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

# TOXICOLOGY AND CARCINOGENESIS

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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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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 lethal-

ity. 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. Pos-

sibilities 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<br>Mice: B6C3F$_1$ | Rats: F344/N<br>Mice: B6C3F$_1$ | Rats: F344/N<br>Mice: B6C3F$_1$ |
| **Animal Source** | | |
| Charles River Laboratories (Portage, MI) | Battelle Columbus Laboratories (Columbus, OH)<br>Rats: Progeny of F/344 breeders from Harlan Industries (Indianapolis, IN)<br>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<br>Mice: 25 days | Rats: 5-6 weeks<br>Mice: 4-6 weeks | Rats: 12 days<br>Mice: 13 days |
| **Age When Placed on Study** | | |
| Rats: 5 weeks<br>Mice: 5 weeks | Rats: 5-6 weeks<br>Mice: 4-6 weeks | Rats: 6 weeks<br>Mice: 6 weeks |
| **Date of First Dose** | | |
| Rats: 19 July 1979<br>Mice: 18 July 1979 | Rats: 6 October 1980<br>Mice: 6 October 1980 | Rats: 7 October 1985<br>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<br>Mice: 31 July 1979 | Rats: 6-7 April 1981<br>Mice: 8-9 April 1981 | 24-week interim sacrifice: Mice, 10-11 April 1986<br>27-week interim sacrifice: Rats, 8-9 April 1986<br>66-week interim sacrifice: Rats, 8-9 January 1987; Mice, 28-29 January 1987<br>105-week scheduled termination: Rats, 27 September 1987; Mice, 19 October 1987 |
| **Necropsy Dates** | | |
| Rats: 3 August 1979<br>Mice: 2 August 1979 | Rats: 6-7 April 1981<br>Mice: 8-9 April 1981 | 24-week interim sacrifice: Mice, 10-11 April 1986<br>27-week interim sacrifice: Rats, 8-9 April 1986<br>66-week interim sacrifice: Rats, 8-9 January 1987; Mice, 28-29 January 1987<br>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<br>Mice: 7 weeks | Rats: 31-32 weeks<br>Mice: 30-32 weeks | 24-week interim sacrifice: Mice, 30 weeks<br>27-week interim sacrifice: Rats, 32 weeks<br>66-week interim sacrifice: 71 weeks<br>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<br>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).<br>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<br>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)<br>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<br>Humidity: 40%-60%<br>Fluorescent light: 12 hours/day<br>Room air changes: 15/hour | Temperature: 22°-24° C<br>Humidity: 40%-60%<br>Fluorescent light: 12 hours/day<br>Room air changes: 15/hour | Temperature: 19.4°-26.1° C<br>Humidity: 22%-76%<br>Fluorescent light: 12 hours/day<br>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*<br>Mice: 0, 10, 50, 100, 200, 300, or 600 ppm sodium fluoride in deionized water, available *ad libitum*<br>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.<br>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) | | | Final Weight Relative to Controls (%) |
|---|---|---|---|---|---|
| | | Initial[b] | Final | Change[c] | |
| **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

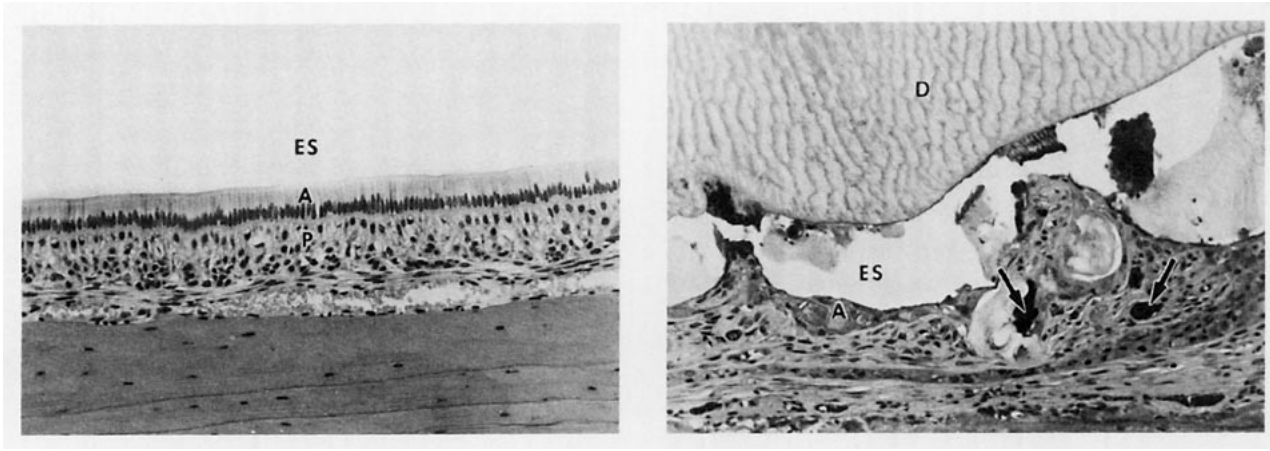



**Plate 1**
Maturation zone of the enamel organ of the incisor tooth from a control male. The maturation zone is characterized by a well-defined layer of tall columnar ameloblasts (A) overlying the maximally developed papillary layer (P). The enamel is mature at this level and is completely removed during 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 | | 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 | 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.

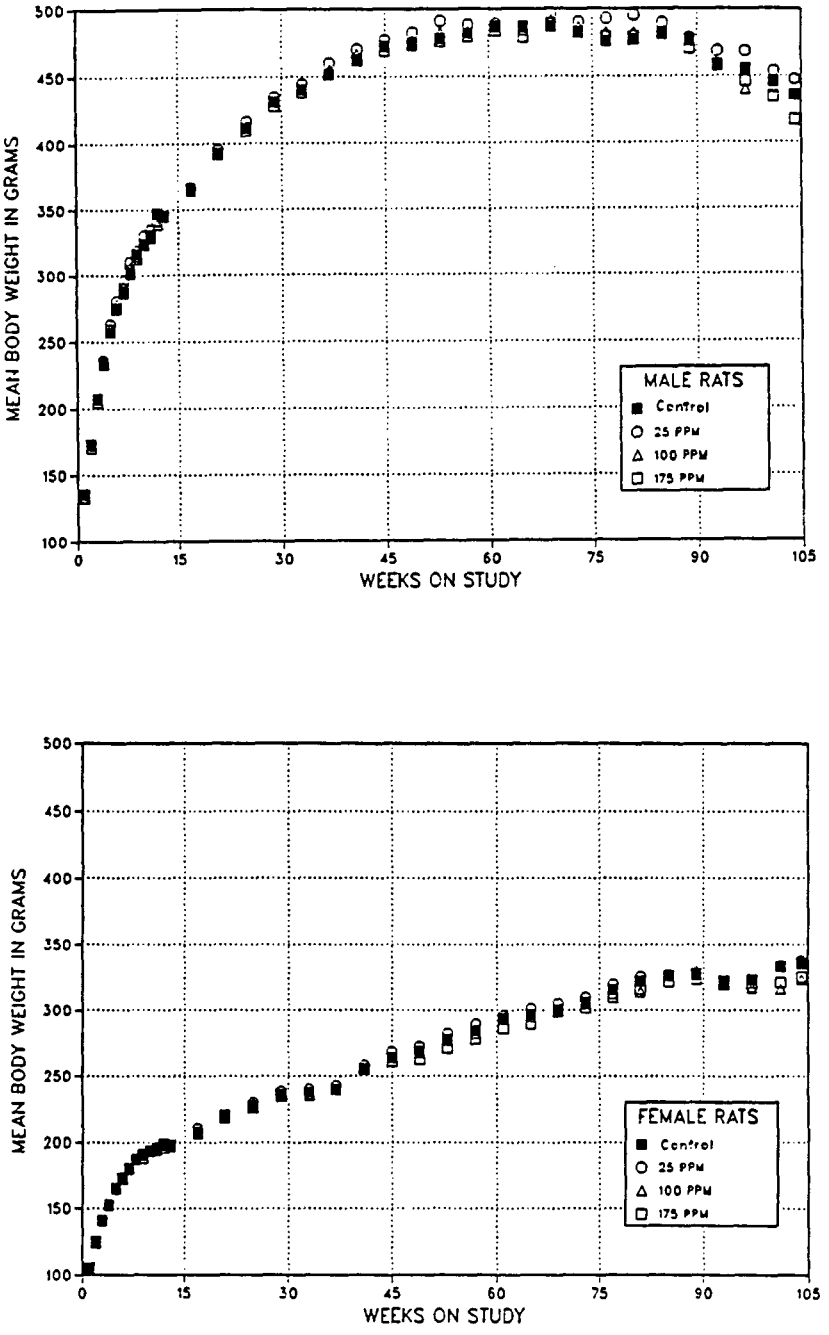



**Figure 1**
**Growth Curves for Male and Female Rats Administered Sodium Fluoride in Drinking Water for 2 Years**

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*

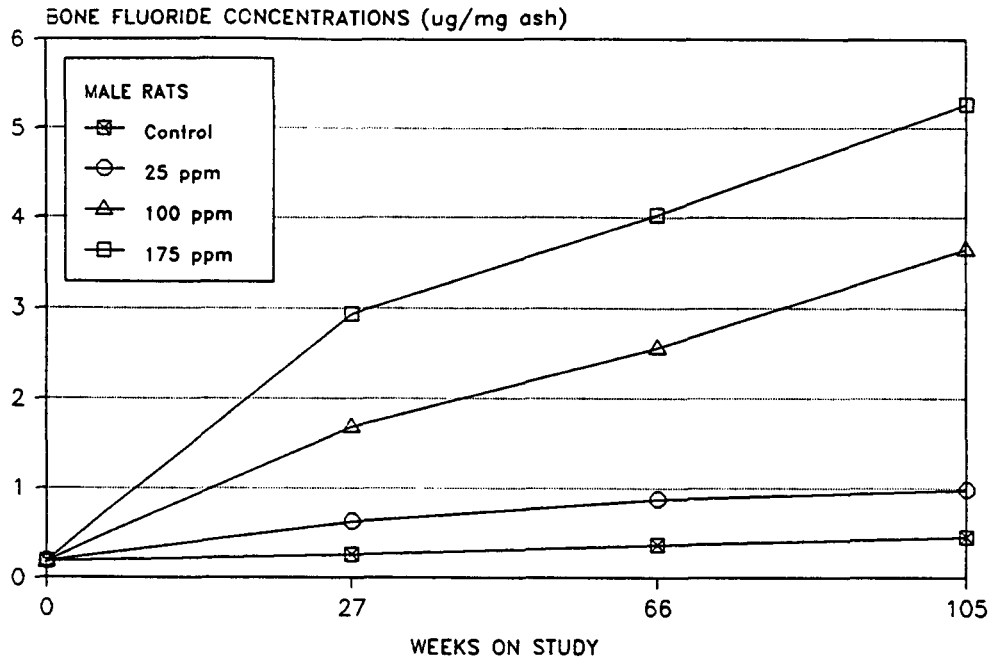
Hematology, clinical chemistry, urinalysis and urine concentrating ability, and fluoride concentrations in serum and urine were measured in all animals sacrificed at 27 and 66 weeks. Fluoride concentrations in bone were measured for all animals sacrificed at 27 and 66 weeks and for selected animals at 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).



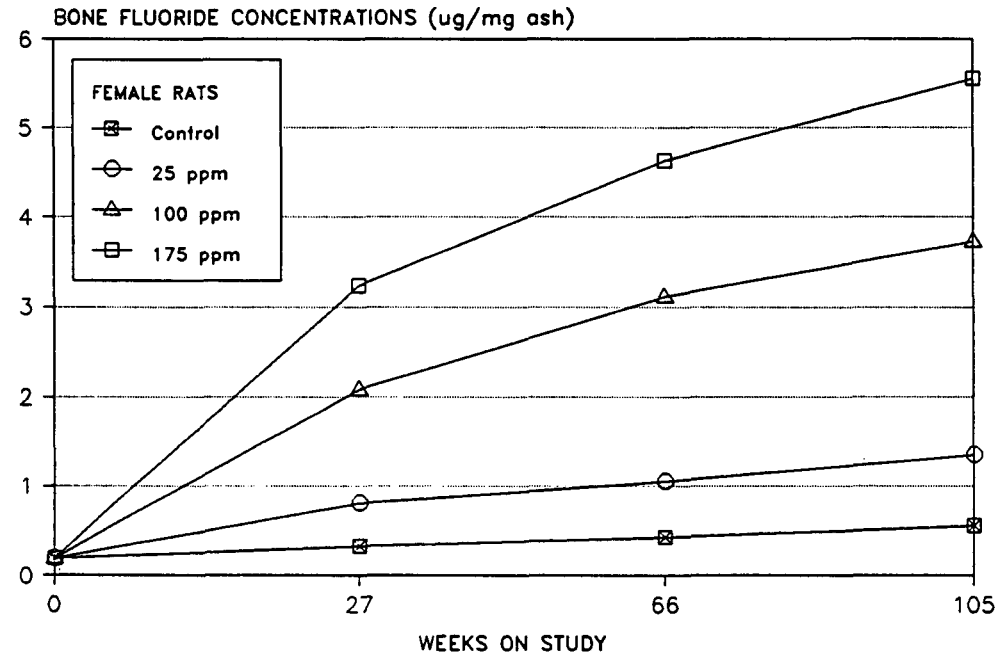




**Figure 2**
**Bone Fluoride Content in Rats in the 2-Year Drinking Water Studies with Sodium Fluoride**

### *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).

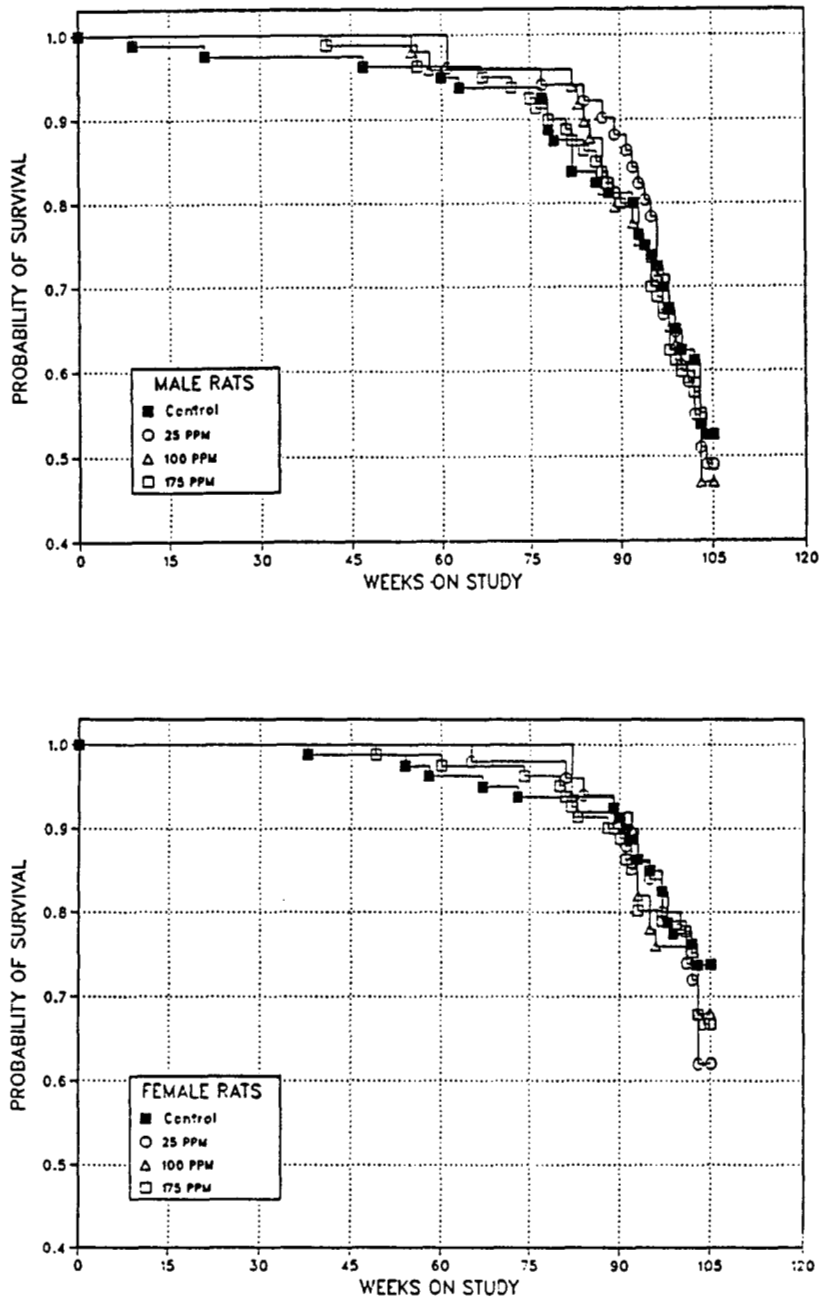



**Figure 3**
**Kaplan-Meier Survival Curves for Male and Female Rats Administered Sodium Fluoride in Drinking Water for 2 Years**

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%)

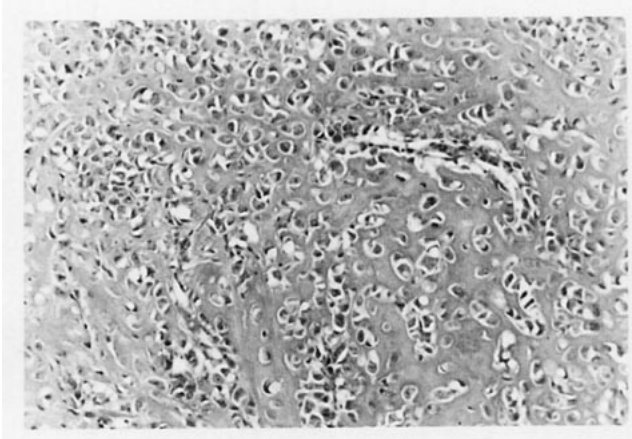


**Plate 3**
Vertebral osteosarcoma in mid-dose male rat CID#0495. Note the abundant osteoid matrix and osteoblasts within lacunae. H&E, 150×

