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Number 38

NTP Technical Report on Toxicity Studies of

Sodium Selenate and Sodium Selenite

(CAS Nos. 13410-01-0 and 10102-18-8)

Administered in Drinking Water to F344/N Rats and B6C3F$_1$ Mice

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Post Office Box 12233
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These studies were supported in part by funds from the Comprehensive Environmental Response, Compensation, and Liability Act trust fund (Superfund) by an interagency agreement with the Agency for Toxic Substances and Disease Registry, U.S. Public Health Service.

United States Department of Health and Human Services
Public Health Service
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National Institutes of Health

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This NTP report on the toxicity studies of sodium selenate and sodium selenite is based primarily on 13-week studies that took place from August 1988 through January 1989.

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ABSTRACT

Sodium Selenate **Sodium Selenite**

	Sodium Selenate	Sodium Selenite
CAS Number	13410-01-0	10102-18-8
Molecular Weight	188.94	172.95

Sodium selenate and sodium selenite are used as supplements to poultry and livestock feed to promote growth and prevent selenium deficiency diseases. Both compounds have been found in chemical waste sites. Thirteen-week toxicity studies were conducted by administering the chemicals to groups of male and female F344/N rats and $B6C3F_1$ mice in drinking water. Animals were evaluated for hematology, clinical chemistry, urinalysis (rats only), histopathology, and reproductive system effects.

In the studies of sodium selenate, groups of 10 male and 10 female rats and mice received 0, 3.75, 7.5, 15, 30, or 60 ppm sodium selenate for 13 weeks. These concentrations were estimated to deliver 0, 0.1, 0.2, 0.4, 0.6, 1.1 (males), or 0.8 (females) mg selenium/kg body weight for rats and 0, 0.3, 0.5, 0.8, 1.5, or 2.6 mg/kg selenium for mice. All male and female rats exposed to 60 ppm died. The final mean body weights of rats exposed to 30 ppm sodium selenate and of mice exposed to 30 or 60 ppm were 13% to 29% lower than those of the controls. Water consumption by rats and mice exposed to 15 ppm or greater was decreased. Decreases in urine volume and increases in erythrocyte counts, hematocrit, hemoglobin concentrations, alanine aminotransferase activities, urea nitrogen, and urine specific gravity were considered related to dehydration, as indicated by the decreased water consumption and mean body weights in groups showing these differences. Administration of 7.5 ppm sodium selenate or greater was associated with increased incidences of renal papillary degeneration in rats. Dehydration may have been a contributing factor. No lesions related to sodium selenate administration occurred in mice.

In the studies of sodium selenite, groups of 10 male and 10 female rats and mice received 0, 2, 4, 8, 16, or 32 ppm sodium selenite for 13 weeks. These concentrations were estimated to deliver 0, 0.08, 0.13, 0.2, 0.4, 0.8 (males), or 0.9 (females) mg/kg selenium for rats and 0, 0.14, 0.3, 0.5, 0.9, or 1.6 mg/kg selenium for mice. Two female rats

exposed to 32 ppm died during the study. The final mean body weights of rats and mice exposed to 32 ppm were 17% to 54% lower than those of the controls. Water consumption by exposed rats and mice decreased with increasing exposure concentration. Changes in hematology, clinical chemistry, and urinalysis parameters similar to those observed in rats exposed to sodium selenate were observed in rats exposed to sodium selenite. These effects were also considered related to dehydration, as indicated by the decreased water consumption and mean body weights in exposed groups. Sodium selenite administration was associated with increased incidences of renal papillary regeneration in rats. Dehydration may have been a contributing factor. No lesions related to sodium selenite administration occurred in mice.

Based on mortality in rats, body weight depression, and renal lesions, sodium selenate and sodium selenite were more toxic to rats than to mice. These chemicals caused increases in estrous cycle length in rats; sodium selenite also caused an increase in estrous cycle length in mice. Based on mortality, body weight depression, decreased water consumption, and renal papillary lesions, the estimated no-observed-adverse-effect level (NOAEL) in rats was 0.4 mg selenium/kg body weight for sodium selenate and for sodium selenite. Based on body weight depression and decreased water consumption, the estimated NOAEL in mice was 0.8 mg selenium/kg body weight for sodium selenate and 0.9 mg selenium/kg body weight for sodium selenite.

INTRODUCTION

Physical and Chemical Properties, Occurrence, and Exposure

Sodium selenate, a solid, has a molecular weight of 188.94 and is soluble in water (83 g/200 g water at 20° C) (Mackison *et al.*, 1981). Selenium in sodium selenate is in the highest oxidation state (+6) and thus is stable under alkaline and other oxidizing conditions. Sodium selenate is the most common form of this element found in alkaline waters (IPCS, 1987).

Sodium selenite, also a solid, has a molecular weight of 172.9 and is also soluble in water (85 g/100 g water at 20° C) (Mackison *et al.*, 1981). Sodium selenite is prepared by evaporating an aqueous solution of sodium hydroxide and selenious acid at a temperature of 60° to 100° C or by heating a mixture of sodium chloride and selenium oxide (*Merck Index*, 1983). Selenium in sodium selenite is in the +4 oxidation state and occurs naturally. In alkaline solution, the selenium oxidizes slowly to the +6 state. No oxidation takes place in acidic medium (IPCS, 1987). Sodium selenate is prepared by heating a mixture of selenide and sodium carbonate to temperatures below the sintering point to ensure the access of air, which is essential for the thorough oxidation of selenides (*Kirk-Othmer*, 1982). The selenate ion is reduced to the selenite state with the addition of hydrochloric acid or sodium chloride.

Selenium is widely distributed in various forms in soils, water, air, vegetation, and foods. Soils in arid and semiarid areas have a high selenium content; these soils are often alkaline and thus favor the formation of sodium selenate (Moxon *et al.*, 1950; Geering *et al.*, 1968). The concentration of selenium occurring naturally in water is generally below 2 to 3 µg/L, although the highest concentration reported is 9,000 µg/L (NAS/NRC, 1976). Less than 0.5% of water samples taken from public water supply systems in the United States contained more than 10 µg/L, the permissible limit established by the U.S. Public Health Service (McCabe *et al.*, 1970). Selenium may be released into the air by soil, plants, animals, and volcanic eruptions; the burning of fossil fuels and the mining, milling, and refining of copper, lead, zinc, phosphate, and selenium may also contribute to the concentration of selenium in the air.

