4	54.8	8.0	4.2	54.2	13.6
73	4.3	55.7	4.2	55.7	1.9	4.4	54.4	8.0	4.2	54.1	13.7
77	4.6	55.5	4.3	55.6	1.9	4.3	54.5	7.8	4.3	53.7	13.9
81	4.2	56.8	4.3	56.3	1.9	4.4	55.6	8.0	4.2	54.9	13.4
85	4.2	57.4	4.0	57.3	1.8	4.4	55.7	8.0	4.1	55.7	12.7
89	3.9	54.4	3.9	53.6	1.8	4.0	53.0	7.5	3.7	53.6	12.1
93	3.9	53.2	4.1	51.6	2.0	4.0	52.0	7.8	4.0	52.3	13.2
97	4.2	54.7	4.7	51.9	2.3	4.6	52.3	8.9	4.5	51.0	15.4
101	4.8	52.7	5.0	51.5	2.4	5.3	51.1	10.5	4.9	49.2	17.4
104	5.3	50.6	5.5	49.3	2.8	5.1	49.7	10.3	5.2	48.4	18.7
Mean for weeks											
1-13	5.0	26.3	5.1	26.1	4.9	4.9	25.8	19.1	4.6	26.1	31.1
14-52	4.4	45.4	4.6	45.1	2.6	4.6	44.4	10.5	4.3	43.8	17.5
52-104	4.4	54.8	4.4	54.4	2.0	4.5	53.7	8.3	4.3	53.2	14.3
1-104	4.5	46.0	4.6	45.6	2.8	4.6	45.0	11.3	4.4	44.7	18.8

[a] Grams of water consumed per animal per day; not corrected for waste
[b] Milligrams of compound consumed per day per kilogram body weight

APPENDIX M
2-YEAR SODIUM FLUORIDE STUDIES
USING A LOW FLUORIDE, SEMISYNTHETIC DIET

2-YEAR SODIUM FLUORIDE STUDIES USING A LOW FLUORIDE, SEMISYNTHETIC DIET

METHODS

From November 1981 to November 1983, 2-year toxicity and carcinogenicity studies of sodium fluoride were performed. Sodium fluoride was administered to F344/N rats and B6C3F$_1$ mice of both sexes in drinking water. The diet used throughout these studies was a semisynthetic, low fluoride (2.1 ppm) feed, formulated as outlined in Appendix K (Tables K3 and K4). Animals for these studies were offspring of parents (F344/N rats, and a cross of CH3/HeN male and C57BL/6N female mice) maintained on the low fluoride diet beginning about 1 month prior to mating and continuing throughout gestation and weaning. Animals were placed on test at 4 to 6 weeks of age. Sodium fluoride concentrations in the drinking water were 0, 10, 30, and 100 ppm.

RESULTS

During month 7 of these 2-year studies, both the male and female rats began to show abnormal clinical signs in all dosed and control groups. These included head tilt or torticollis, megaloglobus, ocular discharge, and opaque cornea. Because of these observations, several special studies were performed during a scheduled 1-year interim evaluation. All rats received an ophthalmologic examination; microbial cultures were taken of the middle ear, nasopharynx, and trachea; the middle ears were examined histopathologically; and otoliths were examined using polarized light. Mice received an ophthalmologic examination, and livers were evaluated for zinc and manganese content. In addition, the diet was analyzed for minerals, vitamins, and amino acids.

The presence of corneal lesions, including anterior bulging of the cornea and associated atrophy of the iris, was confirmed in rats. Bacterial cultures did not support the premise of a middle ear infection as the cause of the torticollis, and no lesions of the middle ear were found upon microscopic examination. However, examination of otoliths (calcium carbonate crystals, which in association with the otolithic membrane, form part of the vestibular apparatus concerned with the detection of directional or positional movement) revealed the lack of a portion of all otoconial masses typically in the utricular cavity. These observations were thought consistent with a congenital defect that had previously been linked to the lack of adequate dietary manganese during a critical period of gestation (Lim and Erway, 1974). Other documented effects of prenatal manganese deficiency in the rat include disproportionate skeletal growth and localized dysplasia of the tibial epiphysis (Hurley, 1981).