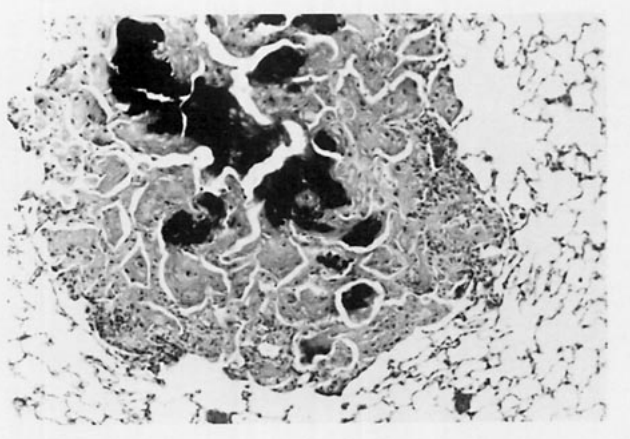


**Plate 4**
Metastatic osteosarcoma in the lung of mid-dose male rat CID#0495. Note the abundant osteoid similar to the primary neoplasm and dark area of mineralization in the center. H&E, 75×

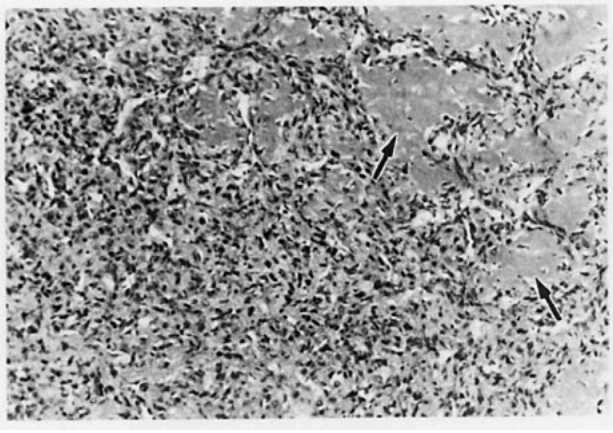


**Plate 5**
Vertebral osteosarcoma in high-dose male rat CID#0775. Note the cellularity in the lower left corner and clumps of osteoid (arrow). H&E, 150×

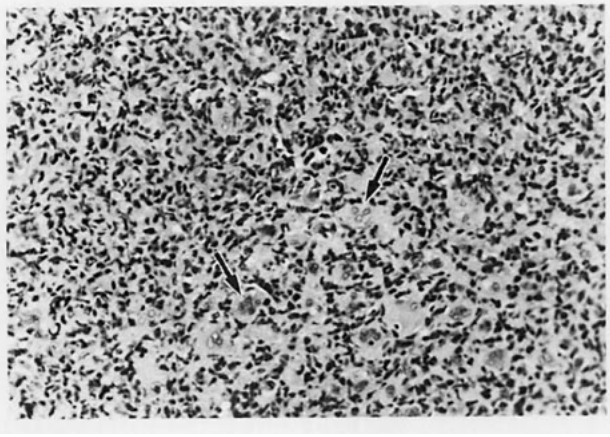


**Plate 6**
Osteosarcoma in high-dose male rat CID#0775 showing multinucleated giant cells (arrows) and smaller pleomorphic cells. H&E, 150×

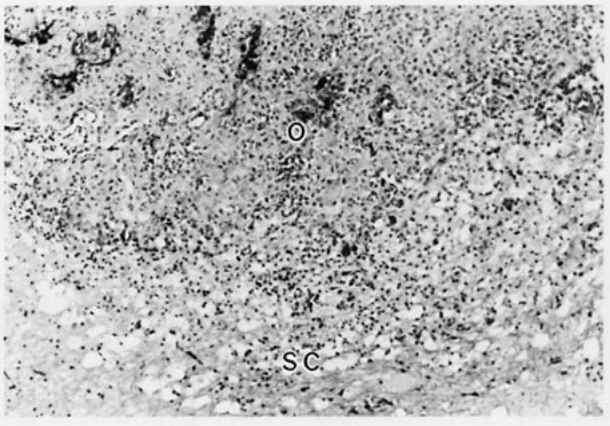



**Plate 7**
Spinal cord (SC) showing invasion by vertebral osteosarcoma (O) in high-dose male rat CID#0713. Note the vacuoles and degeneration of the neuropil surrounding the neoplasm. H&E, 75×

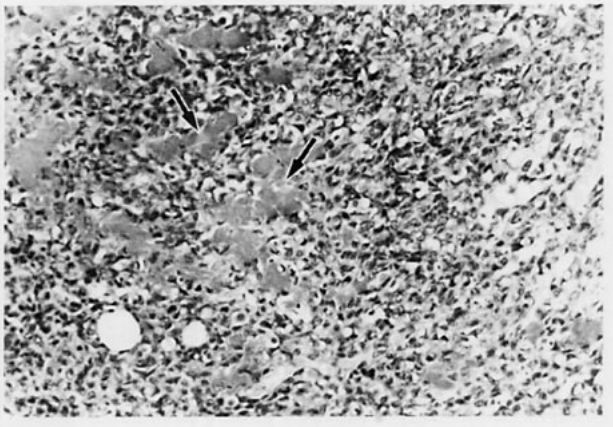


**Plate 8**
Intramedullary osteosarcoma of humerus of high-dose male rat CID#0745. H&E, 150×

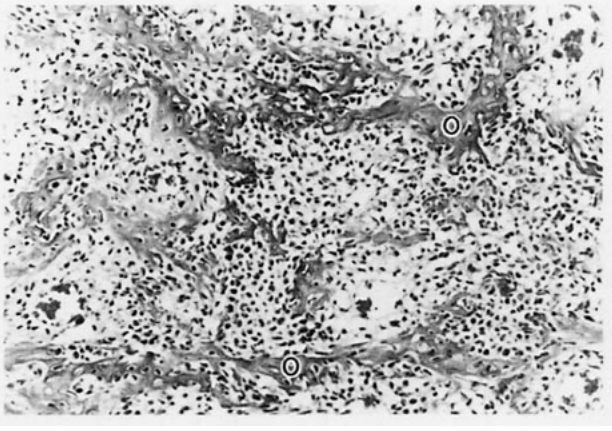



**Plate 9**
Subcutaneous osteosarcoma in high-dose male rat CID#0712 with delicate trabeculae of osteoid (O), which is partially mineralized, separated by highly cellular areas. H&E, 150×

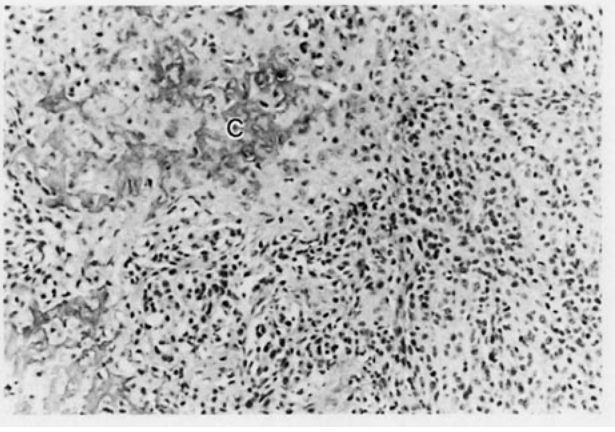



**Plate 10**
Another area of the subcutaneous osteosarcoma in Plate 9 showing cartilaginous differentiation (C). H&E, 150×

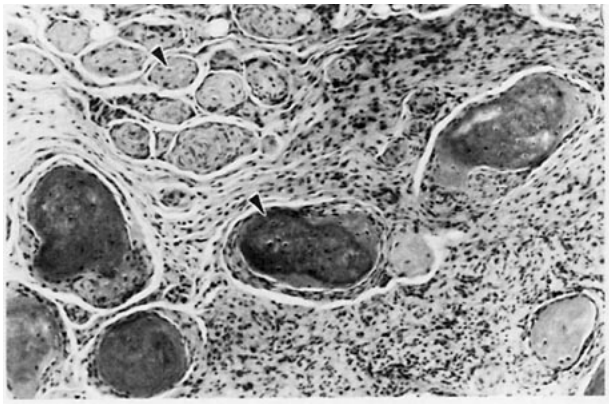


**Plate 11**
Subcutaneous lesion of uncertain classification in control male rat. Note the fibrous connective tissue with discrete islands showing osteoblast differentation, production of osteoid, and bone formation (arrows).

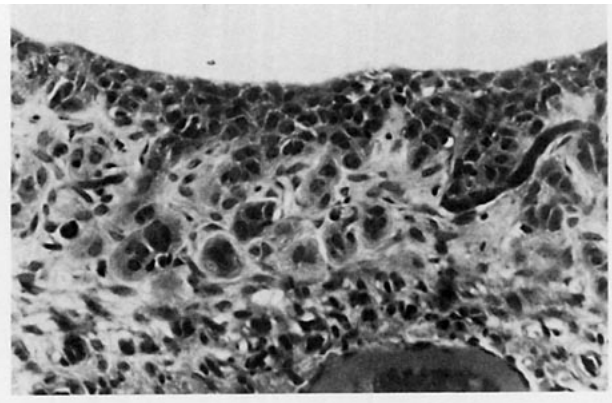


**Plate 12**
Ameloblastic epithelium in late maturation or early transition zone. Note the thin surface layer of flattened, squamous-like cells and the remnants of the papillary layer below.

# 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) | | | Final Weight Relative to Controls (%) |
|---|---|---|---|---|---|
| | | Initial[b] | Final | Change[c] | |
| **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 ($P \leq 0.05$) 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] 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) | | | Final Weight Relative to Controls (%) |
|---|---|---|---|---|---|
| | | Initial[b] | Final | Change[c] | |
| **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×

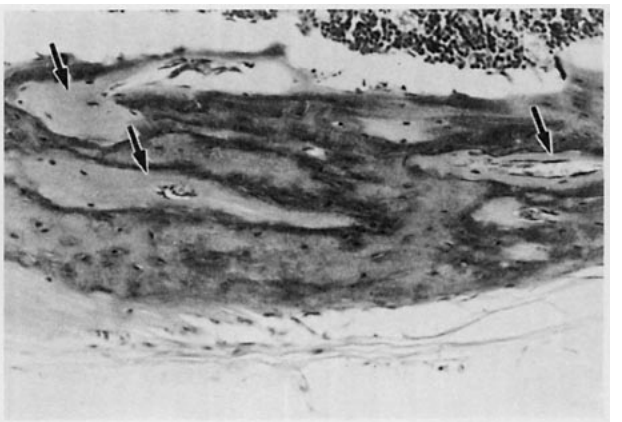


**Plate 14**
Cortex of femur from a male mouse receiving 600 ppm sodium fluoride for six months. The lamellae are thicker and the cement lines are not as distinct as those in the control. Note the thick osteoid seams surrounding several of the vessels (arrows). H&E, 150×

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

| Study Week | Control | | 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 | 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.

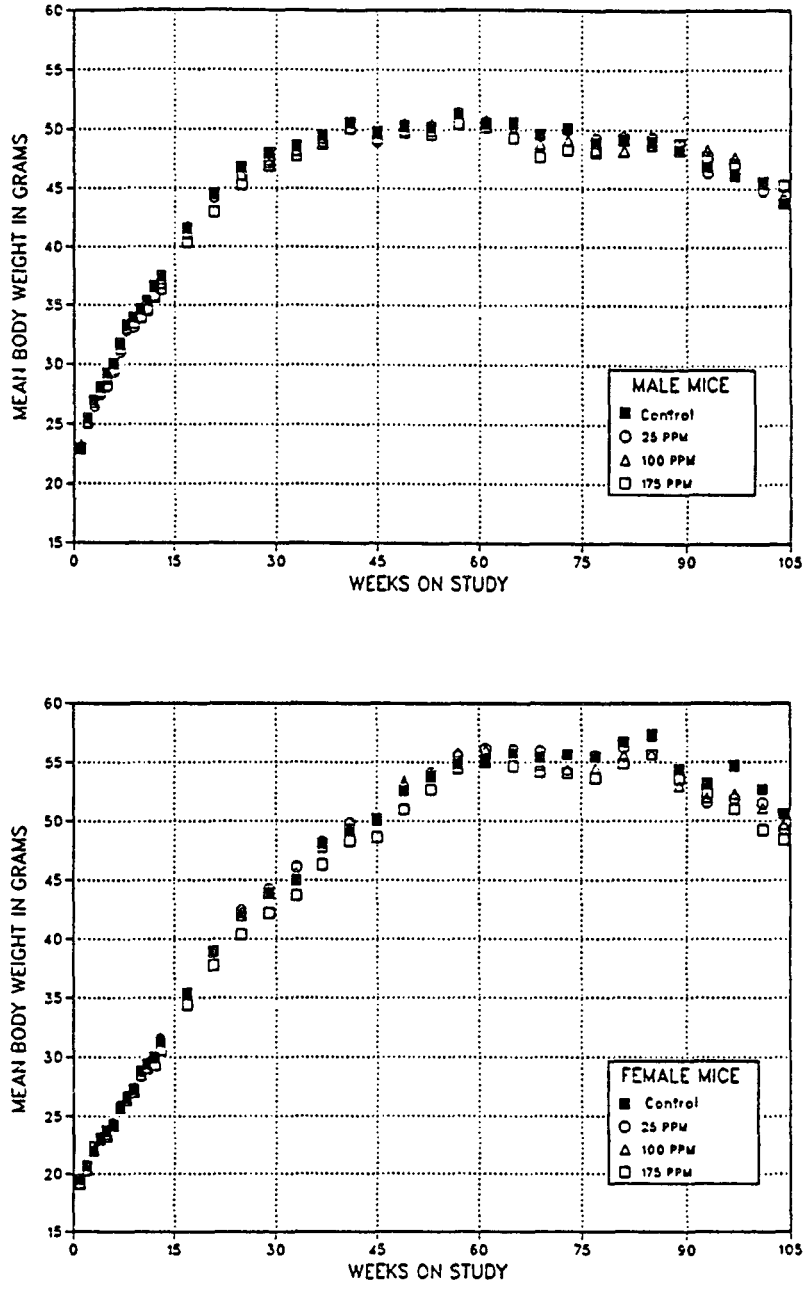



Figure 4
Growth Curves for Male and Female Mice Administered Sodium Fluoride in Drinking Water for 2 Years

### *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.

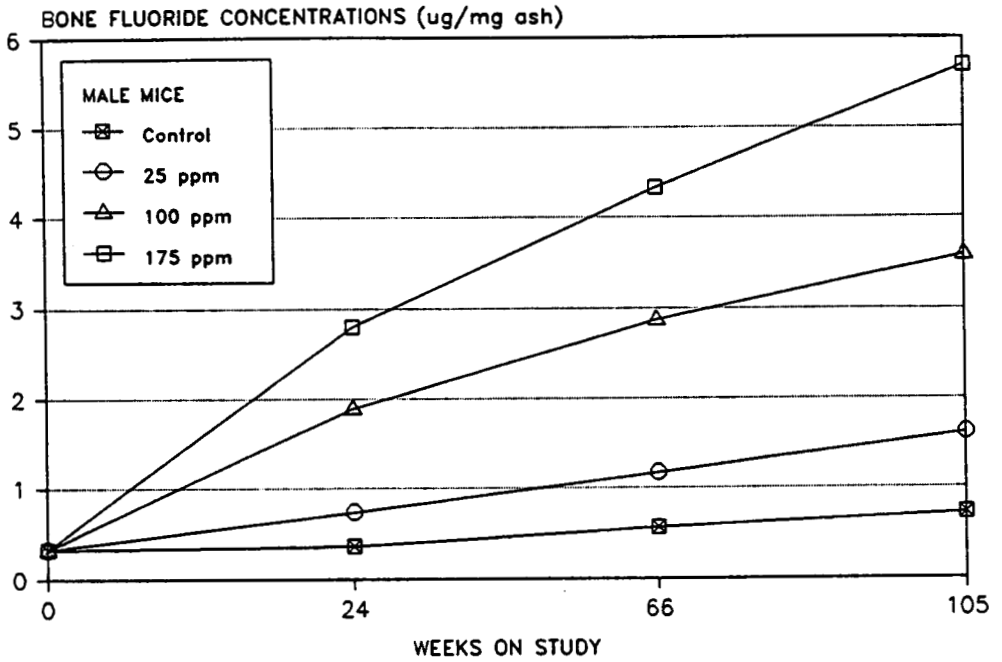
## GENETIC TOXICOLOGY

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.