Sun *et al.* (1985) found a direct correlation between selenium levels in plants and selenium levels in the local soil. In areas with high selenium levels in the soil and with a history of

human selenium intoxication, corn, rice, and soybean crops contained an average of 8.1, 4.0, and 11.9 mg/kg selenium, respectively; in contrast, in areas with low selenium levels in the soil and with a history of Keshan or selenium deficiency diseases, these three crops contained 0.005, 0.007, and 0.01 mg/kg selenium, respectively (Yang *et al.*, 1983). Humans and animals derive selenium primarily from foods. In plants and animals, selenium is primarily localized in the protein fraction (Ferretti and Levandar, 1976). The estimated dietary intake of selenium in North America is 98 to 224 µg/day. In the U.S., the average dietary intake of selenium was estimated to be 108 µg/day (Pennington *et al.*, 1984); the estimated daily intake of selenium by people living in the Western U.S. was 1.3 times that by people living in the Northeast (USFDA, 1974). Daily selenium intake by infants placed on various formulas was estimated to be 8.5 µg/day for milk, 9.5 µg/day for soy protein, 12.6 µg/day for casein, or 31.5 µg/day for meat-based formula (Zabel *et al.*, 1978).

Because selenium is an essential nutritional element (Schwarz and Foltz, 1957, 1958), the U.S. Food and Drug Administration (USFDA) approved the use of selenium as sodium selenate or selenite in animal feed at levels of 0.1 mg selenium/kg complete feed for cattle, sheep, chickens, ducks, and swine, 0.3 mg/kg in starter and prestarter rations, and 0.2 mg/kg for turkey feed (1983 Subcommittee on Selenium - Committee on Animal Nutrition, U.S. Department of Health and Human Services, 1984). Selenium in animal feed causes little increase in the level of selenium in the environment or in human foods (NAS/NRC, 1976; Thomson and Robinson, 1980).

Absorption, Distribution, and Excretion

Selenium from orally administered sodium selenite is efficiently (95% to 100%) absorbed from the gastrointestinal tract of rats. The absorption does not appear to be homeostatically controlled, as no difference in absorption was observed between selenium-deficient and selenium-sufficient rats administered mildly toxic doses of selenium (Brown *et al.*, 1972). The greatest absorption occurs in the duodenum, followed by the jejunum and ilium of rats; little or no absorption occurs in the stomach (Whanger *et al.*, 1976). Selenium is distributed throughout the body, but the highest amounts are present in the liver, kidneys, and muscle (Thomson and Stewart, 1973).

Absorption of ^{75}Se from sodium selenate and sodium selenite was determined in ligated loops from duodena, jejuna, and ilea of weanling Sprague-Dawley rats fed selenium-deficient (0.009 ppm Se) or selenium-sufficient (0.20 ppm Se) diets for 9 to 12 weeks

(Vendeland *et al.*, 1992). Selenium deficiency did not affect the absorption of either compound in any intestinal region. Sodium selenate and sodium selenite were most efficiently absorbed from the ileum. While ^{75}Se from sodium selenate was readily transferred to the body during ileal absorption, a substantial amount of ^{75}Se from sodium selenite was retained within the ileal tissue. This suggests that ^{75}Se from sodium selenite may interact with tissue components in this intestinal segment. Glutathione depletion by buthionine [S,R] sulfoximine treatment depressed ^{75}Se-selenite uptake and transfer to the body, suggesting that glutathione is involved in the transepithelial transport of ^{75}Se from sodium selenite.

In humans, selenium from sodium selenate or selenite administered as a single or repeated dose is efficiently absorbed from the gastrointestinal tract (Thomson and Stewart, 1974; Thomson *et al.*, 1978). Selenium is more efficiently absorbed as selenate than as selenite (94% versus 59%) (Thomson and Robinson, 1986). The highest concentration of radioactivity from an oral dose of radiolabeled selenium (^{75}Se) occurred in the liver, followed by the kidneys, lungs, and muscle (Leeb *et al.*, 1977). In an earlier study, results of autopsy samples showed that the selenium concentration in the kidneys was two to three times greater than in the liver (Blotcky *et al.*, 1976).

Selenium levels in the blood are dependent on selenium levels in the diet and on the nutritional and health status of the subject. People living in areas in the U.S. with high selenium levels in the soil and vegetation had blood levels of selenium that were approximately 40% higher than those of people living in areas with low selenium levels (Allaway *et al.*, 1968). Concentrations of 0.256 mg selenium/L whole blood have been reported in Rapid City, South Dakota, and 0.157 mg selenium/L whole blood in Lima, Ohio. Children suffering from protein-calorie malnutrition (kwashiorkor) have lower selenium levels in the blood than well-nourished children (Burk *et al.*, 1967). Patients with cancer have lower serum selenium levels than their healthy counterparts (McConnell *et al.*, 1975). Lower selenium levels in the blood were associated with lower serum albumin levels in surgical patients with and without cancer (Robinson *et al.*, 1979).

Selenium is excreted in urine, feces, and expired air; however, urinary excretion is considered the primary route. The amount of selenium eliminated in urine depends on dietary selenium levels. The urinary excretion of ^{75}Se was investigated in male rats fed a basal diet containing 0.004 ppm selenium or a diet supplemented with 0.1, 0.25, 0.5, or 1.0 ppm selenium from sodium selenite. During the first 10 days after intraperitoneal injection of the sodium selenite tracer, the percent of dose excreted in the urine was

directly related to dietary selenium levels, increasing from 6% for the group fed the basal diet to 67% for the 1.0 ppm group. Fecal excretion for all groups was approximately 10% of the dose (Burk *et al.*, 1972). In a study to determine the dietary threshold level above which urinary selenium excretion begins to increase, Burk *et al.* (1973) fed male rats a basal diet containing 0.024 ppm selenium or the basal diet supplemented with 0.03 to 0.12 ppm selenium from sodium selenite. Whole-body retention and urinary excretion by the 0.03 ppm group were similar to those by the group receiving only the basal diet. Urinary excretion was significantly increased for the group receiving 0.6 ppm selenium or greater. Based on these results, the dietary threshold in rats was estimated to be 0.054 to 0.84 ppm.

Urinary and fecal excretion of selenium increases with repeated administration. Rats fed diets containing 5 ppm selenium from sodium selenate excreted 36% of the ingested dose on Days 1 through 4 and 63% on Days 13 through 16 (Halverson *et al.*, 1962). Rats that received four daily doses of 0.15 mg selenium from sodium selenate per kilogram body weight excreted 29% of the administered dose on Day 1 and 48% of the dose on Day 4. Fecal excretion ranged between 10% and 20% of the administered dose (Ganther, 1965).

In humans, whole-body retention of selenium was determined in female volunteers given a single oral dose of 1 mg selenium from sodium selenate or selenite (Thomson and Robinson, 1986). After 5 days, 11% of the dose of selenium from sodium selenate and 37% of the dose of selenium from sodium selenite was retained. Although the amount of selenium from sodium selenite retained was greater than that of selenium from sodium selenate, the overall retention of the two forms of selenium was not high.