Analysis of the low fluoride, semisynthetic diet revealed marginal to marked deficiencies in manganese, chromium, choline, and vitamins B_{12} and D, when compared to the typical content of the NIH-07 diet and the recommendations of the National Research Council and the American Institute of Nutrition (Table M1).

Analysis of the livers of mice from all dosed and control groups maintained on the low fluoride, semisynthetic diet found zinc levels that were approximately 80% and manganese concentrations from 40%-50% those of mice fed the standard NIH-07 diet.

DISCUSSION

Based on these findings, the decision of the NTP staff and management was that the study was compromised and was not adequate for assessment of the chronic toxicity and carcinogenicity of sodium fluoride. However, so that all information from this study would not be lost, the in life portion of the study was allowed to go to completion and ten animals per sex per dose and species, plus all animals that died before scheduled sacrifice, were evaluated histopathologically. The information concerning nonneoplastic and neoplastic lesions collected from these animals was collated into preliminary pathology tables. This information was used to aid in dose selection for the second 2-year studies and has been available to the public since July 1985.

The unverified pathology findings from the first 2-year studies included the observation of one osteosarcoma in the occipital bone of one male rat given 10 ppm (low-dose group) sodium fluoride in the drinking water. No osteosarcomas were observed in female rats. One osteoma was observed in the vertebra of one control male mouse, and one subcutaneous osteosarcoma was diagnosed in a female mouse receiving the top concentration of 100 ppm.

TABLE M1
Recommended Levels and Actual Content of Selected Nutrients in Rat and Mouse Feed during the First 2-Year Studies of Sodium Fluoride

Nutrient	NRC	AIN	NIH-07	Low Fluoride Semisynthetic
Manganese (ppm)	50	54	86	2.7
Chromium (ppm)	2	2	2	0.4
Choline (ppm)	1,000	1,000	3,430	450
Vitamin B_{12} (μg/kg)	50	10	15	3
Vitamin D (IU/kg)	1,000	1,000	6,300	$<$400

APPENDIX N
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds, and these animals and the study animals are subject to identical environmental conditions.

Rats

Serum samples were collected from five male and five female rats just before (September 26, 1985) and again just after the 2-year studies began (October 10, 1985) for murine virus assays. The assays were performed by Microbiological Associates (Bethesda, MD). Sera were also collected from nine to ten sentinel rats as part of the NTP's disease screening program at approximately 6, 12, and 18 months after the studies began, and from five male and five female rats from the high-dose group (175 ppm) at scheduled termination.

The following tests were performed on rat sera:

Hemagglutination Inhibition
- KRV (Kilham rat virus)
- H-1 (Toolan's H-1 virus)

ELISA
- *Mycoplasma pulmonis* (0, 6, and 24 months)
- *Mycoplasma arthritidis* (0, 6, and 24 months)
- Sendai virus
- RCV/SDA (sialodacryoadenitis virus)
- PVM (pneumonia virus of mice)

Mice

Serum samples were collected from five mice of each sex just before (October 17, 1985) and again just after the 2-year studies started (October 31, 1985) for murine virus assays. Assays were performed by Microbiological Associates (Bethesda, MD). Sera were also collected from ten sentinel mice at approximately 6, 12, and 18 months after the studies began, and from five male and five female mice from the high-dose group (175 ppm) at scheduled termination.

The following tests were performed on mice sera:

Hemagglutination Inhibition
- K (papovavirus)
- Polyoma virus
- MVM (minute virus of mice)[a]

ELISA
- Reovirus 3
- Mouse adenoma virus
- *Mycoplasma pulmonis*[b]
- *Mycoplasma arthritidis*[b]
- PVM (pneumonia virus of mice)
- Sendai virus
- MHV (mouse hepatitis virus)[c]
- Ectromelia virus
- LCM (18 months, 2-year)
- GDVII

Complement Fixation
- LCM (lymphocytic choriomeningitis virus) (0 and 6 months)

Immunofluorescent Antibody
- EDIM (epizootic diarrhea of infant mice)
- LCM (12 months)

Results

There were no significant titers in rats or mice to any of the rodent pathogens detected at any time during these studies.

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[a] Performed at 0, 6, and 12 months
[b] Performed at 0, 6, and 24 months
[c] Performed at 18 and 24 months

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

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TR No.	CHEMICAL
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	*a*-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3'-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
386	Tetranitromethane

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