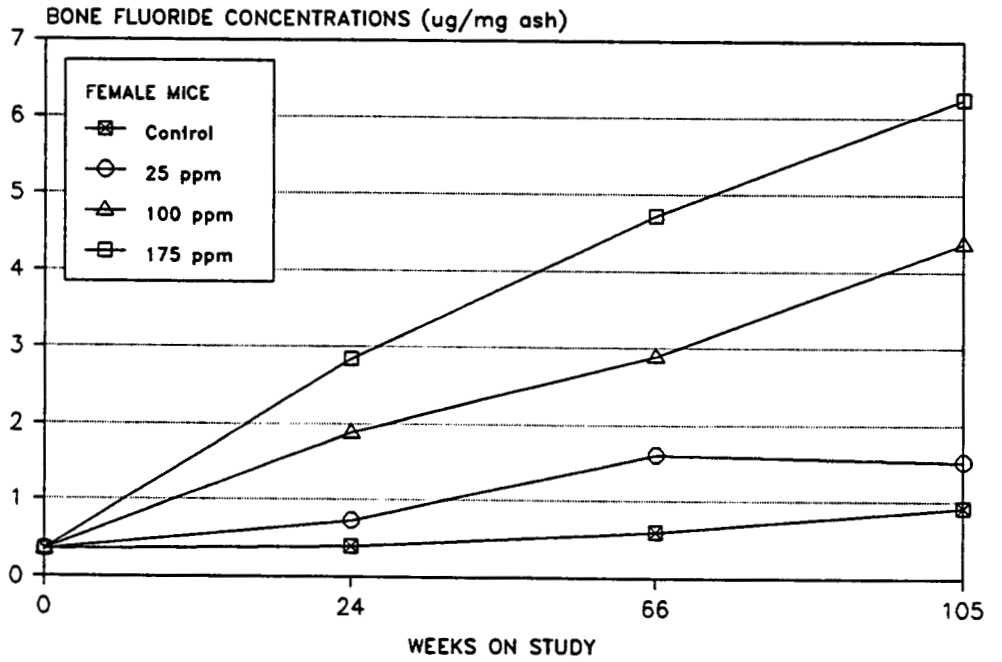




**Figure 5**
**Bone Fluoride Content in Mice in the 2-Year Drinking Water Studies with Sodium Fluoride**

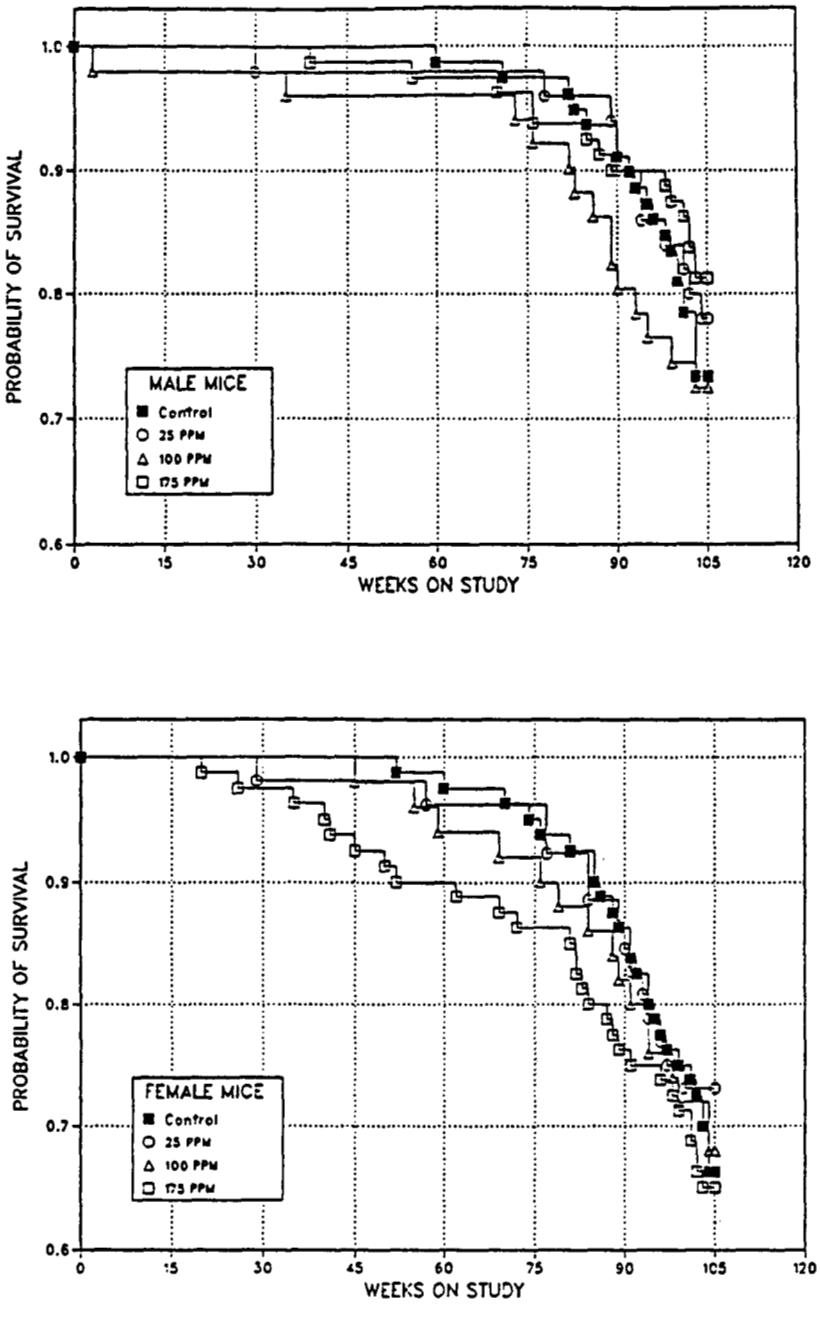



**Figure 6**
**Kaplan-Meier Survival Curves for Male and Female Mice Administered Sodium Fluoride in Drinking Water for 2 Years**

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 $\mu$g/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


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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 | 0 5 9 | 1 4 5 | 3 2 5 | 4 1 7 | 4 4 1 | 5 3 3 | 5 4 3 | 5 4 3 | 5 4 3 | 5 4 9 | 5 7 0 | 5 7 0 | 5 7 1 | 5 9 9 | 6 1 3 | 6 4 4 | 6 4 5 | 6 4 6 | 6 4 8 | 6 5 6 | 6 6 5 | 6 6 9 | 6 7 6 | 6 7 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 2 5 | 1 6 1 | 1 1 4 | 0 1 3 | 1 4 5 | 1 8 1 | 0 2 4 | 1 4 2 | 2 0 1 | 1 9 5 | 1 6 2 | 1 7 4 | 1 0 3 | 1 3 2 | 1 2 4 | 1 1 5 | 1 2 5 | 1 7 3 | 1 5 4 | 0 5 3 | 1 5 3 | 0 5 4 | 1 0 1 | 1 6 4 |
| **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 | 6 8 4 | 6 8 6 | 6 9 0 | 6 9 2 | 6 9 4 | 6 9 7 | 7 1 2 | 7 1 6 | 7 1 8 | 7 1 8 | 7 1 8 | 7 1 9 | 7 1 9 | 7 2 6 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 9 4 | 0 7 2 | 1 4 4 | 1 0 2 | 2 0 2 | 1 2 1 | 0 3 4 | 1 7 5 | 0 1 1 | 0 6 1 | 1 0 4 | 1 3 4 | 1 4 3 | 0 9 3 | 0 1 2 | 0 2 2 | 0 4 2 | 0 7 3 | 0 8 1 | 0 9 1 | 0 9 4 | 1 1 1 | 1 7 2 | 1 9 1 | 0 1 4 |
| **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)

| Number of Days on Study | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 1 5 | 0 2 3 | 0 3 2 | 0 3 5 | 0 4 1 | 0 4 4 | 0 6 2 | 0 6 3 | 0 6 4 | 0 6 5 | 0 7 4 | 0 8 2 | 0 8 4 | 0 9 5 | 1 0 1 | 1 1 2 | 1 1 3 | 1 2 2 | 1 2 3 | 1 3 1 | 1 3 3 | 1 4 1 | 1 5 1 | 1 5 2 | 1 5 5 | 1 6 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 7 7 7 7 7<br>3 3 3 3 3 3<br>3 3 3 3 3 3 | |
|---|---|---|
| **Carcass ID Number** | 1 1 1 1 1 2<br>6 7 8 8 8 0<br>5 1 2 3 5 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)

| Number of Days on Study | 0 5 9 | 1 4 5 | 3 2 5 | 4 1 7 | 4 4 1 | 5 3 3 | 5 4 3 | 5 4 3 | 5 4 3 | 5 4 9 | 5 7 0 | 5 7 0 | 5 7 1 | 5 9 9 | 6 1 3 | 6 4 4 | 6 4 5 | 6 4 6 | 6 4 8 | 6 5 6 | 6 6 5 | 6 6 9 | 6 7 6 | 6 7 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 2 5 | 1 6 1 | 1 1 4 | 0 1 3 | 1 4 5 | 1 8 1 | 0 2 4 | 1 4 2 | 2 0 1 | 1 9 5 | 1 6 2 | 1 7 4 | 1 0 3 | 1 3 2 | 1 2 4 | 1 1 5 | 1 2 5 | 1 7 3 | 1 5 4 | 0 5 3 | 1 5 3 | 0 5 4 | 1 0 1 | 1 6 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 | 6 8 4 | 6 8 6 | 6 9 0 | 6 9 2 | 6 9 4 | 6 9 7 | 7 1 2 | 7 1 6 | 7 1 8 | 7 1 8 | 7 1 8 | 7 1 9 | 7 1 9 | 7 2 6 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 9 1 4 | 0 7 2 4 | 1 4 4 | 1 0 2 | 2 0 2 | 1 2 1 | 0 3 4 | 1 7 5 | 0 1 1 | 0 6 1 | 0 1 4 | 1 3 4 | 1 4 3 | 0 9 3 | 0 1 2 | 0 2 2 | 0 4 2 | 0 7 3 | 0 8 1 | 0 9 1 | 0 9 4 | 1 1 1 | 1 7 2 | 1 9 1 | 0 1 4 |
| **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)

| Number of Days on Study | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 1 5 | 0 2 3 | 0 3 2 | 0 3 5 | 0 4 1 | 0 4 4 | 0 6 2 | 0 6 3 | 0 6 4 | 0 6 5 | 0 7 4 | 0 8 2 | 0 8 4 | 0 9 5 | 1 1 2 | 1 1 3 | 1 2 2 | 1 2 3 | 1 2 3 | 1 3 1 | 1 3 3 | 1 4 1 | 1 5 1 | 1 5 2 | 1 5 5 | 1 6 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 7 7 7 7 7<br>3 3 3 3 3 3<br>3 3 3 3 3 3 | |
|---|---|---|
| **Carcass ID Number** | 1 1 1 1 1 2<br>6 7 8 8 8 0<br>5 1 2 3 5 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)

| Number of Days on Study | 0 5 9 | 1 4 5 | 3 2 5 | 4 1 7 | 4 4 1 | 5 3 3 | 5 4 3 | 5 4 3 | 5 4 3 | 5 4 9 | 5 7 0 | 5 7 0 | 5 7 1 | 5 9 9 | 6 1 3 | 6 4 4 | 6 4 5 | 6 4 6 | 6 4 8 | 6 5 6 | 6 6 5 | 6 7 9 | 6 7 6 | 6 7 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 2 5 | 1 6 1 | 1 1 4 | 0 1 3 | 1 4 5 | 1 8 1 | 0 2 4 | 1 4 2 | 2 0 1 | 1 9 5 | 1 6 2 | 1 7 4 | 1 0 3 | 1 3 2 | 1 2 4 | 1 1 5 | 1 2 5 | 1 7 3 | 1 5 4 | 0 5 3 | 1 5 3 | 0 5 4 | 1 0 1 | 1 6 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)

| Number of Days on Study | 6 8 4 | 6 8 6 | 6 9 0 | 6 9 2 | 6 9 4 | 6 9 7 | 7 1 2 | 7 1 6 | 7 1 8 | 7 1 8 | 7 1 8 | 7 1 9 | 7 1 9 | 7 2 6 | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 9 4 | 0 7 2 | 1 4 4 | 1 0 2 | 2 0 2 | 1 2 1 | 0 3 4 | 1 7 5 | 0 1 1 | 0 6 1 | 0 0 4 | 1 3 4 | 1 4 4 | 1 4 3 | 0 9 3 | 0 1 2 | 0 2 2 | 0 4 2 | 0 7 3 | 0 8 1 | 0 9 1 | 0 9 4 | 1 1 1 | 1 7 2 | 1 9 1 | 0 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)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 |
| **Carcass ID Number** | 0 1 5 | 0 2 3 | 0 3 2 | 0 3 5 | 0 4 1 | 0 4 4 | 0 6 2 | 0 6 3 | 0 6 4 | 0 6 5 | 0 7 4 | 0 8 2 | 0 8 4 | 0 9 5 | 1 0 2 | 1 1 3 | 1 1 2 | 1 2 3 | 1 2 2 | 1 3 3 | 1 3 1 | 1 4 1 | 1 5 1 | 1 5 2 | 1 5 5 | 1 6 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 | 7 7 7 7 7 7<br>3 3 3 3 3 3<br>3 3 3 3 3 3 | |
|---|---|---|
| **Carcass ID Number** | 1 1 1 1 1 2<br>6 7 8 8 8 0<br>5 1 2 3 5 3 | **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 | 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 3 2 | 2 4 1 | 2 8 1 | 2 6 2 | 2 3 5 | 2 2 5 | 2 5 3 |
| **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 6 7 | 6 7 0 | 6 8 0 | 6 8 9 | 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)

| 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 3 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 | 3 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 |
| **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 | 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** |
| **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 | 4 2 2 | 4 2 4 | 5 3 3 | 5 8 4 | 6 0 7 | 6 2 3 | 6 3 4 | 6 3 8 | 6 4 7 | 6 5 4 | 6 6 3 | 6 6 8 | 6 6 9 | 6 7 0 | 6 7 1 | 6 7 3 | 6 7 6 | 6 9 1 | 6 9 7 | 6 9 9 | 7 0 6 | 7 1 0 | 7 1 1 | 7 1 7 | 7 1 8 | 7 2 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 0 2 | 4 1 4 | 3 8 5 | 3 6 5 | 3 6 2 | 4 2 5 | 4 4 5 | 3 7 5 | 3 5 2 | 3 2 3 | 3 3 4 | 3 2 2 | 3 7 3 | 3 5 1 | 3 7 4 | 4 3 4 | 3 5 3 | 3 4 4 | 4 0 3 | 4 4 1 | 3 9 4 | 3 7 1 | 3 4 1 | 4 1 3 | 3 8 5 | 4 4 1 | 4 4 2 |
| **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)

| Number of Days on Study | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 1 3 | 3 1 2 | 3 2 3 | 3 4 5 | 3 5 4 | 3 5 5 | 3 9 1 | 4 2 1 | 4 4 3 | 3 1 4 | 3 2 4 | 3 2 5 | 3 3 1 | 4 4 4 | 3 4 5 | 3 4 1 | 3 4 2 | 3 6 3 | 3 8 3 | 3 9 3 | 4 0 1 | 4 1 2 | 4 3 1 | 4 3 2 | 4 3 5 | **Total Tissues/ 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)

| Number of Days on Study | 4 2 2 | 4 2 4 | 5 3 3 | 5 8 4 | 6 0 7 | 6 2 3 | 6 3 4 | 6 3 8 | 6 4 7 | 6 5 4 | 6 6 3 | 6 6 8 | 6 6 9 | 6 6 0 | 6 7 1 | 6 7 3 | 6 7 6 | 6 9 1 | 6 9 7 | 6 9 9 | 7 0 6 | 7 1 0 | 7 1 1 | 7 1 7 | 7 1 8 | 7 2 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 0 2 | 4 1 4 | 3 8 5 | 3 6 5 | 3 6 2 | 4 2 5 | 4 4 5 | 3 7 5 | 3 5 2 | 3 2 3 | 3 3 4 | 3 2 2 | 3 7 3 | 3 5 1 | 3 7 4 | 4 3 4 | 3 5 4 | 3 8 3 | 4 0 1 | 4 4 4 | 3 9 1 | 3 7 4 | 3 4 1 | 4 1 3 | 3 8 1 | 4 4 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 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 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 1 3 | 3 2 1 | 3 3 2 | 3 4 5 | 3 5 4 | 3 5 5 | 3 9 1 | 4 2 1 | 4 4 3 | 3 1 4 | 3 2 4 | 3 2 5 | 3 3 1 | 4 4 4 | 3 4 5 | 3 4 1 | 3 4 2 | 3 6 3 | 3 8 3 | 3 9 3 | 4 0 1 | 4 1 2 | 4 3 1 | 4 3 2 | 4 3 5 | **Total Tissues/ 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 | 4 2 2 | 4 2 4 | 5 3 3 | 5 8 4 | 6 0 7 | 6 2 3 | 6 3 4 | 6 3 8 | 6 4 7 | 6 5 4 | 6 6 3 | 6 6 8 | 6 6 9 | 6 7 0 | 6 7 1 | 6 7 3 | 6 7 6 | 6 9 1 | 6 9 7 | 6 9 9 | 7 0 6 | 7 1 0 | 7 1 1 | 7 1 7 | 7 1 8 | 7 2 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 0 2 | 4 1 4 | 3 8 5 | 3 6 5 | 3 6 2 | 4 2 5 | 4 4 5 | 3 7 5 | 3 5 2 | 3 2 3 | 3 3 4 | 3 2 2 | 3 7 3 | 5 5 1 | 3 7 4 | 4 3 4 | 3 5 3 | 3 8 4 | 4 0 3 | 4 4 1 | 3 9 4 | 3 7 1 | 4 1 3 | 3 5 5 | 4 1 1 | 4 8 2 | 4 4 4 |
| **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 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 700 | 700 | 730 | 700 | 731 | 711 | 711 | 712 | 722 | 722 | 722 | 723 | 733 | 733 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 313 | 312 | 323 | 345 | 354 | 355 | 391 | 421 | 443 | 414 | 424 | 425 | 431 | 444 | 435 | 344 | 462 | 638 | 939 | 401 | 412 | 413 | 423 | 435 | **Total Tissues/ 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 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 | 5 5 3 | 4 7 2 | 5 4 5 | 5 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)