The respiratory excretion of selenium is also dependent on the dose administered. In male rats that received a subcutaneous dose of 0.005, 0.9, 2, or 3 to 5 mg/kg selenium as selenite, 0.2%, 11%, 42%, or 41% to 60% of the dose, respectively, was eliminated in expired air in 6 hours (McConnell and Roth, 1966). In male rats given an intraperitoneal injection of 0.2, 0.4, 0.9, 1.2, 1.5, or 1.9 mg/kg selenium as sodium selenite, 0.7%, 2.4%, 9.1%, 13.0%, 22.7%, or 29.4% of the administered dose was exhaled after 4 to 6 hours (Olson *et al.*, 1963).

Metabolism

Selenium from selenate or selenite is metabolized by reduction and methylation. Dimethyl selenide was identified in the expired air of rats given sodium selenate subcutaneously (McConnell and Portman, 1952a) and in the volatile selenium fraction from the liver of rats given sodium selenate orally (Nakamuro *et al.*, 1977). Dimethyl selenide present in the expired air is responsible for the garlic-like odor of animals poisoned with selenium (McConnell and Portman, 1952b). The formation of dimethyl selenide from selenite in rat liver and kidney fractions has been extensively studied (Ganther, 1971, 1979; Hsieh and Ganther, 1977). The reaction, which requires the presence of glutathione and is stimulated by NADPH, involves the following steps: 1) nonenzymatic reaction between selenite and glutathione to form the selenotrisulfide derivative; 2) reduction of the selenotrisulfide derivative to selenopersulfide nonenzymatically in the presence of excess glutathione or by means of NADPH and glutathione reductase; 3) decomposition of selenopersulfide, which is chemically unstable, to elemental selenium or reduction of selenopersulfide to hydrogen selenide by the glutathione reductase system; and 4) methylation of hydrogen selenide by methyltransferase to form dimethyl selenide.

Trimethylselenonium was the major urinary metabolite in rats injected with selenite (Byard, 1969; Palmer *et al.*, 1969). Trimethylselenonium was most likely formed by the addition of a third methyl group to dimethyl selenide; in a study conducted by Obermeyer *et al.* (1971), the breath of rats receiving an intraperitoneal injection of trimethylselenonium chloride had a garlic-like odor.

Selenium in tissues is generally associated with protein. In rats and rabbits, selenite is converted to selenocysteine tissue protein (Godwin and Fuss, 1972; Olson and Palmer, 1976). Forstrom *et al.* (1978) proposed that the selenium present at the active site of glutathione peroxidase is in the form of selenocysteine.

Toxicity

SHORT-TERM TOXIC EFFECTS IN ANIMALS

The reported oral LD_{50} values of sodium selenite in rats ranged between 3 and 12 mg selenium/kg body weight (Morss and Olcott, 1967; Cummins and Kimura, 1971). The reported oral LD_{50} value in mice ranged between 7 and 22 mg/kg (Henschler and Kirschner, 1969; Pletnikova, 1970). The oral LD_{50} of sodium selenate in rats is 1.6 mg/kg (NIOSH, 1990). The reported minimum lethal dose after intraperitoneal administration to

rats was 3.25 to 3.50 mg/kg for sodium selenite and 5.25 to 5.75 mg/kg for sodium selenate. Signs of acute selenium toxicity in rats include muscular contractions, breathing difficulties, cyanosis, and convulsions prior to death (Franke and Moxon, 1936). Smith *et al.* (1937) reported that the minimum lethal doses of sodium selenate and sodium selenite in rabbits and cats were similar (1.5 to 3.0 mg/kg selenium) regardless of the route of administration. Results of more recent studies show that the acute toxicity of selenium compounds is directly associated with their aqueous solubility (Cummins and Kimura, 1971). The highly soluble sodium selenite was seven times more toxic than the less soluble compound selenourea and 900 times more toxic than insoluble elemental selenium.

The toxicity of selenium from sodium selenite at concentrations of 0, 1.6, 3.2, 4.8, 6.4, 8.0, 9.6, and 11.2 mg selenium/kg diet was determined in a 6-week feeding study in rats (Halverson *et al.*, 1966). Up to 4.8 ppm selenium did not cause any significant toxicity. Selenium levels of 6.4 ppm or greater caused decreased body weight gains, cirrhosis of the liver, and splenomegaly. Additionally, diets containing selenium at a concentration of 8.0 ppm or greater caused pancreatic enlargement, anemia, elevated serum bilirubin, and death.

Sodium selenite has a cataractogenic effect in suckling rats. Ten-day-old rats receiving a single subcutaneous injection of 10 to 40 µmol/kg sodium selenite developed cataracts of the eye. No eye lesions were seen in 2-month-old rats given a single subcutaneous injection of 20 µmol/kg sodium selenite (Ostadalova *et al.*, 1979).

Rats that received daily intraperitoneal injections of sodium selenate for 13 days had obfuscation of the cellular and lacunar outlines of the tibial epiphyseal plates, a decrease in the basophilic character of the osteoid matrix, a disruption of cellular columnization, and an increased width of the zones of the maturing and proliferating chondrocytes (Campo and Bielen, 1971). Harr *et al.* (1967) reported that 4 to 16 ppm selenium in the diet caused adverse effects in the bones of rats; the bones were soft and the epiphyseal plates were easily separable. Moreover, there was a partial failure of chondrocyte proliferation.

REPRODUCTIVE EFFECTS

Rosenfeld and Beath (1954) studied the effect of selenium from sodium selenate on reproduction in Wistar rats. Groups of five male and five female rats received 0 or 7.5 ppm selenium from sodium selenate from the day of birth to 8 months of age. The mating of dosed females with control males was unsuccessful, whereas the mating of control females with males receiving selenium had no adverse effect on reproduction. These results suggest that at the level tested, selenium did not impair male fertility. Low levels of selenium (1.5 and 2.5 ppm) in the drinking water had little effect on the reproduction of two successive generations. However, dams in the second generation that received 2.5 ppm selenium reared fewer young than second-generation dams receiving 0 or 1.5 ppm (Rosenfeld and Beath, 1954).

In a four-generation study, the administration of 3 ppm selenium from selenate in the drinking water of mice was associated with increased numbers of deaths before weaning. In the fourth (F_3) generation, many of the mice receiving selenium failed to breed (Schroeder and Mitchener, 1971). Administration of 5 or 10 ppm selenium as selenate in the drinking water of female Wistar rats during mating, pregnancy, and lactation decreased the numbers of pups born by 35% and 77%, respectively, relative to the controls (Büttner, 1963).