| Number of Days on Study | 7 1 8 | 7 1 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 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carcass ID Number | 5 0 5 | 5 1 4 | 4 5 5 | 4 9 1 | 4 9 4 | 4 9 5 | 5 3 5 | 5 4 3 | 5 4 4 | 5 5 3 | 5 6 3 | 5 8 5 | 4 8 2 | 4 8 4 | 5 0 3 | 5 4 1 | 4 4 2 | 5 5 2 | 5 6 1 | 5 6 2 | 5 7 3 | 5 7 4 | 5 8 1 | 5 8 2 | 5 8 4 | Total Tissues/ 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 | 7 1 8 | 7 1 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 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carcass ID Number | 5 0 5 | 5 1 4 | 4 5 5 | 4 9 1 | 4 9 4 | 4 9 5 | 5 3 5 | 5 4 3 | 5 4 4 | 5 5 3 | 5 6 3 | 5 8 5 | 4 8 2 | 4 8 4 | 5 0 3 | 5 4 1 | 5 4 2 | 5 5 2 | 5 6 1 | 5 6 2 | 5 7 3 | 5 7 4 | 5 8 1 | 5 8 2 | 5 8 4 | 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 | 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 |
| **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 | 7 1 8 | 7 1 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 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 5 0 5 | 5 1 4 | 4 5 5 | 4 9 1 | 4 9 4 | 4 9 5 | 5 3 5 | 5 4 3 | 5 4 4 | 5 5 3 | 5 6 3 | 5 8 5 | 4 8 2 | 4 8 4 | 5 0 3 | 5 4 1 | 5 4 2 | 5 5 2 | 5 6 1 | 5 6 2 | 5 7 3 | 5 7 4 | 5 8 1 | 5 8 2 | 5 8 4 | **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 8 2 | 3 8 8 | 3 8 9 | 4 6 4 | 5 0 1 | 5 2 2 | 5 2 6 | 5 4 4 | 5 6 1 | 5 7 0 | 5 8 7 | 6 0 2 | 6 0 7 | 6 1 4 | 6 2 0 | 6 2 8 | 6 4 5 | 6 4 6 | 6 4 6 | 6 5 5 | 6 5 9 | 6 6 1 | 6 6 1 | 6 6 4 | 6 7 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 7 7 1 | 7 1 3 | 7 5 1 | 6 0 2 | 6 7 4 | 7 2 5 | 6 5 5 | 7 4 3 | 6 3 3 | 6 1 5 | 6 0 1 | 6 9 2 | 6 5 4 | 7 3 5 | 6 5 1 | 5 9 3 | 6 6 3 | 6 1 4 | 7 8 2 | 7 6 4 | 6 8 5 | 6 2 2 | 6 5 2 | 7 4 1 | 7 7 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 | 6 7 8 | 6 8 1 | 6 8 1 | 6 8 3 | 6 8 3 | 6 8 7 | 6 9 5 | 7 1 0 | 7 1 1 | 7 1 8 | 7 1 8 | 7 2 6 | 7 2 6 | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 6 4 1 | 7 0 5 | 7 4 2 | 7 1 1 | 7 6 5 | 6 1 2 | 7 4 4 | 6 8 4 | 6 5 1 | 7 6 1 | 7 6 3 | 6 7 2 | 6 7 3 | 6 3 2 | 6 3 4 | 6 4 4 | 6 5 3 | 6 8 1 | 6 9 4 | 7 0 3 | 7 1 2 | 7 2 4 | 7 8 3 | 5 9 2 | 5 9 4 |
| **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)

| Number of Days on Study | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 6 0 4 | 6 0 5 | 6 1 1 | 6 1 3 | 6 2 1 | 6 2 4 | 6 3 1 | 6 3 5 | 6 4 2 | 6 4 3 | 6 4 5 | 6 6 2 | 6 6 2 | 6 8 3 | 7 0 1 | 7 0 4 | 7 1 4 | 7 2 1 | 7 2 2 | 7 2 3 | 7 3 2 | 7 3 3 | 7 3 4 | 7 4 5 | 7 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 | 2 8 2 | 3 8 8 | 3 8 9 | 4 6 4 | 5 0 1 | 5 2 2 | 5 2 6 | 5 4 4 | 5 6 1 | 5 7 0 | 5 8 7 | 6 0 2 | 6 0 7 | 6 1 4 | 6 2 0 | 6 2 8 | 6 4 5 | 6 4 6 | 6 5 6 | 6 5 9 | 6 6 1 | 6 6 1 | 6 6 4 | 6 7 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 7 7 1 | 7 1 3 | 7 5 1 | 6 0 2 | 6 7 4 | 7 2 5 | 6 5 5 | 7 4 3 | 6 3 3 | 6 1 5 | 6 0 1 | 6 9 2 | 6 5 4 | 7 3 5 | 6 5 1 | 5 9 3 | 6 6 3 | 6 1 4 | 7 8 2 | 7 6 4 | 6 8 5 | 6 2 2 | 6 5 2 | 7 4 1 | 7 7 5 |
| **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 | 6 7 8 | 6 8 1 | 6 8 1 | 6 8 3 | 6 8 3 | 6 8 7 | 6 9 5 | 7 1 0 | 7 1 1 | 7 1 8 | 7 1 8 | 7 2 6 | 7 2 6 | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 6 4 1 | 7 0 5 | 7 4 2 | 7 1 1 | 7 6 5 | 6 1 2 | 7 4 4 | 6 8 4 | 6 5 1 | 7 6 1 | 7 6 3 | 6 7 2 | 6 7 3 | 6 3 2 | 6 3 4 | 6 4 4 | 6 5 3 | 6 8 1 | 6 9 4 | 7 0 3 | 7 1 2 | 7 2 4 | 7 8 3 | 5 9 2 | 5 9 4 |
| **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)

| 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 | 733 | 733 | 733 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 6004 | 6005 | 6011 | 6013 | 6021 | 6024 | 6031 | 6035 | 6042 | 6043 | 6045 | 6062 | 6082 | 6083 | 7001 | 7014 | 7041 | 7041 | 7042 | 7043 | 7043 | 7043 | 7044 | 7045 | 7052 |
| **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 7 7 7 7<br>3 3 3 3 3<br>3 3 3 3 3 | |
|---|---|---|
| **Carcass ID Number** | 7 7 7 7 7<br>5 5 6 7 8<br>3 5 2 4 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 | 2 8 2 | 3 8 2 | 3 8 3 | 4 6 4 | 5 0 1 | 5 2 2 | 5 2 6 | 5 4 4 | 5 6 1 | 5 7 0 | 5 8 7 | 6 0 2 | 6 0 7 | 6 1 4 | 6 2 0 | 6 2 8 | 6 4 5 | 6 4 6 | 6 4 6 | 6 5 5 | 6 5 9 | 6 6 1 | 6 6 1 | 6 6 4 | 6 7 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 7 7 1 | 7 1 3 | 7 5 1 | 6 0 2 | 6 7 4 | 7 2 5 | 6 5 5 | 7 4 3 | 6 3 3 | 6 1 5 | 6 0 1 | 6 9 2 | 6 5 4 | 7 3 5 | 6 9 1 | 5 9 3 | 6 6 3 | 1 4 | 7 8 2 | 7 6 4 | 6 8 5 | 6 2 2 | 6 5 2 | 7 4 1 | 7 7 5 |
| **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 | 6 7 8 | 6 8 1 | 6 8 1 | 6 8 3 | 6 8 3 | 6 8 7 | 6 9 5 | 7 1 0 | 7 1 1 | 7 1 8 | 7 1 8 | 7 2 6 | 7 2 6 | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 6 4 1 | 7 0 5 | 7 4 2 | 7 1 1 | 7 1 5 | 6 1 2 | 7 4 4 | 6 8 4 | 6 5 1 | 7 6 1 | 6 6 3 | 6 7 2 | 6 7 3 | 6 3 2 | 6 3 4 | 6 4 4 | 6 5 3 | 6 8 1 | 6 9 4 | 7 0 3 | 7 1 2 | 7 2 4 | 7 8 3 | 5 9 2 | 5 9 4 |
| **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 | 733 | 733 | 733 | 733 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 6044 | 6045 | 6111 | 6113 | 6221 | 6224 | 6331 | 6335 | 6442 | 6443 | 6445 | 6622 | 6822 | 6823 | 7001 | 7004 | 7014 | 7212 | 7222 | 7223 | 7323 | 7333 | 7334 | 7515 | 7522 |
| **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 7 7 7 7<br>3 3 3 3 3<br>3 3 3 3 3 | |
|---|---|---|
| **Carcass ID Number** | 7 7 7 7 7<br>5 5 6 7 8<br>3 5 2 4 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)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 2 8 2 | 3 8 8 | 3 8 9 | 4 6 4 | 5 0 1 | 5 2 2 | 5 2 6 | 5 4 4 | 5 6 1 | 5 7 0 | 5 8 7 | 6 0 2 | 6 0 7 | 6 1 4 | 6 2 0 | 6 2 8 | 6 4 5 | 6 4 6 | 6 4 6 | 6 5 5 | 6 5 9 | 6 6 1 | 6 6 1 | 6 6 4 | 6 7 1 |
| **Carcass ID Number** | 7 7 1 | 7 1 3 | 7 5 1 | 6 0 2 | 6 7 4 | 7 2 5 | 6 5 5 | 7 4 3 | 6 3 3 | 6 1 5 | 6 0 1 | 6 9 2 | 6 5 4 | 7 3 5 | 6 9 1 | 5 9 3 | 6 6 3 | 6 1 4 | 7 8 2 | 7 6 4 | 6 8 5 | 6 2 2 | 6 5 2 | 7 4 1 | 7 7 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 | 668 | 681 | 681 | 683 | 683 | 687 | 695 | 710 | 711 | 718 | 718 | 726 | 726 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 64 1 | 70 5 | 74 2 | 71 1 | 76 5 | 61 2 | 74 4 | 68 4 | 65 1 | 76 1 | 76 3 | 67 2 | 67 3 | 63 2 | 63 4 | 64 4 | 65 3 | 68 1 | 69 4 | 70 3 | 71 2 | 72 4 | 78 3 | 59 2 | 59 4 |
| **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** | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 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 |
| **Carcass ID Number** | 6 0 4 | 6 0 5 | 6 1 1 | 6 1 3 | 6 2 1 | 6 2 4 | 6 3 1 | 6 3 5 | 6 4 2 | 6 4 3 | 6 4 5 | 6 6 2 | 6 8 2 | 6 8 3 | 7 0 1 | 7 0 4 | 7 1 4 | 7 2 1 | 7 2 2 | 7 2 3 | 7 3 2 | 7 3 3 | 7 3 4 | 7 4 5 | 7 5 2 |
| **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 7 7 7 7<br>3 3 3 3 3<br>3 3 3 3 3 | |
|---|---|---|
| **Carcass ID Number** | 7 7 7 7 7<br>5 5 6 7 8<br>3 5 2 4 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


| | | |
|---|---|---|
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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 | 2 6 0 | 3 7 0 | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 9 0 1 | 0 8 1 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 |
| **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
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water 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 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carcass ID Number | 08661 | 08664 | 08885 | 08894 | 08905 | 08993 | 09795 | 08801 | 08802 | 08803 | 08805 | 08811 | 08814 | 08815 | 08823 | 08824 | 08831 | 08832 | 08974 | 08975 | 08992 | 08833 | 08835 | 08844 |
| **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** | 08454 | 08851 | 08554 | 08662 | 08663 | 08665 | 08771 | 08882 | 08883 | 08991 | 08992 | 09003 | 09911 | 09912 | 09913 | 09915 | 09921 | 09925 | 09931 | 09933 | 09934 | 09935 | 04442 | 04443 | 04444 |
| **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 | 2 6 0 | 3 7 6 | 4 0 0 | 4 6 3 | 5 0 9 | 6 0 0 | 6 3 0 | 6 3 4 | 6 4 3 | 6 4 6 | 6 4 7 | 6 6 3 | 6 6 4 | 6 7 7 | 6 8 2 | 6 8 3 | 6 8 3 | 6 9 1 | 7 1 0 | 7 1 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 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 |
| **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)

| Number of Days on Study | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 08661 | 08664 | 08885 | 08994 | 09095 | 09293 | 09795 | 08801 | 08802 | 08803 | 08805 | 08811 | 08814 | 08815 | 08823 | 08824 | 08831 | 08832 | 08974 | 09075 | 09282 | 08333 | 08354 | 08444 |
| 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)

| 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** | 08445 | 08851 | 08554 | 08662 | 08863 | 08665 | 08771 | 08882 | 08883 | 08991 | 08992 | 09003 | 09911 | 09912 | 09913 | 09915 | 09921 | 09925 | 09931 | 09933 | 09934 | 09935 | 09942 | 09943 | 09944 |
| **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 7 7 7 7<br>3 3 3 3 3<br>3 3 3 3 3 | |
|---|---|---|
| **Carcass ID Number** | 0 0 0 0 0<br>9 9 9 9 9<br>4 5 5 6 6<br>5 2 4 3 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 0 | 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 6 4 | 6 7 7 | 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 8 2 2 | 0 9 8 3 | 0 8 8 1 | 0 8 8 5 | 0 8 7 1 | 0 8 1 6 | 0 9 6 4 | 0 8 4 3 | 0 9 5 5 | 0 8 1 3 | 0 9 1 6 | 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)

| Number of Days on Study | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 00861 | 00864 | 00885 | 00894 | 00905 | 00923 | 00975 | 00981 | 00992 | 00993 | 00995 | 01011 | 01014 | 01015 | 01023 | 01034 | 01041 | 01051 | 01062 | 01074 | 01085 | 01092 | 01093 | 01104 | 01104 |
| **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 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 8 4 5 | 0 8 5 1 | 0 8 5 4 | 0 8 6 2 | 0 8 6 3 | 0 8 6 5 | 0 8 7 1 | 0 8 8 2 | 0 8 8 3 | 0 8 9 1 | 0 8 9 2 | 0 9 0 3 | 0 9 1 1 | 0 9 1 2 | 0 9 1 3 | 0 9 1 5 | 0 9 2 1 | 0 9 2 5 | 0 9 3 1 | 0 9 3 2 | 0 9 3 4 | 0 9 3 5 | 0 9 4 2 | 0 9 4 3 | 0 9 4 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 7 7 7 7<br>3 3 3 3 3<br>3 3 3 3 3 | |
|---|---|---|
| **Carcass ID Number** | 0 0 0 0 0<br>9 9 9 9 9<br>4 5 5 6 6<br>5 2 4 3 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 | 451 | 515 | 613 | 651 | 757 | 761 | 858 | 959 | 604 | 659 | 609 | 641 | 620 | 662 | 683 | 732 | 733 | 741 | 743 | 746 | 761 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 10882 | 10991 | 10055 | 10072 | 10993 | 10065 | 10088 | 10002 | 10074 | 10001 | 10035 | 10094 | 10033 | 10031 | 10011 | 10012 | 10024 | 10034 | 10045 | 10045 | 10040 | 10041 | 10043 | 10044 | 10030 |
| **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)

| Number of Days on Study | 6 7 0 | 6 7 7 | 6 7 8 | 7 0 5 | 7 1 0 | 7 1 6 | 7 2 6 | |
|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 0 3 3 | 1 0 2 3 | 1 0 5 2 | 1 0 0 2 | 1 0 7 3 | 0 9 9 5 | 1 0 7 5 | **Total Tissues/ 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)

| Number of Days on Study | 3 2 0 | 3 3 8 | 3 7 9 | 4 0 2 | 4 1 5 | 4 5 1 | 4 6 3 | 5 1 5 | 5 5 7 | 5 6 1 | 5 6 8 | 5 7 9 | 5 8 4 | 5 9 9 | 6 0 9 | 6 1 4 | 6 2 0 | 6 2 8 | 6 3 2 | 6 3 3 | 6 4 1 | 6 4 3 | 6 4 3 | 6 4 6 | 6 6 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carcass ID Number | 1 0 8 2 | 0 9 1 | 1 0 5 5 | 1 0 7 2 | 0 9 9 3 | 1 0 6 5 | 1 0 8 1 | 1 0 2 1 | 1 0 7 4 | 1 0 1 3 | 1 0 3 5 | 0 9 9 4 | 1 0 3 2 | 1 0 3 1 | 1 0 1 4 | 1 0 1 2 | 1 0 2 4 | 1 0 3 4 | 1 0 5 4 | 1 0 4 5 | 1 0 0 1 | 1 0 4 1 | 1 0 8 3 | 1 0 4 4 | 1 0 0 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)

| Number of Days on Study | 6 7 0 | 6 7 7 | 6 7 8 | 7 0 5 | 7 1 0 | 7 1 6 | 7 2 6 | |
|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 0 3 3 | 1 0 2 3 | 1 0 5 2 | 1 0 0 2 | 1 0 7 3 | 0 9 9 5 | 1 0 7 5 | **Total Tissues/ 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 | 4 5 1 | 5 6 1 | 5 8 2 | 6 1 8 | 6 2 0 | 6 3 1 | 6 3 9 | 6 5 9 | 6 7 7 | 6 7 7 | 6 9 6 | 7 0 2 | 7 0 4 | 7 0 9 | 7 1 5 | 7 1 8 | 7 1 9 | 7 1 9 | 7 1 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 1 3 3 | 1 7 5 | 1 3 4 | 1 0 2 | 1 9 2 | 1 5 3 | 1 4 3 | 1 8 2 | 1 5 4 | 1 8 4 | 2 0 1 | 2 1 2 | 2 1 3 | 1 1 4 | 1 5 2 | 1 3 1 | 1 7 1 | 1 7 2 | 1 7 3 | 1 0 4 | 1 2 2 | 1 2 3 | 1 2 4 | 1 5 1 | 1 6 2 |
| **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)

| Number of Days on Study | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 1 8 1 | 1 1 9 1 | 1 2 0 2 | 1 2 1 1 | 1 0 9 2 | 1 0 9 3 | 1 0 9 5 | 1 1 0 1 | 1 1 0 5 | 1 1 1 3 | 1 1 1 5 | 1 1 4 1 | 1 1 4 2 | 1 1 6 1 | 1 1 6 3 | 1 1 6 4 | 1 1 7 4 | 1 1 8 3 | 1 1 8 5 | 1 1 9 3 | 1 2 0 3 | 1 2 2 4 | 1 2 2 5 | 1 2 2 2 | 1 2 2 5 | **Total Tissues/ Tumors** |
| **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 | 4 5 1 | 5 6 5 | 5 8 2 | 6 1 8 | 6 2 0 | 6 3 1 | 6 3 9 | 6 5 9 | 6 7 7 | 6 7 7 | 6 9 6 | 7 0 2 | 7 0 4 | 7 0 9 | 7 1 5 | 7 1 8 | 7 1 9 | 7 1 9 | 7 1 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carcass ID Number | 1 1 3 3 | 1 1 7 5 | 1 1 3 4 | 1 1 0 2 | 1 1 9 2 | 1 1 5 3 | 1 1 4 3 | 1 1 8 2 | 1 1 5 4 | 1 1 8 4 | 1 2 0 1 | 1 2 1 2 | 1 2 1 3 | 1 1 1 4 | 1 1 5 2 | 1 1 3 1 | 1 1 7 1 | 1 1 7 2 | 1 1 7 3 | 1 1 0 4 | 1 1 2 2 | 1 1 2 3 | 1 1 2 4 | 1 1 5 1 | 1 1 6 2 |
| **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)

| Number of Days on Study | 729 | 729 | 729 | 729 | 730 | 000 | 000 | 000 | 001 | 111 | 111 | 111 | 111 | 122 | 226 | 226 | 227 | 228 | 228 | 229 | 233 | 233 | 233 | 233 | 233 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 118 | 119 | 120 | 121 | 129 | 093 | 995 | 011 | 105 | 133 | 355 | 014 | 042 | 161 | 633 | 644 | 743 | 833 | 855 | 893 | 033 | 044 | 125 | 222 | 255 | **Total Tissues/ 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<br>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<br>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<br>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<br>3 7 3 0 9 5 4 8 5 8 0 1 1 1 5 3 7 7 7 0 2 2 2 4 5 6<br>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 |
| 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 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 1 8 1 | 1 1 9 1 | 1 2 0 2 | 1 2 1 1 | 1 0 9 2 | 1 0 9 3 | 1 0 9 5 | 1 1 1 1 | 1 1 0 5 | 1 1 1 3 | 1 1 3 5 | 1 1 4 1 | 1 1 4 2 | 1 1 6 1 | 1 1 6 3 | 1 1 6 4 | 1 1 7 4 | 1 1 8 3 | 1 1 8 5 | 1 1 9 3 | 1 2 0 3 | 1 2 1 4 | 1 2 1 5 | 1 2 2 2 | 1 2 2 5 | **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**

| Number of Days on Study | 5 6 8 | 5 6 8 | 5 7 1 | 5 7 5 | 6 4 3 | 6 4 6 | 6 4 7 | 6 4 7 | 6 4 7 | 6 6 2 | 6 6 3 | 6 7 0 | 7 0 8 | 7 1 5 | 7 1 6 | 7 1 6 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 2 4 5 | 1 2 7 4 | 1 3 0 4 | 1 3 0 5 | 1 3 3 5 | 1 3 1 3 | 1 2 4 1 | 1 2 9 3 | 1 3 4 1 | 1 2 3 3 | 1 2 3 5 | 1 3 2 1 | 1 3 0 1 | 1 3 4 3 | 1 3 5 2 | 1 3 5 3 | 1 2 8 1 | 1 2 5 5 | 1 2 7 2 | 1 2 8 2 | 1 3 0 3 | 1 3 1 4 | 1 3 2 4 | 1 3 4 5 | 1 3 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)

| Number of Days on Study | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 3 6 3 | 1 2 4 3 | 1 2 5 1 | 1 2 5 2 | 1 2 5 3 | 1 2 6 3 | 1 2 6 5 | 1 2 7 5 | 1 2 8 4 | 1 2 9 1 | 1 2 9 4 | 1 3 1 2 | 1 3 1 5 | 1 3 2 2 | 1 3 2 3 | 1 3 3 1 | 1 3 3 2 | 1 3 3 4 | 1 3 4 2 | 1 3 4 4 | 1 3 5 1 | 1 3 5 5 | 1 3 6 1 | 1 3 6 2 | 1 3 6 5 | **Total Tissues/ 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)

| Number of Days on Study | 5 6 8 | 5 6 8 | 5 7 1 | 5 7 5 | 6 4 3 | 6 4 6 | 6 4 7 | 6 4 7 | 6 4 7 | 6 6 2 | 6 6 3 | 6 7 0 | 7 0 8 | 7 1 5 | 7 1 6 | 7 1 6 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 2 4 5 | 1 2 7 4 | 1 3 0 4 | 1 3 0 5 | 1 3 3 5 | 1 3 1 3 | 1 2 4 1 | 1 2 9 3 | 1 3 4 1 | 1 2 3 3 | 1 2 3 5 | 1 3 2 1 | 1 3 0 1 | 1 3 4 3 | 1 3 5 2 | 1 3 5 3 | 1 2 8 1 | 1 2 2 5 | 1 2 7 2 | 1 2 8 2 | 1 3 0 3 | 1 3 1 4 | 1 3 2 4 | 1 3 4 5 | 1 3 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)

| Number of Days on Study | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 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 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 3 6 3 | 1 2 4 3 | 1 2 5 1 | 1 2 5 2 | 1 2 5 3 | 1 2 6 3 | 1 2 6 5 | 1 2 7 5 | 1 2 8 4 | 1 2 9 1 | 1 2 9 4 | 1 3 1 2 | 1 3 1 5 | 1 3 2 2 | 1 3 2 3 | 1 3 3 1 | 1 3 3 2 | 1 3 3 4 | 1 3 4 2 | 1 3 4 4 | 1 3 5 1 | 1 3 5 5 | 1 3 6 1 | 1 3 6 2 | 1 3 6 5 | **Total Tissues/ 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 | 5 6 8 | 5 6 8 | 5 7 1 | 5 7 5 | 6 4 3 | 6 4 6 | 6 4 7 | 6 4 7 | 6 4 7 | 6 6 2 | 6 6 3 | 6 7 0 | 7 0 8 | 7 1 5 | 7 1 6 | 7 1 6 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 2 4 5 | 1 2 7 4 | 1 3 0 4 | 1 3 0 5 | 1 3 3 5 | 1 3 1 3 | 1 2 4 1 | 1 2 9 3 | 1 3 4 1 | 1 2 3 3 | 1 2 3 5 | 1 3 2 1 | 1 3 0 1 | 1 3 4 3 | 1 3 5 2 | 1 3 5 3 | 1 2 8 1 | 2 2 5 5 | 2 2 7 2 | 2 2 8 2 | 2 3 0 3 | 3 3 1 4 | 3 3 2 4 | 3 3 4 5 | 1 3 5 4 |
| **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)

| Number of Days on Study | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 3 6 3 | 1 2 4 3 | 1 2 5 1 | 1 2 5 2 | 1 2 5 3 | 1 2 6 3 | 1 2 6 5 | 1 2 7 5 | 1 2 8 4 | 1 2 9 1 | 1 2 9 4 | 1 3 1 2 | 1 3 1 5 | 1 3 2 2 | 1 3 2 3 | 1 3 3 1 | 1 3 3 2 | 1 3 3 4 | 1 3 4 2 | 1 3 4 4 | 1 3 5 1 | 1 3 5 5 | 1 3 6 1 | 1 3 6 2 | 1 3 6 5 | **Total Tissues/ 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 | 3 3 8 | 4 1 5 | 5 1 5 | 5 5 7 | 5 6 1 | 5 7 1 | 5 7 8 | 6 1 3 | 6 2 8 | 6 3 1 | 6 3 1 | 6 3 9 | 6 4 6 | 6 4 7 | 6 4 7 | 6 4 7 | 6 7 8 | 7 0 5 | 7 0 9 | 7 1 4 | 7 1 6 | 7 1 6 | 7 1 6 | 7 1 9 | 7 1 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 4 4 5 | 1 3 7 3 | 1 4 3 3 | 1 4 2 4 | 1 4 1 1 | 1 4 0 4 | 1 4 4 2 | 1 4 5 5 | 1 4 4 1 | 1 3 9 1 | 1 4 5 1 | 1 5 0 2 | 1 4 0 5 | 1 3 8 3 | 1 4 8 1 | 1 4 8 3 | 1 5 2 3 | 1 4 1 2 | 1 3 9 5 | 1 5 2 4 | 1 4 7 2 | 1 4 7 4 | 1 5 3 2 | 1 4 9 1 | 1 4 9 3 |
| **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 | 7 1 9 | 7 2 2 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 4 9 4 | 1 4 3 1 | 1 4 1 4 | 1 4 2 1 | 1 4 4 4 | 1 4 5 3 | 1 4 6 4 | 1 5 0 1 | 1 5 0 4 | 1 5 1 2 | 1 5 3 3 | 1 5 5 1 | 1 3 7 5 | 1 3 8 1 | 1 3 8 2 | 1 3 8 4 | 1 3 8 5 | 1 3 9 2 | 1 3 9 4 | 1 4 0 1 | 1 4 0 2 | 1 4 0 3 | 1 4 1 3 | 1 4 2 2 | 1 4 2 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 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| 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 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carcass ID Number | 1 4 3 2 | 1 4 3 4 | 1 4 3 5 | 1 4 4 3 | 1 4 5 2 | 1 4 5 4 | 1 4 6 2 | 1 4 7 1 | 1 4 7 3 | 1 4 7 5 | 1 5 0 3 | 1 5 0 5 | 1 5 1 4 | 1 5 1 5 | 1 5 2 1 | 1 5 2 2 | 1 5 2 3 | 1 5 3 4 | 1 5 3 5 | 1 5 4 1 | 1 5 4 2 | 1 5 4 3 | 1 5 4 5 | 1 5 5 2 | 1 5 5 3 |
| **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)

| 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** |
| **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 | 3 3 8 | 4 1 5 | 5 1 5 | 5 5 7 | 5 6 1 | 5 7 1 | 5 7 8 | 6 1 3 | 6 2 8 | 6 3 1 | 6 3 1 | 6 3 9 | 6 4 6 | 6 4 7 | 6 4 7 | 6 4 7 | 6 7 8 | 7 0 5 | 7 0 9 | 7 1 4 | 7 1 6 | 7 1 6 | 7 1 6 | 7 1 9 | 7 1 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 4 4 5 | 1 3 7 3 | 1 4 3 3 | 1 4 2 4 | 1 4 1 1 | 1 4 0 4 | 1 4 4 2 | 1 4 5 5 | 1 4 4 1 | 1 3 9 1 | 1 4 5 1 | 1 5 0 2 | 1 4 0 5 | 1 3 8 3 | 1 4 8 1 | 1 4 8 3 | 1 5 2 3 | 1 4 1 2 | 1 3 9 5 | 1 5 2 4 | 1 4 7 2 | 1 4 7 4 | 1 5 3 2 | 1 4 9 1 | 1 4 9 3 |
| **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)

| Number of Days on Study | 719 | 723 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 14494 | 14431 | 14414 | 14421 | 14443 | 14453 | 14464 | 15014 | 15024 | 15012 | 15033 | 15051 | 15075 | 15081 | 15082 | 15084 | 15085 | 15092 | 15094 | 15101 | 15122 | 15143 | 15132 | 15225 |
| **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)

| Number of Days on Study | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 733 | 733 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 14332 | 14424 | 14435 | 14443 | 14552 | 14644 | 14762 | 14771 | 14773 | 14775 | 15030 | 15055 | 15141 | 15255 | 15521 | 15622 | 15721 | 15834 | 15933 | 16145 | 16242 | 16343 | 16451 | 16552 | 16653 |
| **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 | 3 3 8 | 4 1 5 | 5 1 5 | 5 5 7 | 5 6 1 | 5 7 1 | 5 7 8 | 6 1 3 | 6 2 8 | 6 3 1 | 6 3 1 | 6 3 9 | 6 4 6 | 6 4 7 | 6 4 7 | 6 4 7 | 6 7 8 | 7 0 5 | 7 0 9 | 7 1 4 | 7 1 6 | 7 1 6 | 7 1 6 | 7 1 9 | 7 1 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 4 4 5 | 1 3 7 3 | 1 4 3 3 | 1 4 2 4 | 1 4 1 1 | 1 4 0 4 | 1 4 4 2 | 1 4 5 5 | 1 4 4 1 | 1 4 9 1 | 1 4 5 1 | 1 5 0 2 | 1 4 0 5 | 1 4 3 3 | 1 4 8 1 | 1 4 8 3 | 1 5 2 3 | 1 4 1 2 | 1 4 9 5 | 1 5 2 4 | 1 4 7 2 | 1 4 7 4 | 1 5 3 2 | 1 4 9 1 | 1 4 9 3 |
| **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)

| Number of Days on Study | 7 1 9 | 7 2 2 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 4 9 4 | 1 4 3 1 | 1 4 1 4 | 1 4 2 1 | 1 4 4 4 | 1 4 5 3 | 1 4 6 4 | 1 5 0 1 | 1 5 0 4 | 1 5 1 2 | 1 5 3 3 | 1 5 5 1 | 1 3 7 5 | 1 3 8 1 | 1 3 8 2 | 1 3 8 4 | 1 3 8 5 | 1 3 9 2 | 1 3 9 4 | 1 4 0 1 | 1 4 0 2 | 1 4 0 3 | 1 4 1 3 | 1 4 2 2 | 1 4 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)

| Number of Days on Study | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 4 3 2 | 1 4 3 4 | 1 4 3 5 | 1 4 4 3 | 1 4 5 2 | 1 4 5 4 | 1 4 6 2 | 1 4 7 1 | 1 4 7 3 | 1 4 7 5 | 1 5 0 3 | 1 5 0 5 | 1 5 1 4 | 1 5 1 5 | 1 5 2 1 | 1 5 2 2 | 1 5 3 1 | 1 5 3 4 | 1 5 3 5 | 1 5 4 1 | 1 5 4 2 | 1 5 4 3 | 1 5 4 5 | 1 5 5 2 | 1 5 5 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 | 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** |
| **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


| | | |
|---|---|---|
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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 | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **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 1 1 | 0 2 8 1 | 0 2 9 1 | 0 3 7 1 |
| **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 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 3 9 1 | 0 4 9 1 | 0 6 2 1 | 0 8 2 1 | 0 8 4 1 | 0 8 8 1 | 0 0 5 1 | 0 0 6 1 | 0 0 7 1 | 0 0 9 1 | 0 1 0 1 | 0 1 2 1 | 0 1 3 1 | 0 1 5 1 | 0 1 9 1 | 0 9 5 1 | 0 1 6 1 | 0 1 7 1 | 0 1 8 1 | 0 2 1 1 | 0 2 5 1 | 0 2 6 1 | 0 3 0 1 | 0 3 2 1 | 0 3 3 1 |
| **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 | 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 3 | 7 3 3 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 3 5 1 | 0 3 6 1 | 0 4 3 1 | 0 4 4 1 | 0 4 6 1 | 0 4 7 1 | 0 4 8 1 | 0 5 1 1 | 0 5 2 1 | 0 5 4 1 | 0 5 7 1 | 0 5 9 1 | 0 6 3 1 | 0 6 4 1 | 0 6 5 1 | 0 7 0 1 | 0 7 1 1 | 0 7 2 1 | 0 7 3 1 | 0 7 5 1 | 0 7 7 1 | 0 7 8 1 | 0 8 0 1 | 0 8 3 1 | 0 8 9 1 |
| **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 | 420 | 429 | 457 | 578 | 591 | 625 | 626 | 641 | 645 | 662 | 669 | 684 | 691 | 696 | 698 | 701 | 704 | 715 | 720 | 721 | 722 | 729 | 729 | 729 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 06711 | 00211 | 04011 | 06811 | 03111 | 08511 | 02211 | 01111 | 01031 | 02011 | 02511 | 04511 | 05611 | 07611 | 06911 | 09311 | 06111 | 08811 | 03311 | 03211 | 04111 | 04011 | 02211 | 03711 |
| **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 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 0 3 9 1 | 0 4 9 1 | 0 6 2 1 | 0 8 2 1 | 0 8 4 1 | 0 8 8 1 | 0 0 5 1 | 0 0 6 1 | 0 0 7 1 | 0 0 9 1 | 0 1 0 1 | 0 1 2 1 | 0 1 3 1 | 0 1 5 1 | 0 1 9 1 | 0 1 5 1 | 0 1 6 1 | 0 1 7 1 | 0 1 8 1 | 0 2 1 1 | 0 2 5 1 | 0 2 6 1 | 0 3 0 1 | 0 3 2 1 | 0 3 3 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)