CHRONIC TOXICITY AND CARCINOGENICITY

Tinsley *et al.* (1967) and Harr *et al.* (1967) examined the toxicity and carcinogenicity of sodium selenate and sodium selenite in Wistar rats fed one of three diets: a commercial laboratory chow diet, a semipurified diet containing 12% casein, or a semipurified diet containing 22% casein. The levels of selenium as sodium selenate or selenite were 0, 0.5, 2, 4, 8, and 16 ppm in the diet. Only a small number of the rats exposed to 8 or 16 ppm survived for 1 year. Acute toxic hepatitis was observed in rats fed the semipurified diet containing 4 to 16 ppm selenium or the commercial diet containing 16 ppm selenium. Chronic hepatitis was the predominant lesion in rats receiving commercial diet containing 8 ppm selenium. No evidence of carcinogenic activity by these selenium compounds was observed.

Schroeder and Mitchener (1971) studied the toxicity and carcinogenicity of sodium selenate and sodium selenite in weanling male and female Long-Evans rats. Groups of 50 male and 50 female rats were administered 0 or 2 ppm selenium as sodium selenate or selenite in the drinking water. After 1 year, the selenium level in the drinking water of

the sodium selenate group was increased to 3 ppm. During the first year, mortality reached 50% after 58 days of treatment for male rats and after 348 days for female rats receiving sodium selenite. In rats receiving sodium selenate, 50% mortality was reached in males after 962 days and in females after 1,014 days. Sodium selenite was more toxic than sodium selenate, as the latter did not adversely affect the life span of the animals. The overall tumor incidence was significantly increased in male and female rats receiving sodium selenate (0 ppm, 20/65; 2 to 3 ppm, 30/48). The authors did not tabulate the incidence of tumors by sex.

Schroeder (1967) and Schroeder and Mitchener (1972) also studied the toxicity and carcinogenicity of selenium in weanling Charles River CD mice. Groups of 50 male and 50 female mice were given 0 or 3 ppm selenium as sodium selenate in drinking water and groups of 54 male and 54 or 56 female mice were given 0 or 2 mg/mL selenium as sodium selenite in drinking water. No significant effects on the life span or overall tumor incidence resulted from the ingestion of either of these compounds. No increases in tumor incidences occurred in female Swiss mice that received 1, 4, or 8 ppm selenium from sodium selenite in the drinking water for up to 50 weeks (Jacobs and Forst, 1981a).

None of the studies described above were considered adequate for determining the carcinogenicity of sodium selenate or selenite. In the Schroeder and Mitchener studies (1971, 1972), the doses used were too low, not all exposed animals were examined histopathologically, and the cause of death of rats was not identified. The duration of the Jacobs and Forst (1981a) study was too short.

SELENIUM DEFICIENCY DISORDERS

Selenium deficiency causes poor growth, loss of hair, liver necrosis, testicular atrophy, aspermatogenesis, reproductive failure, and lens cataracts in rats (Schwarz, 1965; McCoy and Weswig, 1969; Hurt *et al.*, 1971; Burk, 1978). Liver necrosis was attributed to lipid peroxidation resulting from deficiency of glutathione peroxidase, a selenium-containing enzyme (Schwarz, 1976; Hafeman and Hoekstra, 1976, 1977). Multiple necrotic degeneration disease occurred in mice fed diets low in cysteine and deficient in selenium and vitamin E (DeWitt and Schwarz, 1958). The disease was characterized by degeneration of cardiac and peripheral muscles, degeneration of testes, pancreatic dystrophy, and liver and kidney necrosis. Selenium deficiency in chickens resulted in depressed growth, poor feathering, and pancreatic atrophy (Thompson and Scott, 1970; Gries and Scott, 1972; Noguchi *et al.*, 1973).

Dietary deficiencies of selenium and vitamin E resulted in exudative diathesis in chickens (Patterson *et al.*, 1957; Schwarz *et al.*, 1957); this disease is characterized by subcutaneous accumulation of a green, viscous fluid. In sheep and cattle, selenium and vitamin E deficiencies resulted in white muscle disease (Muth *et al.*, 1958). Deficiencies of these two essential nutrients in a wide range of animal species resulted in three syndromes: 1) hepatosis dietitica, characterized by liver necrosis; 2) muscular dystrophy, characterized by degeneration of skeletal muscle fibers; and 3) mulberry heart, characterized by heart failure, congestion, and hemorrhage and necrosis of cardiac muscles (Underwood, 1971; Burk, 1978). Supplementing the diet with either selenium or vitamin E prevented these disorders in all of these animal species.

The nutritional interaction between vitamin E and selenium appears to be related to their roles in protecting against oxidative damage. As an intracellular antioxidant, vitamin E prevents damage to cell membranes by terminating chain reactions of lipid peroxides formed from unsaturated fatty acids in these membranes (Hoekstra, 1975). As a part of glutathione peroxidase, selenium protects against oxidative damage by catalyzing the destruction of hydrogen peroxide or by catalyzing the decomposition of lipid peroxides.

GENETIC TOXICITY

Both mutagenic activity and antimutagenic activity have been attributed to selenium; the concentration and the chemical form in which selenium is administered appear to be critical in determining its effects. At the trace levels normally found in biological systems, selenium apparently acts as an antimutagenic, oxygen-radical scavenger, but at higher concentrations selenium is capable of inducing mutations in some systems, particularly in mammalian cells *in vitro* (Arciszewska *et al.*, 1982; Shamberger, 1985; Kramer and Ames, 1988). For many cell types, the narrow concentration range in which mutagenicity but not lethality can be observed causes difficulty in defining the mutagenic potential of selenium. Shamberger (1985) has reviewed the genotoxicity of selenium.

No evidence of mutagenicity was observed in *Salmonella typhimurium* strains TA98, TA100, TA1537, or TA1538 treated with sodium selenite at concentrations up to 100 µg/plate with or without S9 activation (Noda *et al.*, 1979; Reddy *et al.*, 1983; Arlauskas *et al.*, 1985; Prasanna *et al.*, 1987; Chortyk *et al.*, 1988). In addition, Arciszewska *et al.* (1982) reported that increasing concentrations of selenium (up to 40 ppm, administered as sodium selenate or selenite or selenium dioxide) progressively decreased the number of revertants induced in *S. typhimurium* TA100 by 50 µg dimethylbenzanthracene. Selenium (as sodium

selenite or selenium dioxide) decreased the rate of spontaneous reversion in TA100 (Arciszewska *et al.*, 1982). The Shamberger (1985) review provides details of several other reports of the antimutagenic activity of selenium in *S. typhimurium.*

In contrast to the evidence of antimutagenicity of selenium in *S. typhimurium*, mutations were reported to be induced by higher doses of sodium selenite in the absence of S9 in *S. typhimurium* strains TA100 (2,400 µg/plate; Noda *et al.*, 1979) and TA104 (4,000 µg/plate; Kramer and Ames, 1988). Strain TA104 is sensitive to oxidizing agents, and Kramer and Ames proposed that the mutagenic activity observed in strain TA104 resulted from the formation of active oxygen species generated by the reaction of selenite with intracellular sulfhydryl compounds. Further, sodium selenate was reported to induce gene mutations in *S. typhimurium* strain TA1535 but not in strain TA100 when tested in a standard plate incorporation assay without S9 at doses of 6 to 20 mg/plate (Arlauskas *et al.*, 1985). Weakly positive responses were also reported for selenium (as sodium selenate or selenite) in assays for bacterial DNA damage, measured as differential growth inhibition in wild-type versus repair-deficient strains of *Bacillus subtilis* (Noda *et al.*, 1979) and *S. typhimurium* (Russell *et al.*, 1980).