| 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 | 737 | 737 | 737 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 03511 | 03611 | 03411 | 04411 | 04611 | 04711 | 04811 | 05111 | 05211 | 05411 | 05711 | 05911 | 06311 | 06411 | 06511 | 06711 | 07011 | 07111 | 07211 | 07311 | 07511 | 07711 | 07811 | 08011 | 08311 | 08911 |
| **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 7 7 7<br>3 3 3 3<br>7 7 7 7 | |
|---|---|---|
| **Carcass ID Number** | 0 0 0 0<br>9 9 9 9<br>1 2 7 8<br>1 1 1 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 | 622 | 626 | 641 | 645 | 646 | 662 | 669 | 684 | 691 | 696 | 698 | 701 | 704 | 715 | 720 | 721 | 721 | 729 | 729 | 729 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 06771 | 00211 | 04011 | 06811 | 03111 | 08511 | 02211 | 01111 | 01311 | 02011 | 02911 | 05011 | 04511 | 05611 | 07611 | 06911 | 09311 | 06111 | 08111 | 03211 | 02411 | 04111 | 02211 | 02911 | 03711 |
| **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 | | 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 | 729 | 729 | 729 | 729 | 729 | 729 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 301 | 311 | 311 | 311 | 311 | 311 | 311 | 312 | 312 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 03911 | 04911 | 06211 | 08211 | 08411 | 08811 | 00511 | 00611 | 00711 | 00911 | 01011 | 01211 | 01311 | 01511 | 01911 | 01611 | 01711 | 01811 | 02111 | 02211 | 02611 | 03011 | 03311 | 03411 |
| **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 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| 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)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 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 3 | 7 3 3 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 |
| **Carcass ID Number** | 0 3 5 1 | 0 3 6 1 | 0 4 3 1 | 0 4 4 1 | 0 4 6 1 | 0 4 7 1 | 0 4 8 1 | 0 5 1 1 | 0 5 2 1 | 0 5 4 1 | 0 5 7 1 | 0 5 9 1 | 0 6 3 1 | 0 6 4 1 | 0 6 5 1 | 0 7 0 1 | 0 7 1 1 | 0 7 2 1 | 0 7 3 1 | 0 7 5 1 | 0 7 7 1 | 0 7 8 1 | 0 8 0 1 | 0 8 3 1 | 0 8 9 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 | 7 7 7 7<br>3 3 3 3<br>7 7 7 7 | |
|---|---|---|
| **Carcass ID Number** | 0 0 0 0<br>9 9 9 9<br>1 2 7 8<br>1 1 1 1 | **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**

| Number of Days on Study | 0 1 7 | 2 0 8 | 2 4 1 | 2 7 3 | 3 5 9 | 3 8 6 | 4 2 0 | 4 2 0 | 4 3 3 | 4 8 8 | 5 0 5 | 5 1 9 | 5 2 3 | 5 2 7 | 5 3 0 | 5 4 0 | 5 6 4 | 5 6 8 | 5 7 9 | 5 9 3 | 5 9 9 | 6 0 9 | 6 1 9 | 6 2 3 | 6 5 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 2 2 1 | 1 3 9 1 | 1 1 9 1 | 1 1 7 1 | 1 4 1 1 | 1 3 2 1 | 1 1 3 1 | 1 4 2 1 | 1 3 0 1 | 1 3 7 1 | 1 1 5 1 | 1 2 0 1 | 1 3 3 1 | 1 5 0 1 | 1 2 8 1 | 1 0 5 1 | 1 2 9 1 | 1 3 1 1 | 1 4 8 1 | 1 4 9 1 | 1 2 1 1 | 1 1 8 1 | 1 0 3 1 | 1 3 6 1 | 1 0 2 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 | 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** |
| **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 1 7 | 2 0 8 | 2 4 1 | 2 7 3 | 3 5 9 | 3 8 6 | 4 2 0 | 4 2 0 | 4 3 3 | 4 8 8 | 5 0 5 | 5 1 9 | 5 2 3 | 5 2 7 | 5 3 0 | 5 4 0 | 5 6 4 | 5 6 8 | 5 7 9 | 5 9 3 | 5 9 9 | 6 0 9 | 6 1 9 | 6 2 3 | 6 5 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 2 2 1 | 1 3 9 1 | 1 1 9 1 | 1 1 7 1 | 1 4 1 1 | 1 3 2 1 | 1 1 3 1 | 1 4 2 1 | 1 3 0 1 | 1 3 7 1 | 1 1 5 1 | 1 2 0 1 | 1 3 3 1 | 1 5 0 1 | 1 2 3 1 | 1 0 8 1 | 1 2 5 1 | 1 3 9 1 | 1 4 1 1 | 1 4 9 1 | 1 2 1 1 | 1 1 8 1 | 1 0 3 1 | 1 3 6 1 | 1 0 2 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 | 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** |
| **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)

| Number of Days on Study | 0 1 7 | 2 0 8 | 2 4 1 | 2 7 3 | 3 5 9 | 3 8 6 | 4 2 0 | 4 2 0 | 4 3 3 | 4 8 8 | 5 0 5 | 5 1 9 | 5 2 3 | 5 2 7 | 5 3 0 | 5 4 0 | 5 6 4 | 5 6 8 | 5 7 9 | 5 9 3 | 5 9 9 | 6 0 9 | 6 1 9 | 6 2 3 | 6 5 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 2 2 1 | 1 3 9 1 | 1 1 9 1 | 1 1 7 1 | 1 4 1 1 | 1 3 2 1 | 1 1 3 1 | 1 4 2 1 | 1 3 0 1 | 1 3 7 1 | 1 1 5 1 | 1 2 0 1 | 1 3 3 1 | 1 5 0 1 | 1 2 8 1 | 1 0 5 1 | 1 3 9 1 | 1 2 1 1 | 1 3 8 1 | 1 4 9 1 | 1 2 1 1 | 1 1 8 1 | 1 0 3 1 | 1 3 6 1 | 1 0 2 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 | 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 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 6 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 |
| **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 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 6 0 1 | 1 6 1 1 | 1 6 2 1 | 1 6 3 1 | 1 6 7 1 | 1 7 2 1 | 1 7 3 1 | 1 7 5 1 | 1 7 7 1 | 1 8 6 1 | 1 8 9 1 | 1 9 4 1 | 1 9 5 1 | 1 9 7 1 | 2 0 1 1 | 2 0 2 1 | 2 0 6 1 | 2 0 7 1 | 2 0 8 1 | 2 1 1 1 | 2 1 5 1 | 2 1 7 1 | 2 1 8 1 | 2 1 9 1 | 2 2 0 1 | **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 | 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 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 |
| **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)

| Number of Days on Study | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 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** | 1 6 0 1 | 1 6 1 1 | 1 6 2 1 | 1 6 3 1 | 1 6 7 1 | 1 7 2 1 | 1 7 3 1 | 1 7 5 1 | 1 7 7 1 | 1 8 6 1 | 1 8 9 1 | 1 9 4 1 | 1 9 5 1 | 1 9 7 1 | 2 0 1 1 | 2 0 2 1 | 2 0 6 1 | 2 0 7 1 | 2 0 8 1 | 2 1 1 1 | 2 1 5 1 | 2 1 7 1 | 2 1 8 1 | 2 1 9 1 | 2 2 0 1 | **Total Tissues/ 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)

| Number of Days on Study | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 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 7 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1 6 0 1 1 | 1 6 1 1 1 | 1 6 2 1 1 | 1 6 3 1 1 | 1 6 7 1 1 | 1 7 2 1 1 | 1 7 3 1 1 | 1 7 5 1 1 | 1 7 7 1 1 | 1 8 6 1 1 | 1 8 9 1 1 | 1 9 4 1 1 | 1 9 5 1 1 | 1 9 7 1 1 | 2 0 1 1 1 | 2 0 2 1 1 | 2 0 6 1 1 | 2 0 7 1 1 | 2 0 8 1 1 | 2 1 1 1 1 | 2 1 5 1 1 | 2 1 7 1 1 | 2 1 8 1 1 | 2 1 9 1 1 | 2 2 0 1 1 | **Total Tissues/ 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 | 0 1 7 | 2 4 1 | 5 0 5 | 5 2 8 | 5 6 8 | 5 7 9 | 5 9 8 | 6 1 9 | 6 2 0 | 6 2 6 | 6 5 1 | 6 6 0 | 6 9 2 | 7 2 1 | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 9 0 1 | 2 3 0 1 | 2 2 5 1 | 2 3 2 1 | 2 4 4 1 | 2 6 8 1 | 2 3 7 1 | 2 5 6 1 | 2 8 9 1 | 2 3 5 1 | 2 3 8 1 | 2 4 7 1 | 2 6 7 1 | 2 4 5 1 | 2 2 4 1 | 2 2 1 1 | 2 3 4 1 | 2 4 1 1 | 2 5 2 1 | 2 6 4 1 | 2 6 2 1 | 2 8 4 1 | 2 8 4 1 | 2 2 3 1 | 2 2 9 1 |
| **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 | | | | | | | | X |
| Hepatocellular adenoma | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Hepatocellular adenoma, multiple | | | | | | 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)

| Number of Days on Study | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 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 7 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 3 3 1 | 2 3 6 1 | 2 3 9 1 | 2 4 0 1 | 2 4 1 1 | 2 4 3 1 | 2 4 6 1 | 2 4 8 1 | 2 4 9 1 | 2 5 2 1 | 2 5 5 1 | 2 5 7 1 | 2 5 9 1 | 2 6 0 1 | 2 6 1 1 | 2 6 5 1 | 2 6 6 1 | 2 6 9 1 | 2 7 6 1 | 2 7 8 1 | 2 7 9 1 | 2 8 3 1 | 2 8 5 1 | 2 8 7 1 | 2 8 8 1 | **Total Tissues/ 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 | 0 1 7 | 2 4 1 | 5 0 5 | 5 2 8 | 5 6 8 | 5 7 9 | 5 9 8 | 6 1 9 | 6 2 0 | 6 2 6 | 6 5 1 | 6 6 0 | 6 9 2 | 7 2 1 | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 9 0 1 | 2 3 0 1 | 2 2 5 1 | 2 3 2 1 | 2 4 4 1 | 2 6 8 1 | 2 3 7 1 | 2 5 6 1 | 2 8 9 1 | 2 3 5 1 | 2 3 8 1 | 2 4 7 1 | 2 6 7 1 | 2 4 5 1 | 2 2 2 1 | 2 2 4 1 | 2 3 1 1 | 2 4 2 1 | 2 5 8 1 | 2 6 2 1 | 2 6 4 1 | 2 8 2 1 | 2 8 4 1 | 2 8 6 1 | 2 2 3 1 | 2 2 9 1 |
| **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 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 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 7 | 7 3 7 | 7 3 7 | 7 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 3 3 1 | 2 3 6 1 | 2 3 9 1 | 2 4 0 1 | 2 4 1 1 | 2 4 3 1 | 2 4 6 1 | 2 4 8 1 | 2 4 9 1 | 2 5 2 1 | 2 5 5 1 | 2 5 7 1 | 2 5 9 1 | 2 6 0 1 | 2 6 1 1 | 2 6 5 1 | 2 6 6 1 | 2 6 9 1 | 2 7 6 1 | 2 7 8 1 | 2 7 9 1 | 2 8 3 1 | 2 8 5 1 | 2 8 7 1 | 2 8 8 1 | **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)

| Number of Days on Study | 0 1 7 | 2 4 1 | 5 0 5 | 5 2 8 | 5 6 8 | 5 7 9 | 5 9 8 | 6 1 9 | 6 2 0 | 6 2 6 | 6 5 1 | 6 6 0 | 6 9 2 | 7 2 1 | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 9 0 1 | 2 3 0 1 | 2 2 5 1 | 2 3 2 1 | 2 4 4 1 | 2 6 8 1 | 2 3 7 1 | 2 5 6 1 | 2 8 9 1 | 2 3 5 1 | 2 3 8 1 | 2 4 7 1 | 2 6 7 1 | 2 4 5 1 | 2 2 2 1 | 2 2 4 1 | 2 3 1 1 | 2 4 2 1 | 2 5 8 1 | 2 6 2 1 | 2 6 4 1 | 2 8 2 1 | 2 8 4 1 | 2 8 6 1 | 2 2 3 1 | 2 2 9 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 |
| 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 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 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 7 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 3 3 1 | 2 3 6 1 | 2 3 9 1 | 2 4 0 1 | 2 4 1 1 | 2 4 3 1 | 2 4 6 1 | 2 4 8 1 | 2 4 9 1 | 2 5 2 1 | 2 5 5 1 | 2 5 7 1 | 2 5 9 1 | 2 6 0 1 | 2 6 1 1 | 2 6 5 1 | 2 6 6 1 | 2 6 9 1 | 2 7 6 1 | 2 7 8 1 | 2 7 9 1 | 2 8 3 1 | 2 8 5 1 | 2 8 7 1 | 2 8 8 1 | **Total Tissues/ 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 | 2 7 3 | 3 8 6 | 4 8 8 | 5 2 7 | 5 2 9 | 5 9 3 | 6 0 9 | 6 2 3 | 6 8 4 | 6 9 1 | 7 0 5 | 7 1 4 | 7 1 4 | 7 1 9 | 7 2 1 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 3 5 1 | 2 9 6 1 | 3 2 6 1 | 3 4 3 1 | 3 6 2 1 | 3 7 8 1 | 3 6 3 1 | 2 9 9 1 | 3 0 2 1 | 3 8 3 1 | 3 6 1 1 | 3 2 9 1 | 3 5 1 1 | 3 0 1 1 | 3 1 8 1 | 3 1 1 1 | 3 1 0 1 | 3 1 8 1 | 3 2 1 1 | 3 2 4 1 | 3 3 7 1 | 3 3 8 1 | 3 5 6 1 | 3 7 3 1 | 3 7 6 1 | 3 8 8 1 |
| **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 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 9 3 1 | 2 9 4 1 | 2 9 5 1 | 2 9 7 1 | 3 0 1 1 | 3 0 3 1 | 3 0 5 1 | 3 0 6 1 | 3 0 7 1 | 3 1 2 1 | 3 1 3 1 | 3 1 4 1 | 3 1 5 1 | 3 1 6 1 | 3 1 9 1 | 3 2 0 1 | 3 2 2 1 | 3 2 5 1 | 3 2 7 1 | 3 3 0 1 | 3 3 1 1 | 3 3 6 1 | 3 4 0 1 | 3 4 1 1 | 3 4 4 1 |
| **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 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 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 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** | 3 4 5 1 | 3 4 6 1 | 3 4 8 1 | 3 4 9 1 | 3 5 0 1 | 3 5 2 1 | 3 5 3 1 | 3 5 5 1 | 3 5 7 1 | 3 5 9 1 | 3 6 0 1 | 3 6 4 1 | 3 6 5 1 | 3 6 6 1 | 3 6 7 1 | 3 6 8 1 | 3 6 9 1 | 3 7 1 1 | 3 7 2 1 | 3 7 4 1 | 3 7 5 1 | 3 7 9 1 | 3 8 0 1 | 3 8 1 1 | 3 8 2 1 |
| **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 | 2 7 3 | 3 8 6 | 4 8 8 | 5 2 7 | 5 2 9 | 5 9 3 | 6 0 9 | 6 2 3 | 6 8 4 | 6 9 1 | 7 0 5 | 7 1 4 | 7 1 4 | 7 1 9 | 7 2 1 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 3 5 1 | 2 9 6 1 | 3 2 6 1 | 3 4 3 1 | 3 6 2 1 | 3 7 8 1 | 3 6 3 1 | 2 9 9 1 | 3 0 2 1 | 3 8 3 1 | 3 6 1 1 | 3 2 9 1 | 3 5 1 1 | 3 0 8 1 | 3 1 1 1 | 3 1 0 1 | 3 1 8 1 | 3 2 1 1 | 3 2 4 1 | 3 3 7 1 | 3 3 8 1 | 3 5 6 1 | 3 7 3 1 | 3 7 6 1 | 3 8 8 1 |
| **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, hepatocholangio-carcinoma, metastatic, liver | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Pancreatic, hepatocholangio-carcinoma, metastatic, liver | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Renal, hepatocholangio-carcinoma, 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 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 9 3 1 | 2 9 4 1 | 2 9 5 1 | 2 9 7 1 | 3 0 1 1 | 3 0 3 1 | 3 0 5 1 | 3 0 6 1 | 3 0 7 1 | 3 1 2 1 | 3 1 3 1 | 3 1 4 1 | 3 1 5 1 | 3 1 6 1 | 3 1 9 1 | 3 2 0 1 | 3 2 2 1 | 3 2 5 1 | 3 2 7 1 | 3 3 0 1 | 3 3 1 1 | 3 3 6 1 | 3 4 0 1 | 3 4 1 1 | 3 4 4 1 |
| **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, hepatocholangio-carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreatic, hepatocholangio-carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | |
| Renal, hepatocholangio-carcinoma, 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 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 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 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** | 3 4 5 1 | 3 4 6 1 | 3 4 8 1 | 3 4 9 1 | 3 5 0 1 | 3 5 2 1 | 3 5 3 1 | 3 5 5 1 | 3 5 7 1 | 3 5 9 1 | 3 6 0 1 | 3 6 4 1 | 3 6 5 1 | 3 6 6 1 | 3 6 7 1 | 3 6 8 1 | 3 6 9 1 | 3 7 1 1 | 3 7 2 1 | 3 7 4 1 | 3 7 5 1 | 3 7 9 1 | 3 8 0 1 | 3 8 1 1 | 3 8 2 1 |
| **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, hepatocholangio-carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreatic, hepatocholangio-carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Renal, hepatocholangio-carcinoma, 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 7 7 7 7<br>3 3 3 3 3<br>7 7 7 7 7 | |
|---|---|---|
| **Carcass ID Number** | 3 3 3 3 3<br>8 8 8 8 9<br>4 6 7 9 0<br>1 1 1 1 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)

| Number of Days on Study | 2 7 3 | 3 8 6 | 4 8 8 | 5 2 7 | 5 2 9 | 5 9 3 | 6 0 9 | 6 2 3 | 6 8 4 | 6 9 1 | 7 0 5 | 7 1 4 | 7 1 4 | 7 1 9 | 7 2 1 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 3 5 1 | 2 9 6 1 | 3 2 6 1 | 3 4 3 1 | 3 6 2 1 | 3 7 8 1 | 3 6 3 1 | 2 9 9 1 | 3 0 2 1 | 3 8 3 1 | 3 6 1 1 | 3 2 9 1 | 3 5 1 1 | 3 0 8 1 | 3 1 1 1 | 3 1 0 1 | 3 1 8 1 | 3 2 1 1 | 3 2 4 1 | 3 3 7 1 | 3 5 8 1 | 3 7 6 1 | 3 7 3 1 | 3 8 8 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 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 2 9 3 1 | 2 9 4 1 | 2 9 5 1 | 2 9 7 1 | 3 0 1 1 | 3 0 3 1 | 3 0 5 1 | 3 0 6 1 | 3 0 7 1 | 3 1 2 1 | 3 1 3 1 | 3 1 4 1 | 3 1 5 1 | 3 1 6 1 | 3 1 9 1 | 3 2 0 1 | 3 2 2 1 | 3 2 5 1 | 3 2 7 1 | 3 3 0 1 | 3 3 1 1 | 3 3 6 1 | 3 4 0 1 | 3 4 1 1 | 3 4 4 1 |
| **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)

| Number of Days on Study | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 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 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** | 3 4 5 1 | 3 4 6 1 | 3 4 8 1 | 3 4 9 1 | 3 5 0 1 | 3 5 2 1 | 3 5 3 1 | 3 5 5 1 | 3 5 7 1 | 3 5 9 1 | 3 6 0 1 | 3 6 4 1 | 3 6 5 1 | 3 6 6 1 | 3 6 7 1 | 3 6 8 1 | 3 6 9 1 | 3 7 1 1 | 3 7 2 1 | 3 7 4 1 | 3 7 5 1 | 3 7 9 1 | 3 8 0 1 | 3 8 1 1 | 3 8 2 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 7 7 7 7<br>3 3 3 3 3<br>7 7 7 7 7 | |
|---|---|---|
| **Carcass ID Number** | 3 3 3 3 3<br>8 8 8 8 9<br>4 6 7 9 0<br>1 1 1 1 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 | 2 7 3 | 3 8 6 | 4 8 8 | 5 2 7 | 5 2 9 | 5 9 3 | 6 0 9 | 6 2 3 | 6 8 4 | 6 9 1 | 7 0 5 | 7 1 4 | 7 1 4 | 7 1 9 | 7 2 1 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 3 3 5 1 | 2 9 6 1 | 3 2 6 1 | 3 4 3 1 | 3 6 2 1 | 3 7 8 1 | 3 6 3 1 | 2 9 9 1 | 3 0 2 1 | 3 8 3 1 | 3 6 1 1 | 3 2 9 1 | 3 5 1 1 | 3 0 8 1 | 3 1 1 1 | 3 1 0 1 | 3 1 8 1 | 3 2 1 1 | 3 2 4 1 | 3 3 7 1 | 3 3 8 1 | 3 5 6 1 | 3 7 3 1 | 3 7 6 1 | 3 8 8 1 |
| **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)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 |
| **Carcass ID Number** | 2 9 3 1 | 2 9 4 1 | 2 9 5 1 | 2 9 7 1 | 3 0 1 1 | 3 0 3 1 | 3 0 5 1 | 3 0 6 1 | 3 0 7 1 | 3 1 2 1 | 3 1 3 1 | 3 1 4 1 | 3 1 5 1 | 3 1 6 1 | 3 1 9 1 | 3 2 0 1 | 3 2 2 1 | 3 2 5 1 | 3 2 7 1 | 3 3 0 1 | 3 3 1 1 | 3 3 6 1 | 3 4 0 1 | 3 4 1 1 | 3 4 4 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** | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 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 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 |
| **Carcass ID Number** | 3 4 5 1 | 3 4 6 1 | 3 4 8 1 | 3 4 9 1 | 3 5 0 1 | 3 5 2 1 | 3 5 3 1 | 3 5 5 1 | 3 5 7 1 | 3 5 9 1 | 3 6 0 1 | 3 6 4 1 | 3 6 5 1 | 3 6 6 1 | 3 6 7 1 | 3 6 8 1 | 3 6 9 1 | 3 7 1 1 | 3 7 2 1 | 3 7 4 1 | 3 7 5 1 | 3 7 9 1 | 3 8 0 1 | 3 8 1 1 | 3 8 2 1 |
| **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 7 7 7 7<br>3 3 3 3 3<br>7 7 7 7 7 | |
|---|---|---|
| **Carcass ID Number** | 3 3 3 3 3<br>8 8 8 8 9<br>4 6 7 9 0<br>1 1 1 1 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


| | | |
|---|---|---|
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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 | 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 6 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 |
| **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
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

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

| Number of Days on Study | 7 2 2 | 7 2 2 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 1 7 1 | 4 4 8 1 | 4 0 5 1 | 4 1 3 1 | 4 1 8 1 | 4 3 2 1 | 4 3 8 1 | 4 4 5 1 | 4 4 9 1 | 4 5 2 1 | 4 6 0 1 | 4 7 4 1 | 3 9 1 1 | 3 9 3 1 | 3 9 4 1 | 3 9 8 1 | 3 9 9 1 | 4 0 0 1 | 4 0 1 1 | 4 0 2 1 | 4 0 7 1 | 4 1 0 1 | 4 1 1 1 | 4 1 2 1 | 4 1 4 1 |
| **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)

| Number of Days on Study | 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 3 | 7 3 3 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 2 2 1 | 4 2 3 1 | 4 2 7 1 | 4 2 9 1 | 4 3 0 1 | 4 3 1 1 | 4 3 3 1 | 4 3 6 1 | 4 4 1 1 | 4 4 4 1 | 4 4 7 1 | 4 5 1 1 | 4 5 3 1 | 4 5 5 1 | 4 5 6 1 | 4 5 8 1 | 4 6 2 1 | 4 6 5 1 | 4 6 7 1 | 4 6 8 1 | 4 7 2 1 | 4 7 3 1 | 4 7 7 1 | 4 7 8 1 | 4 8 0 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)

| 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** |
| **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 | 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 6 2 | 6 7 0 | 6 7 6 | 6 9 1 | 7 0 4 | 7 1 3 | 7 1 5 | 7 5 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 |
| **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 2 2 | 7 2 2 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 1 7 1 | 4 4 8 1 | 4 0 5 1 | 4 1 3 1 | 4 1 8 1 | 4 3 2 1 | 4 3 8 1 | 4 4 5 1 | 4 4 9 1 | 4 5 2 1 | 4 6 0 1 | 4 7 4 1 | 3 9 1 1 | 3 9 3 1 | 3 9 4 1 | 3 9 8 1 | 3 9 9 1 | 4 0 0 1 | 4 0 1 1 | 4 0 2 1 | 4 0 7 1 | 4 1 0 1 | 4 1 1 1 | 4 1 2 1 | 4 1 4 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 | 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 3 | 7 3 3 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 2 2 1 | 4 2 3 1 | 4 2 7 1 | 4 2 9 1 | 4 3 0 1 | 4 3 1 1 | 4 3 3 1 | 4 3 6 1 | 4 4 1 1 | 4 4 4 1 | 4 4 7 1 | 4 5 1 1 | 4 5 3 1 | 4 5 5 1 | 4 5 6 1 | 4 5 8 1 | 4 6 2 1 | 4 6 5 1 | 4 6 7 1 | 4 6 8 1 | 4 7 2 1 | 4 7 3 1 | 4 7 7 1 | 4 7 8 1 | 4 8 0 1 |
| **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 | 345 | 402 | 448 | 518 | 528 | 562 | 592 | 599 | 602 | 610 | 620 | 630 | 632 | 644 | 652 | 655 | 662 | 670 | 677 | 679 | 701 | 711 | 715 | 722 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 47911 | 46111 | 44211 | 42511 | 45011 | 45711 | 45211 | 46911 | 44311 | 45011 | 45811 | 46211 | 46911 | 41211 | 42311 | 43911 | 47611 | 40211 | 43611 | 44911 | 46311 | 46811 | 46611 | 43911 |
| **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)

| Number of Days on Study | 7 2 2 | 7 2 2 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 1 7 1 | 4 4 8 1 | 4 0 5 1 | 4 1 3 1 | 4 1 8 1 | 4 3 2 1 | 4 3 8 1 | 4 4 5 1 | 4 4 9 1 | 4 5 2 1 | 4 6 0 1 | 4 7 4 1 | 3 9 1 1 | 3 9 3 1 | 3 9 4 1 | 3 9 8 1 | 3 9 9 1 | 4 0 0 1 | 4 0 1 1 | 4 0 2 1 | 4 0 7 1 | 4 1 0 1 | 4 1 1 1 | 4 1 2 1 | 4 1 4 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)

| Number of Days on Study | 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 3 | 7 3 3 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 2 2 1 | 4 2 3 1 | 4 2 7 1 | 4 2 9 1 | 4 3 0 1 | 4 3 1 1 | 4 3 3 1 | 4 3 6 1 | 4 4 1 1 | 4 4 4 1 | 4 4 7 1 | 4 5 1 1 | 4 5 3 1 | 4 5 5 1 | 4 5 6 1 | 4 5 8 1 | 4 6 2 1 | 4 6 5 1 | 4 6 7 1 | 4 6 8 1 | 4 7 2 1 | 4 7 3 1 | 4 7 7 1 | 4 8 0 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 6 2 | 6 7 0 | 7 7 6 | 7 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 | 7 2 2 | 7 2 2 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 2 9 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 1 7 1 | 4 1 8 1 | 4 0 5 1 | 4 1 3 1 | 4 1 8 1 | 4 3 2 1 | 4 3 8 1 | 4 4 5 1 | 4 4 9 1 | 4 5 2 1 | 4 6 0 1 | 4 7 4 1 | 4 9 1 1 | 4 9 3 1 | 3 9 4 1 | 3 9 8 1 | 3 9 9 1 | 4 0 1 1 | 4 0 2 1 | 4 0 7 1 | 4 0 1 1 | 4 1 0 1 | 4 1 2 1 | 4 1 4 1 |
| **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 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 3 | 7 3 3 | 7 3 3 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 2 2 1 | 4 2 3 1 | 4 2 7 1 | 4 2 9 1 | 4 3 0 1 | 4 3 1 1 | 4 3 3 1 | 4 3 6 1 | 4 4 1 1 | 4 4 4 1 | 4 4 7 1 | 4 5 1 1 | 4 5 3 1 | 4 5 5 1 | 4 5 6 1 | 4 5 8 1 | 4 6 2 1 | 4 6 5 1 | 4 6 7 1 | 4 6 8 1 | 4 7 2 1 | 4 7 3 1 | 4 7 7 1 | 4 7 8 1 | 4 8 0 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 7 7 7 7<br>3 3 3 3 3<br>7 7 7 7 7 | |
|---|---|---|
| **Carcass ID Number** | 4 4 4 4 4<br>8 8 8 8 9<br>1 2 4 5 0<br>1 1 1 1 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**

| Number of Days on Study | 1 3 5 | 1 7 9 | 1 9 8 | 2 4 1 | 2 5 9 | 2 7 8 | 2 8 6 | 3 1 3 | 3 4 9 | 3 4 9 | 3 6 1 | 3 7 9 | 3 9 5 | 4 1 1 | 4 2 0 | 4 3 3 | 4 3 7 | 4 5 6 | 4 7 7 | 4 7 8 | 5 0 0 | 5 2 7 | 5 3 4 | 5 5 2 | 5 6 6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 5 2 0 1 | 4 9 1 1 | 5 1 2 1 | 5 1 5 1 | 5 0 5 1 | 5 3 4 1 | 5 2 6 1 | 5 0 4 1 | 5 9 4 1 | 5 1 9 1 | 5 3 1 1 | 5 0 6 1 | 5 0 9 1 | 5 1 6 1 | 5 2 7 1 | 5 0 1 1 | 5 3 3 1 | 5 9 2 1 | 5 1 7 1 | 5 4 0 1 | 5 5 0 1 | 5 0 0 1 | 5 3 9 1 | 5 2 8 1 | 5 0 8 1 | 5 1 0 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 | 1 3 5 | 1 7 9 | 1 9 8 | 2 4 1 | 2 5 9 | 2 7 8 | 2 8 6 | 3 1 3 | 3 4 9 | 3 4 9 | 3 6 1 | 3 7 9 | 3 9 5 | 4 1 1 | 4 2 0 | 4 3 3 | 4 3 7 | 4 5 6 | 4 7 7 | 4 7 8 | 5 0 0 | 5 2 7 | 5 3 4 | 5 5 2 | 5 6 6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 5 2 0 1 | 4 9 1 1 | 5 1 2 1 | 5 1 5 1 | 5 0 5 1 | 5 3 4 1 | 5 2 6 1 | 5 0 4 1 | 5 9 4 1 | 5 1 9 1 | 5 3 1 1 | 5 0 6 1 | 5 0 9 1 | 5 1 6 1 | 5 2 7 1 | 5 0 1 1 | 5 3 1 1 | 5 9 3 1 | 5 1 2 1 | 5 4 0 1 | 5 5 0 1 | 5 3 0 1 | 5 2 9 1 | 5 0 8 1 | 5 1 0 1 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | | | | | | | | | | M | | | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lumbar, fibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mediastinal, hepatocholangio-carcinoma, 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 | 5 5 5 5 6 6 6 6 6 6 6 6 6 6 7 7<br>6 7 7 8 0 1 1 3 4 5 6 7 8 9 9 0 1<br>8 1 9 7 3 1 7 1 8 2 6 6 0 1 8 6 3 | |
|---|---|---|
| **Carcass ID Number** | 5 5 5 5 4 5 5 5 5 4 5 5 5 4 4 5 5<br>3 3 3 1 9 2 2 2 3 9 1 1 2 9 9 0 0<br>8 2 6 8 7 9 3 1 5 3 3 4 4 8 6 2 3<br>1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 | **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, hepatocholangio-carcinoma, 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** | 1 3 5 | 1 7 9 | 1 9 8 | 2 4 1 | 2 5 9 | 2 7 8 | 2 8 6 | 3 1 3 | 3 4 9 | 3 4 9 | 3 6 1 | 3 7 9 | 3 9 5 | 4 1 1 | 4 2 0 | 4 3 3 | 4 3 7 | 4 5 6 | 4 7 7 | 4 7 8 | 5 0 0 | 5 2 7 | 5 3 4 | 5 5 2 | 5 6 6 |
| **Carcass ID Number** | 5 2 0 1 | 4 9 1 1 | 5 1 2 1 | 5 1 5 1 | 5 0 5 1 | 5 3 4 1 | 5 2 6 1 | 5 0 4 1 | 4 9 4 1 | 5 1 9 1 | 5 3 1 1 | 5 0 6 1 | 5 0 9 1 | 5 1 6 1 | 5 2 7 1 | 5 0 1 1 | 5 3 3 1 | 4 9 2 1 | 5 1 7 1 | 5 4 0 1 | 5 0 0 1 | 5 3 9 1 | 5 2 8 1 | 5 0 8 1 | 5 1 0 1 |
| **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 | 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** |
| **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 | 1 9 8 | 3 9 5 | 5 3 4 | 5 3 4 | 5 8 4 | 5 8 7 | 6 1 7 | 6 2 4 | 6 3 6 | 6 4 8 | 6 5 2 | 6 7 0 | 6 7 8 | 6 9 8 | 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 1 | 7 3 1 | 7 3 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 5 5 5 1 | 6 0 4 1 | 5 9 4 1 | 6 0 4 1 | 5 4 8 1 | 5 9 9 1 | 5 8 3 1 | 5 7 4 1 | 5 6 7 1 | 5 6 5 1 | 5 7 5 1 | 5 9 3 1 | 5 6 2 1 | 5 9 6 1 | 5 5 4 1 | 5 5 7 1 | 5 6 0 1 | 5 7 0 1 | 5 7 7 1 | 5 8 4 1 | 6 1 0 1 | 5 4 6 1 | 5 5 1 1 | 5 6 3 1 | 5 4 3 1 | 5 4 4 1 | 5 4 5 1 |
| **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 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** |
| **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 | 1 9 8 | 3 9 5 | 5 3 4 | 5 3 4 | 5 8 4 | 5 8 7 | 6 1 7 | 6 2 4 | 6 3 6 | 6 4 8 | 6 5 2 | 6 7 0 | 6 7 8 | 6 9 8 | 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 1 | 7 3 1 | 7 3 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carcass ID Number | 5 5 5 1 | 6 0 1 1 | 5 9 4 1 | 6 0 4 1 | 5 4 8 1 | 5 9 9 1 | 5 8 3 1 | 5 7 4 1 | 5 6 7 1 | 5 6 5 1 | 5 7 5 1 | 5 9 3 1 | 5 6 2 1 | 5 9 6 1 | 5 5 4 1 | 5 5 7 1 | 5 6 0 1 | 5 7 0 1 | 5 7 7 1 | 5 8 4 1 | 6 1 0 1 | 5 4 6 1 | 5 5 1 1 | 5 6 3 1 | 5 4 3 1 | 5 4 4 1 | 5 4 5 1 |
| **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 | 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 |
| **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 | 1 9 8 | 3 9 5 | 5 3 4 | 5 3 4 | 5 8 4 | 5 8 7 | 6 1 7 | 6 2 4 | 6 3 6 | 6 4 8 | 6 5 2 | 6 7 0 | 6 7 8 | 6 9 8 | 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 1 | 7 3 1 | 7 3 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 5 5 5 1 | 6 0 1 1 | 5 9 4 1 | 6 0 4 1 | 5 4 8 1 | 5 9 9 1 | 5 8 3 1 | 5 7 4 1 | 5 6 7 1 | 5 6 5 1 | 5 7 5 1 | 5 9 3 1 | 5 6 2 1 | 5 9 6 1 | 5 5 4 1 | 5 5 7 1 | 5 6 0 1 | 5 7 0 1 | 5 7 7 1 | 5 8 4 1 | 6 1 0 1 | 5 4 6 1 | 5 5 1 1 | 5 6 3 1 | 5 4 3 1 | 5 4 4 1 | 5 4 5 1 |
| **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 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 | 3 1 3 | 3 7 9 | 4 1 1 | 4 7 8 | 5 2 7 | 5 5 2 | 5 8 7 | 6 1 1 | 6 1 7 | 6 3 4 | 6 5 3 | 6 5 7 | 6 8 4 | 6 9 2 | 7 2 4 | 7 2 4 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 6 2 0 1 | 6 4 5 1 | 6 3 4 1 | 6 6 1 1 | 6 3 7 1 | 6 7 8 1 | 6 1 2 1 | 6 3 2 1 | 6 4 9 1 | 6 7 1 1 | 6 1 7 1 | 6 4 3 1 | 6 6 7 1 | 6 5 0 1 | 6 2 3 1 | 6 4 4 1 | 6 2 4 1 | 6 2 6 1 | 6 2 8 1 | 6 2 9 1 | 6 3 3 1 | 6 3 6 1 | 6 6 5 1 | 6 6 8 1 | 6 6 9 1 |
| **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 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 4 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 6 7 7 1 | 6 1 5 1 | 6 1 6 1 | 6 1 9 1 | 6 2 2 1 | 6 2 5 1 | 6 2 7 1 | 6 3 0 1 | 6 3 1 1 | 6 3 9 1 | 6 4 6 1 | 6 4 7 1 | 6 4 8 1 | 6 5 2 1 | 6 5 3 1 | 6 5 8 1 | 6 5 4 1 | 6 6 0 1 | 6 6 2 1 | 6 6 4 1 | 6 6 6 1 | 6 7 3 1 | 6 7 4 1 | 6 7 5 1 | 6 8 0 1 | **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 | 3 1 3 | 3 7 9 | 4 1 1 | 4 7 8 | 5 2 7 | 5 5 2 | 5 8 7 | 6 1 1 | 6 1 7 | 6 3 4 | 6 5 3 | 6 5 7 | 6 8 4 | 6 9 2 | 7 2 4 | 7 2 4 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 6 2 0 1 | 6 4 5 1 | 6 3 4 1 | 6 6 1 1 | 6 3 7 1 | 6 7 8 1 | 6 1 2 1 | 6 3 2 1 | 6 4 9 1 | 6 7 1 1 | 6 1 7 1 | 6 4 3 1 | 6 6 7 1 | 6 5 0 1 | 6 2 3 1 | 6 4 4 1 | 6 2 4 1 | 6 2 6 1 | 6 2 8 1 | 6 2 9 1 | 6 3 3 1 | 6 3 6 1 | 6 6 5 1 | 6 6 8 1 | 6 6 9 1 |
| **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 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 4 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 6 7 7 1 | 6 1 5 1 | 6 1 6 1 | 6 1 9 1 | 6 2 2 1 | 6 2 5 1 | 6 2 7 1 | 6 3 0 1 | 6 3 1 1 | 6 3 9 1 | 6 4 6 1 | 6 4 7 1 | 6 4 8 1 | 6 5 2 1 | 6 5 3 1 | 6 5 8 1 | 6 6 4 1 | 6 6 0 1 | 6 6 2 1 | 6 6 4 1 | 6 6 6 1 | 6 7 3 1 | 6 7 4 1 | 6 7 5 1 | 6 8 0 1 | **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 | 3 1 3 | 3 7 9 | 4 1 1 | 4 7 8 | 5 2 7 | 5 5 2 | 5 8 7 | 6 1 1 | 6 1 7 | 6 3 4 | 6 5 3 | 6 5 7 | 6 8 4 | 6 9 2 | 7 2 4 | 7 2 4 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 6 2 0 1 | 6 4 5 1 | 6 3 4 1 | 6 6 1 1 | 6 3 7 1 | 6 7 8 1 | 6 1 2 1 | 6 3 2 1 | 6 4 9 1 | 6 7 1 1 | 6 1 7 1 | 6 4 3 1 | 6 6 7 1 | 6 5 0 1 | 6 2 3 1 | 6 4 4 1 | 6 2 4 1 | 6 2 6 1 | 6 2 8 1 | 6 2 9 1 | 6 3 3 1 | 6 3 6 1 | 6 6 5 1 | 6 6 8 1 | 6 6 9 1 |
| **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 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 3 | 7 3 4 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 | 7 3 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 6 7 7 1 | 6 1 5 1 | 6 1 6 1 | 6 1 9 1 | 6 2 2 1 | 6 2 5 1 | 6 2 7 1 | 6 3 0 1 | 6 3 1 1 | 6 3 9 1 | 6 4 6 1 | 6 4 7 1 | 6 4 8 1 | 6 5 2 1 | 6 5 3 1 | 6 5 8 1 | 6 5 4 1 | 6 6 0 1 | 6 6 2 1 | 6 6 4 1 | 6 6 6 1 | 6 7 3 1 | 6 7 4 1 | 6 7 5 1 | 6 8 0 1 | **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 0 9 | 7 1 2 | 7 1 5 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 6 8 5 1 | 7 1 0 1 | 7 7 6 1 | 7 0 1 1 | 7 0 5 1 | 7 0 7 1 | 7 1 5 1 | 7 2 3 1 | 7 2 8 1 | 7 3 0 1 | 7 3 7 1 | 7 4 5 1 | 7 7 9 1 | 6 8 1 1 | 6 8 3 1 | 6 8 6 1 | 6 8 9 1 | 6 9 0 1 | 6 9 3 1 | 6 9 4 1 | 6 9 5 1 | 6 9 6 1 | 7 6 6 1 | 7 0 2 1 | 7 0 6 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)