In one study, 1 to 15 mM sodium selenite/plate (173 to 2,600 µg/mL) was reported to inhibit spontaneous mutations in two strains of *Saccharomyces cerevisiae* at the *his 1-7* and *lys 1-1* loci (Rosin, 1981); this inhibition was strain and locus specific and correlated directly with dose. In a second study with *S. cerevisiae* strains BZ 34 and D_7, 1 mM sodium selenite (173 µg/mL) was reported to produce gene conversion at the argininosuccinase and *trp* loci, as well as mitotic crossing over and aberrant mitoses (Anjaria and Madhvanath, 1988). The effects noted in this second study, however, were highly inconsistent between trials.

Positive responses were noted in most genetic toxicity tests with mammalian cell cultures independent of S9 activation enzymes. Chromosomal aberrations were induced in Chinese hamster ovary cells (Whiting *et al.*, 1980), in lymphocytes of Wistar rats (Newton and Lilly, 1986), and in human lymphocytes (Nakamuro *et al.*, 1976; Khalil, 1989) and fibroblasts (Lo *et al.*, 1978). Sister chromatid exchanges were induced by sodium selenite in Chinese hamster V79 cells (Sirianni and Huang, 1983) and in human lymphocytes cultured in whole blood (Ray and Altenburg, 1978, 1980; Mehnert *et al.*, 1984; Ray, 1984). Specifically, red blood cell lysate was shown to be necessary for selenite induction of sister chromatid exchanges; isolated human lymphocytes did not have increased frequencies of sister chromatid exchanges following treatment with sodium selenite (Ray and Altenburg,

1978; Ray, 1984). Sodium selenate and sodium selenite induced unscheduled DNA synthesis in hepatocytes of female Wistar rats (Russell *et al.*, 1980) and in human fibroblasts (Lo *et al.*, 1978; Whiting *et al.*, 1980) treated *in vitro*.

Results of *in vivo* genetic toxicity assays with sodium selenite have generally been negative. There is a single report of increased numbers of chromosomal aberrations and sister chromatid exchanges in bone marrow cells of Chinese hamsters injected intraperitoneally with highly toxic doses (3 or 4 mg/kg) of sodium selenite (Norppa *et al.*, 1980a), but the authors postulated that overall systemic toxicity was responsible for the observed chromosomal effects. Results of other *in vivo* chromosomal aberration tests in mice (Norppa *et al.*, 1980b) and rats (Newton and Lilly, 1986) were negative. Chromosomal aberration and sister chromatid exchange frequencies in human lymphocytes were not affected by chronic therapeutic administration of 0.004 to 0.05 mg/kg selenium as sodium selenite daily for up to 13.5 months (Norppa *et al.*, 1980c).

Study Rationale and Design

Sodium selenate and sodium selenite were nominated to the NTP for study by the National Institute of Environmental Health Sciences as part of an interagency agreement with the Agency for Toxic Substances and Disease Registry to obtain toxicity data for chemicals found in chemical waste sites. The drinking water route of administration was used because both of these compounds are water soluble. In addition, sodium selenate may leach into ground water from the soil, and both sodium selenate and sodium selenite can be formed from other selenium compounds at a pH greater than 6 in aqueous media (NAS/NRC, 1976). Endpoints evaluated in the drinking water studies included clinical pathology and histopathology in F344/N rats and B6C3F$_1$ mice. The effects of sodium selenate and sodium selenite on some sentinel reproductive endpoints were assessed by evaluation of testicular and spermatozoal parameters and determination of the length of the estrous cycle in animals in the 13-week studies.

MATERIALS AND METHODS

Procurement and Characterization of Sodium Selenate and Sodium Selenite

Single lots of sodium selenate (Lot 44645) and sodium selenite (Lot 43489) were obtained from the Noah Chemical Division of Noah Industrial Corporation (Farmingdale, NY). Initial identity and purity analyses were performed by Midwest Research Institute (MRI, Kansas City, MO).

Sodium Selenate: The chemical, a white powder, was identified as sodium selenate by infrared and ultraviolet/visible spectroscopy; spectra were consistent with those expected for the structure of sodium selenate. The results of elemental analysis for sodium were in agreement with theoretical values; results for selenium were slightly low (41.1% to 41.4% versus a theoretical value of 41.8%). Elemental analysis also indicated 0.04% potassium. Spark source mass spectroscopy indicated sodium and selenium as major components, with approximately 0.5% phosphorus, more than 4,000 ppm chlorine, and 120 ppm tellurium; all other impurities detected by spark source mass spectroscopy were present at a total concentration of less than 447 ppm. Weight loss on drying indicated 0.31% ± 0.00% water. Thin-layer chromatography (TLC) by two solvent systems indicated a major product spot only. Analysis by ion chromatography indicated approximately 0.2% sodium selenite. The cumulative data indicated a purity of approximately 98%.

Because literature references indicate that sodium selenate is stable under normal laboratory conditions (NTP, 1986a), no accelerated stability studies were performed on the bulk chemical. Throughout the 13-week studies, sodium selenate was stored in the dark at 4° ± 3° C; periodic reanalyses performed by the study laboratory with TLC and infrared or visible spectroscopy indicated no decomposition of the bulk chemical.

Sodium Selenite: The chemical, a white powder, was identified as sodium selenite by infrared and ultraviolet/visible spectroscopy; spectra were consistent with those expected for the structure of sodium selenite. The results of elemental analysis for selenium were in agreement with theoretical values; the results for sodium were low. Elemental analysis also indicated 0.14% potassium. Spark source mass spectroscopy indicated sodium and selenium as major components, with 120 ppm sulfur also present; all other impurities detected by spark source mass spectroscopy were present at a total concentration of less than 293 ppm. Karl Fischer analysis indicated 0.21% ± 0.06% water. TLC by two solvent

systems indicated a major product spot only. Analysis by ion chromatography indicated approximately 0.2% sodium selenate. The cumulative data indicated a purity of approximately 98%.

Because literature references indicate that sodium selenite is stable under normal laboratory conditions (NTP, 1986b), no accelerated stability studies were performed on the bulk chemical. Throughout the 13-week studies, sodium selenite was stored in the dark at 4° ± 3° C; periodic reanalyses performed by the study laboratory using TLC and infrared or visible spectroscopy indicated no decomposition of the bulk chemical.

Dose Formulations

Drinking water solutions were prepared by mixing sodium selenate or sodium selenite with filtered, deionized water and stirring the mixtures for 1.5 minutes.

Stability studies of the drinking water solutions were performed at MRI using ion chromatography. The results indicated that aqueous solutions of 3.9 µg/mL (3.9 ppm) sodium selenate or sodium selenite were stable for 3 weeks when stored in the dark at room temperature and for 4 days when stored under animal room conditions.

During the 13-week studies, the drinking water formulations were stored in the dark at 4° ± 3° C. The study laboratory periodically analyzed the drinking water formulations and animal room samples by visible light (421 nm) spectroscopy. All dose formulations administered to rats and mice were within 10% of the theoretical concentrations. Twelve of 13 animal room samples for rats in the sodium selenate study and 14 of 15 animal room samples for rats in the sodium selenite study were within 10% of the theoretical concentrations. In each study, the same dose formulations were administered to rats and mice; therefore no animal room samples were analyzed for mice. Results of referee analyses performed by MRI on the drinking water solutions were within 10% of study laboratory results; discrepancies between the results of MRI and the study laboratory occurred for one sample each from the sodium selenate studies and sodium selenite studies. For the 7.5 ppm sodium selenate formulation prepared on 10 October 1988, the study laboratory determined an actual concentration of 7.8 ppm; MRI determined an actual concentration of 6.4 ppm. Results of analyses of an animal room sample of this dose formulation were 7.0 ppm by the study laboratory and 8.6 ppm by MRI. For the 32 ppm sodium selenite formulation prepared on 26 September 1988, the study laboratory

determined an actual concentration of 32.3 ppm; MRI found concentrations of 38.2 and 38.9 ppm in repeated analyses. No reason for these discrepancies was discovered.

Toxicity Study Designs

BASE STUDIES

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Taconic Farms (Germantown, NY) and were 30 to 32 days old at receipt. Rats and mice were quarantined 11 to 14 days and were 6 weeks old when the studies began. For the sodium selenate studies, blood samples were collected from three sentinel female rats and five sentinel mice of each sex at the beginning of the studies and from five sentinel rats of each sex and five sentinel female mice at the end of the studies. For the sodium selenite studies, blood samples were collected from five sentinel rats and five sentinel mice of each sex at the beginning and the end of the studies. The sera were analyzed for antibody titers to rodent viruses (Boorman *et al.*, 1986; Rao *et al.*, 1989a,b); all results were negative. Additional details concerning the study design are provided in Table 1.

The exposure levels selected for the 13-week studies were based on increased mortality and decreased body weights and water consumption observed at higher concentrations in previous 2-week studies (EG&G Mason Research Institute, 1988a,b,c,d). In the 13-week base studies, groups of 10 rats and 10 mice per sex were administered 0, 3.75, 7.5, 15, 30, or 60 ppm sodium selenate (0, 1.6, 3.2, 6.4, 12.8, or 25.4 ppm selenium) or 0, 2, 4, 8, 16, or 32 ppm sodium selenite (0, 0.9, 1.8, 3.7, 7.3, or 14.6 ppm selenium) in drinking water 7 days a week for 13 weeks.

Rats were housed five per cage by sex and mice were housed individually. NIH-07 Open Formula Diet (Zeigler Brothers, Inc., Gardners, PA) was available *ad libitum*. Animal rooms were maintained at 69° to 75° F and 35% to 65% relative humidity, with 12 hours of fluorescent light per day and at least 10 room air changes per hour.

Complete necropsies were performed on all base-study animals. Organs and tissues were examined for gross lesions and fixed in 10% neutral buffered formalin. Tissues to be examined microscopically were trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Complete histopathologic examinations were performed on all animals in the control and highest exposure groups in all studies and on rats in the 30 ppm groups in the sodium selenate study. Gross lesions and selected organs of rats

and mice in lower exposure groups were examined until a no-observed-effect level was determined. Organs weighed and tissues examined microscopically are listed in Table 1.

Upon completion of the laboratory pathologist's histologic evaluation, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent pathology laboratory where quality assessment was performed. Results of the sodium selenate studies were reviewed and evaluated by the NTP Pathology Working Group (PWG); the final diagnoses represent a consensus of contractor pathologists and the PWG. Results of the sodium selenite studies were reviewed and evaluated by the NTP. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman *et al.* (1985).

SUPPLEMENTAL EVALUATIONS

Clinical Pathology

Clinical pathology studies were performed on male rats designated for clinical pathology testing and on all base-study rats and mice at the end of the 13-week studies. Ten animals per sex and exposure level were evaluated. Blood for hematology and clinical chemistry evaluations was collected from supplemental clinical pathology study rats on Days 3, 14, 42, 70, and 90; blood was collected from base-study rats and mice at the end of the study. Due to the high mortality of rats in the 60 ppm (highest exposure) groups in the clinical pathology and base studies of sodium selenate, blood collected for the Day 42 evaluations from clinical pathology study rats exposed to 60 ppm was supplemented by blood drawn from four base-study rats exposed to 60 ppm. For all time points except the Day 3 evaluation in the sodium selenate study, supplemental clinical pathology study rats were fasted overnight before blood was collected. Urinalysis samples for the sodium selenate and sodium selenite studies were collected from supplemental study rats on Days 7, 14, 42, 70, and 90; due to contamination by spilled feed, the urine samples collected on Day 7 of the sodium selenite study were not analyzed. For the hematology and clinical chemistry evaluations, animals were anesthetized with CO_2, and blood samples were drawn from the retroorbital sinus. Samples for hematology analysis were placed in pediatric collection tubes coated with EDTA; samples for clinical chemistry evaluations were placed in similar tubes devoid of anticoagulant. The latter samples were allowed to clot at room temperature; the samples were then centrifuged and serum was removed.

Hematologic determinations were made on a Baker Series 7000 Cell Counter (Baker Instruments Corp., Allentown, PA) using reagents obtained from the manufacturer. The parameters that were evaluated are listed in Table 1. Differential leukocyte counts and morphologic evaluation of blood cells were determined by light microscopy from blood smears stained with Wright-Giemsa. Smears made from blood samples stained with New Methylene Blue N (Sigma Chemical Company, St. Louis, MO) were examined microscopically for quantitative determination of reticulocytes.