| Number of Days on Study | 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 3 | 7 3 3 | 7 3 3 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 7 0 9 1 | 7 1 2 1 | 7 1 3 1 | 7 1 4 1 | 7 1 6 1 | 7 1 7 1 | 7 2 2 1 | 7 2 4 1 | 7 2 5 1 | 7 2 7 1 | 7 2 9 1 | 7 3 1 1 | 7 3 8 1 | 7 3 9 1 | 6 8 8 1 | 7 4 1 1 | 7 4 2 1 | 7 4 3 1 | 7 4 7 1 | 7 4 9 1 | 7 5 0 1 | 7 5 4 1 | 7 5 8 1 | 7 6 2 1 | 7 6 3 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 | 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** |
| **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)

| 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 1 | 6 9 1 1 1 | 7 1 9 1 1 | 7 5 9 1 1 | 7 6 0 1 1 | 7 7 3 1 1 | 7 7 1 1 1 | 7 4 0 1 1 | 6 9 8 1 1 | 7 3 5 1 1 | 7 3 6 1 1 | 7 3 2 1 1 | 7 6 1 1 1 | 7 5 2 1 1 | 7 6 7 1 1 | 7 1 8 1 1 | 7 4 8 1 1 | 6 9 7 1 1 | 7 2 0 1 1 | 7 3 3 1 1 | 7 2 6 1 1 | 7 5 1 1 1 | 7 2 1 1 1 | 7 6 8 1 1 | 7 6 0 8 1 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | X | | X | | | | | | |
| Pericardium, hepatocholangio-carcinoma, 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)

| 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 | 732 | 732 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carcass ID Number | 68511 | 71011 | 77611 | 70111 | 70051 | 70771 | 71551 | 72331 | 72381 | 73001 | 73371 | 74551 | 74791 | 76811 | 76831 | 76861 | 76891 | 76901 | 76931 | 76941 | 76951 | 76961 | 76991 | 77021 | 77061 |
| **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)

| Number of Days on Study | 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 3 | 7 3 3 | 7 3 3 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 7 0 9 1 | 7 1 2 1 | 7 1 3 1 | 7 1 4 1 | 7 1 6 1 | 7 1 7 1 | 7 2 2 1 | 7 2 4 1 | 7 2 5 1 | 7 2 7 1 | 7 2 9 1 | 7 3 1 1 | 7 3 8 1 | 7 3 9 1 | 6 8 8 1 | 7 4 1 1 | 7 4 2 1 | 7 4 3 1 | 7 4 7 1 | 7 4 9 1 | 7 5 0 1 | 7 5 4 1 | 7 5 8 1 | 7 6 2 1 | 7 6 3 1 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | X | | | | |
| Hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pericardium, hepatocholangio-carcinoma, 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 | 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** |
| **Cardiovascular System** | | | | | | |
| Heart | + | + | + | + | + | 80 |
| Hemangiosarcoma, metastatic, liver | | | | | | 1 |
| Hepatocholangiocarcinoma, metastatic, liver | | | | | | 1 |
| Histiocytic sarcoma | | | | | | 2 |
| Pericardium, hepatocholangio-carcinoma, 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 | 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 3 6 1 | 7 2 5 1 | 7 5 2 1 | 7 6 0 1 | 7 7 8 1 |
| **Hematopoietic System** (continued) | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Inguinal, histiocytic sarcoma | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Mediastinal, hepatocholangio-carcinoma, 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)

| Number of Days on Study | 7 0 9 | 7 1 2 | 7 1 5 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 6 8 5 1 | 7 1 0 1 | 7 7 6 1 | 7 0 1 1 | 7 0 5 1 | 7 0 7 1 | 7 1 5 1 | 7 2 3 1 | 7 2 8 1 | 7 3 0 1 | 7 3 7 1 | 7 4 5 1 | 7 7 9 1 | 6 8 1 1 | 6 8 3 1 | 6 8 6 1 | 6 8 9 1 | 6 9 0 1 | 6 9 3 1 | 6 9 4 1 | 6 9 5 1 | 6 9 6 1 | 7 6 6 1 | 7 0 2 1 | 7 0 6 1 |
| **Hematopoietic System** (continued) | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Inguinal, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mediastinal, hepatocholangio-carcinoma, 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 | 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 3 | 7 3 3 | 7 3 3 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 7 0 9 1 | 7 1 2 1 | 7 1 3 1 | 7 1 4 1 | 7 1 6 1 | 7 1 7 1 | 7 2 2 1 | 7 2 4 1 | 7 2 5 1 | 7 2 7 1 | 7 2 9 1 | 7 3 1 1 | 7 3 8 1 | 7 3 9 1 | 6 8 8 1 | 7 4 1 1 | 7 4 2 1 | 7 4 3 1 | 7 4 7 1 | 7 4 9 1 | 7 5 0 1 | 7 5 4 1 | 7 5 8 1 | 7 6 2 1 | 7 6 3 1 |
| **Hematopoietic System** (continued) | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Inguinal, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mediastinal, hepatocholangio-carcinoma, 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, hepatocholangio-carcinoma, 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 | 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 1 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 |
| **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 | 7 0 9 | 7 1 2 | 7 1 5 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carcass ID Number | 6 8 5 1 | 7 1 0 1 | 7 7 6 1 | 7 0 1 1 | 7 0 5 1 | 7 0 7 1 | 7 1 5 1 | 7 2 3 1 | 7 2 8 1 | 7 3 0 1 | 7 3 7 1 | 7 4 5 1 | 7 7 9 1 | 6 8 1 1 | 6 8 3 1 | 6 8 6 1 | 6 8 9 1 | 6 9 0 1 | 6 9 3 1 | 6 9 4 1 | 6 9 5 1 | 6 9 6 1 | 7 6 6 1 | 7 0 2 1 | 7 0 6 1 |
| **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 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 3 | 7 3 3 | 7 3 3 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 6 | 7 3 7 | 7 3 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carcass ID Number | 7 0 9 1 | 7 1 2 1 | 7 1 3 1 | 7 1 4 1 | 7 1 6 1 | 7 1 7 1 | 7 2 2 1 | 7 2 4 1 | 7 2 5 1 | 7 2 7 1 | 7 2 9 1 | 7 3 1 1 | 7 3 8 1 | 7 3 9 1 | 7 6 8 1 | 7 4 1 1 | 7 4 2 1 | 7 4 3 1 | 7 4 7 1 | 7 4 9 1 | 7 5 0 1 | 7 5 4 1 | 7 5 8 1 | 7 6 2 1 | 7 6 3 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**[c] | | | | |
| 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 | 356 |
| 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 | 357 |
| 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 | 359 |
| 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 | 360 |

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 | 362 |
| 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 | 364 |
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| 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 | 374 |

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


| | | |
|---|---|---|
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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≤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

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# 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 $6\times10^6$ 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, $3\times10^6$ 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 ($21 \pm 2$ 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/$1\times10^6$ 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 ($6\times10^6$) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, $3\times10^6$ 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 ($3\times10^6$) 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 Chromosomes | No. of SCEs | SCEs/ Chromosome | 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[c] | 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[c] | 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 Chromosomes | No. of SCEs | SCEs/ Chromosome | 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]**

| -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 Environmental Health Research and Testing** | | | | | | | | | |
| **Trial 1--Harvest time: 12.0 hours** | | | | | **Trial 1--Harvest time: 13.0 hours** | | | | |
| Medium | 100 | 3 | 0.03 | 3.0 | Medium | 100 | 0 | 0.00 | 0.0 |
| Sodium fluoride | | | | | Sodium fluoride | | | | |
| 16 | 100 | 3 | 0.03 | 1.0 | 50 | 100 | 1 | 0.01 | 1.0 |
| 50 | 100 | 1 | 0.01 | 1.0 | 160 | 100 | 0 | 0.00 | 0.0 |
| 160 | 100 | 1 | 0.01 | 1.0 | 500 | 100 | 9 | 0.09 | 8.0* |
| 500 | 100 | 3 | 0.03 | 3.0 | 1000 | 100 | 6 | 0.06 | 2.0 |
| | | Summary: Negative | | | | | Summary: Weak Positive | | |
| Mitomycin-C | | | | | Cyclophosphamide | | | | |
| 0.1250 | 100 | 18 | 0.18 | 18.0 | 15 | 100 | 78 | 0.78 | 47.0 |
| 0.2500 | 50 | 16 | 0.32 | 30.0 | | | P=0.259 | | |
| | | P=0.500 | | | | | | | |
| **Trial 2--Harvest Time: 13.0 Hours** | | | | | **Trial 2--Harvest Time: 13.0 Hours** | | | | |
| Medium | 100 | 0 | 0.00 | 0.0 | Medium | 100 | 0 | 0.00 | 0.0 |
| Sodium fluoride | | | | | Sodium fluoride | | | | |
| 300 | 100 | 3 | 0.03 | 3.0 | 400 | 100 | 3 | 0.03 | 3.0 |
| 400 | 100 | 19 | 0.19 | 19.0* | 600 | 100 | 3 | 0.03 | 3.0 |
| 500 | 100 | 39 | 0.39 | 39.0* | 800 | 100 | 2 | 0.02 | 2.0 |
| 600 | 100 | 34 | 0.34 | 33.0* | 1000 | 100 | 5 | 0.05 | 4.0 |
| | | Summary: Positive | | | | | Summary: Negative | | |
| Mitomycin-C | | | | | | | | | |
| 0.1250 | 100 | 17 | 0.17 | 16.0 | Cyclophosphamide | | | | |
| 0.2500 | 50 | 13 | 0.26 | 24.0 | 10 | 100 | 43 | 0.43 | 35.0 |
| | | P<0.001 | | | 15 | 50 | 55 | 1.10 | 52.0 |
| | | | | | | | P=0.078 | | |
| **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 | | | | | | | |

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.

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# SUPPLEMENTAL STUDIES


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# 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≤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 ($P \leq 0.01$) 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≤0.05) from the control group by Dunn's or Shirley's test
** P≤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 17
**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 ($\mu m^3$) | 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 ($\mu m^3$) | 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 ($P \le 0.05$) 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 ($\mu m^3$) | 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 ($\mu m^3$) | 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 ($\mu m^3$) | 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 ($\mu m^3$) | 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 ($\mu m^3$) | 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 ($\mu m^3$) | 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≤0.05) from the control group by Dunn's or Shirley's test
** P≤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 $\mu$L. 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 $\mu$L 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≤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

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# 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] | | | Postdosing Analyses[b] | | |
|---|---|---|---|---|---|---|
| | Samples (n) | Dose Concentration (ppm)[c] | Range | 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] | | | Postdosing Analyses[b] | | |
|---|---|---|---|---|---|---|
| | Samples (n) | Dose Concentration (ppm)[c] | Range | Samples (n) | Dose Concentration (ppm)[c] | 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] | | | Postdosing Analyses[b] | | |
|---|---|---|---|---|---|---|
| | Samples (n) | Dose Concentration (ppm)[c] | Range | Samples (n) | Dose Concentration (ppm)[c] | 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


| | | |
|---|---|---|
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**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


| | | |
|---|---|---|
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| Table L2 | Water and Compound Consumption by Female Rats in the 2-Year Drinking Water Studies of Sodium Fluoride | 437 |
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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**

| Week | Control | | 25 ppm | | | 100 ppm | | | 175 ppm | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 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

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DISCUSSION ..... 443
Table M1 Recommended Levels and Actual Content of Selected Nutrients in Rat and Mouse Feed during the First 2-Year Studies of Sodium Fluoride ..... 444

# 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

METHODS ..... 446
RESULTS ..... 447

# 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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# PRINTED AS OF OCTOBER 1990

| 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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