Clinical chemistry variables were measured using a Cobas FARA chemistry analyzer (Roche Diagnostic Systems, Inc., Montclair, NJ). The parameters that were evaluated are listed in Table 1. Reagents for assays of sorbitol dehydrogenase, 5′-nucleotidase, and total bile acids were obtained from Sigma Diagnostics (St. Louis, MO); other reagents were obtained from the equipment manufacturer.

Urine samples were collected over a 16-hour period from male rats individually housed in metabolism cages (Lab Products, Inc., Rochelle Park, NJ). The urine collection container was immersed in an ice-water bath during the testing period to minimize evaporation and suppress bacterial growth. After volume, pH, and specific gravity were measured, alkaline phosphatase and *N*-acetyl-β-D-glucosaminidase were measured using a Cobas FARA chemistry analyzer. Reagents for alkaline phosphatase were obtained from the manufacturer; reagents for *N*-acetyl-β-D-glucosaminidase were obtained from Boehringer Mannheim Biochemicals (Indianapolis, IN).

Sperm Motility and Vaginal Cytology in Rats and Mice

Vaginal cytology and sperm motility evaluations were performed on base-study rats and mice at the end of the studies. Ten male and 10 female rats from the 0, 3.75, 15, and 30 ppm groups in the sodium selenate study and the 0, 4, 8, and 16 ppm groups in the sodium selenite study were evaluated; 10 male and 10 female mice from the 0, 3.75, 15, and 60 ppm groups in the sodium selenate study and the 0, 2, 8, and 32 ppm groups in the sodium selenite study were evaluated. The parameters that were evaluated are listed in Table 1. Methods were those described by Morrissey *et al.* (1988). Briefly, for the 12 days prior to sacrifice, the vaginal vaults of 10 females of each species per dose group were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (*i.e.*, diestrus, proestrus, estrus, and metestrus).

Sperm motility was evaluated at necropsy in the following manner. The left epididymis was isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers.

Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae were finely minced and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

Liver Selenium Concentration Analyses

The median lobes of the livers of all surviving male rats in the base studies were analyzed for selenium by neutron activation analysis at MRI. Liver lobes were frozen in liquid nitrogen at the end of the studies and stored at -70° C prior to shipment to MRI. For analysis, the tissues were freeze-dried for 24 hours and then homogenized with a Plexiglas rod. Triplicate 40 to 80 mg samples were prepared for each tissue. The samples were irradiated for 5 seconds in a neutron flux of approximately 8×10^{13} neutrons/cm^2 per second. The samples were then decayed for 15 seconds and the Se-77m isotope was counted on a 28% Li(Ge) detector using the face-spinning position. Selenium levels were determined by comparing the instrument response to the samples to the response to spiked filter paper pulp standards. Concentration data obtained from the analysis of spiked rodent liver quality control samples were used to evaluate the analysis methods for linearity, accuracy, precision, and recovery. The data were processed with a Nuclear Data 66 computer-based, multichannel analyzer with an ND599 Loss-Free counting module and a region-of-interest peak extraction program. National Bureau of Standards SRM bovine liver standards were also used for quality control.

The actual versus theoretical selenium concentration for the quality control samples showed good linearity, with a correlation coefficient of 0.999. The minimum detection limit, determined by calculating three standard deviations of a blank sample, was

0.1728 ppm. The percent relative standard deviation (%RSD or precision) ranged from 1.4% to 4.0%; the percent relative error, or accuracy, averaged less than 5% at the minimum level quantitated (MLQ) and above. The MLQ (calculated dry weight spike concentration at which the %RSD was less than or equal to 10% and the percent relative error was less than or equal to 15%) was 0.4686 ppm. The estimated recovery above the MLQ averaged 93% ± 5%.

TABLE 1 Experimental Design and Materials and Methods in the 13-Week Drinking Water Studies of Sodium Selenate and Sodium Selenite

Sodium Selenate Studies	Sodium Selenite Studies
EXPERIMENTAL DESIGN	
Study Laboratory EG&G Mason Research Institute (Worcester, MA)	Same as sodium selenate studies
Strain and Species F344/N rats B6C3F$_1$ mice	Same as sodium selenate studies
Animal Source Taconic Farms (Germantown, NY)	Same as sodium selenate studies
Size of Study Groups Base Studies: 10 males and 10 females Clinical Pathology Study: 10 male rats	Same as sodium selenate studies
Doses 0, 3.75, 7.5, 15, 30, or 60 ppm (0, 1.6, 3.2, 6.4, 12.8, or 25.4 ppm selenium) daily in drinking water for 13 weeks	0, 2, 4, 8, 16, or 32 ppm (0, 0.9, 1.8, 3.7, 7.3, or 14.6 ppm selenium) daily in drinking water for 13 weeks
Date of First Dose Rats: 25 October 1988 (males), 27 October 1988 (females) Mice: 18 October 1988 (males), 20 October 1988 (females)	Rats: 16 August 1988 (males), 18 August 1988 (females) Mice: 30 August 1988 (males), 1 September 1988 (females)
Date of Last Dose and Necropsy Rats: 24-25 January 1989 (males), 26-27 January 1989 (females) Mice: 17-18 January 1989 (males), 19-20 January 1989 (females)	Rats: 15-16 November 1988 (males), 17-18 November 1988 (females) Mice: 29-30 November 1988 (males), 1-2 December 1988 (females)
Type and Frequency of Observation Animals were observed twice daily and were weighed at the start of the study, weekly thereafter, and at necropsy. Clinical observations were recorded weekly. Water consumption by cage was measured twice weekly.	Same as sodium selenate studies

TABLE 1 Experimental Design and Materials and Methods in the 13-Week Drinking Water Studies of Sodium Selenate and Sodium Selenite (continued)

Sodium Selenate Studies	Sodium Selenite Studies
Necropsy Complete necropsies were performed on all animals in the base studies. The following organs were weighed: brain, heart, right kidney, liver, lungs, right testis, and thymus.	Same as sodium selenate studies
Histopathologic Examination Histopathologic evaluations were performed on all animals in the control and highest exposure groups and on rats in the 30 ppm groups. The following tissues were examined: adrenal glands, brain (three sections), clitoral glands, esophagus, eyes (if grossly abnormal), femur and marrow, gallbladder (mice only), gross lesions and tissue masses, heart, kidneys, large intestine (cecum, colon, rectum), liver, lungs, lymph nodes (mandibular and mesenteric), mammary gland, nasal cavity and turbinates (three sections), ovaries, pancreas, parathyroid glands, pharynx (if grossly abnormal), pituitary gland, preputial glands, prostate gland, salivary gland, seminal vesicle, small intestine (duodenum, jejunum, ileum), spinal cord/sciatic nerve (if neurological signs were present), spleen, stomach (forestomach and glandular stomach), testes (with epididymis), thigh muscle, thymus, thyroid gland, trachea, urinary bladder, uterus, and vagina (females in vaginal cytology studies only). Gross lesions of rats and mice in all lower exposure groups were examined. Organs examined in lower exposure groups included: femur and marrow, liver, lymph nodes, kidneys, ovary, and uterus in rats; and kidneys, liver, salivary glands, and uterus in female mice.	Histopathologic evaluations were performed on all animals in the control and highest exposure groups. Tissues routinely examined were the same as in the sodium selenate studies. Organs examined in lower exposure groups included: kidneys, mandibular lymph node, and thymus of male and female rats and clitoral glands, femur and marrow, liver, mammary gland, mesenteric lymph node, pancreas, salivary gland, and uterus in female rats.
Supplemental Evaluations Clinical Pathology Studies: Blood for hematology and clinical chemistry evaluations was collected on Days 3, 14, 42, 70, and 90 from male rats in the clinical pathology supplemental study groups. Base-study rats and mice were evaluated at the end of the studies. Urine samples were collected from supplemental male rats overnight on Days 7, 14, 42, 70, and 90. Hematology parameters included hematocrit (Hct), hemoglobin (Hgb) concentration, erythrocyte (RBC) count, reticulocyte count, nucleated erythrocyte count, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), and leukocyte (WBC) count and differential. Clinical chemistry parameters included urea nitrogen, creatinine, alanine aminotransferase (ALT), alkaline phosphatase, sorbitol dehydrogenase (SDH), 5′-nucleotidase, and total bile acids. Urinalysis parameters included alkaline phosphatase, *N*-acetyl-β-D-glucosaminidase (NAG), volume, specific gravity, and pH.	Same as sodium selenate studies
Liver Selenium Level Analyses: The median lobes of the livers of all surviving male base-study rats were collected at the end of the study and analyzed for selenium.	Same as sodium selenate studies

TABLE 1 Experimental Design and Materials and Methods in the 13-Week Drinking Water Studies of Sodium Selenate and Sodium Selenite (continued)

Sodium Selenate Studies	Sodium Selenite Studies
Supplemental Evaluations (continued)	
Sperm Motility and Vaginal Cytology Evaluations: Sperm motility and vaginal cytology evaluations were performed on base-study animals at the end of the studies. Rats in the 0, 3.75, 15, and 30 ppm groups and mice in the 0, 3.75, 15, and 60 ppm groups were evaluated. Male rats and mice were evaluated for necropsy body and reproductive tissue weights, spermatozoal data, and spermatogenesis. Females were evaluated for necropsy body weight, estrous cycle length, and the percent of cycle spent in the various stages.	Sperm motility and vaginal cytology evaluations were performed on base-study animals at the end of the studies. Rats in the 0, 4, 8, and 16 ppm groups and mice in the 0, 2, 8, and 32 ppm groups were evaluated. Parameters evaluated were the same as in the sodium selenate studies.
ANIMAL MAINTENANCE	
Time Held Before Study	
Rats: 12 days (males), 14 days (females) Mice: 11-12 days (males), 14 days (females)	12 days (males), 14 days (females)
Age When Study Began	
6 weeks	Same as sodium selenate studies
Age When Killed	
19 weeks	Same as sodium selenate studies
Method of Animal Distribution	
Animals were weighed and were randomized with a table of random numbers.	Same as sodium selenate studies
Diet	
NIH-07 Open Formula Diet (Zeigler Brothers, Inc., Gardners, PA) in pellet form and deionized, filtered water (City of Worcester) containing the appropriate doses were available *ad libitum*.	Same as sodium selenate studies
Animal Room Environment	
Rats were housed five animals per cage and mice were housed individually. The temperature was maintained at 69° to 75° F and relative humidity at 35% to 65%, with at least 10 air changes per hour. Fluorescent light was provided for 12 hours per day.	Same as sodium selenate studies

Statistical Methods

ANALYSIS OF CONTINUOUS VARIABLES

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous variables. Organ and body weight data, which are approximately normally distributed, were analyzed with the parametric multiple comparisons procedures of Williams (1971, 1972) or Dunnett (1955). Clinical chemistry, hematology, spermatid, and spermatozoal data, which typically have skewed distributions, were analyzed with the nonparametric multiple comparisons methods of Shirley (1977) or Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test (Williams, Shirley) was more appropriate for pairwise comparisons than a test capable of detecting departures from monotonic dose response (Dunnett, Dunn). If the P-value from Jonckheere's test was greater than or equal to 0.10, Dunn's or Dunnett's test was used rather than Shirley's or Williams' test.

The outlier test of Dixon and Massey (1951) was employed to detect extreme values. No value selected by the outlier test was eliminated unless it was at least twice the next largest value or at most half of the next smallest value. The extreme values chosen by the statistical test were subject to approval by NTP personnel. In addition, values indicated by the laboratory report as being inadequate due to technical problems were eliminated from the analysis.

ANALYSIS OF VAGINAL CYTOLOGY DATA

Because the data are proportions (the proportion of the observation period that an animal was in a given estrous state), an arcsine transformation was used to bring the data into closer conformance with normality assumptions. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across dose levels.

Quality Assurance

The animal studies of sodium selenate and sodium selenite were performed in compliance with USFDA Good Laboratory Practices regulations (21 CFR 58). The Quality Assurance Unit of EG&G Mason Research Institute performed audits and inspections of protocols, procedures, data, and reports throughout the course of the studies.

RESULTS

13-Week Drinking Water Studies in F344/N Rats

All male and female rats exposed to 60 ppm sodium selenate (Table 2) and two females exposed to 32 ppm sodium selenite (Table 3) died or were killed moribund before the end of the studies. The final mean body weights and mean body weight gains of rats in the 15 and 30 ppm groups in the sodium selenate study and males and females in the 16 and 32 ppm groups in the sodium selenite study were lower than those of the respective controls (Tables 2 and 3 and Figures 1 and 2).

In the sodium selenate study, all rats exposed to 60 ppm and two males and one female exposed to 30 ppm were emaciated; other clinical signs in rats in the 60 ppm groups included abnormal posture, pallor, and ruffled fur in males and females and urine stain and hypoactivity in females. These signs were also noted in a few rats in the 15 and 30 ppm groups. In the sodium selenite study, male and female rats in the 32 ppm groups had abnormal posture, and females exposed to 32 ppm were emaciated and had ruffled fur and urine stain.

Water consumption by male and female rats in both studies decreased with increasing exposure concentration (Tables 2 and 3). Drinking water concentrations of 3.75, 7.5, 15, 30, and 60 ppm sodium selenate were estimated to deliver 0.1, 0.2, 0.4, 0.6, 1.1 (males), and 0.8 (females) mg selenium/kg body weight per day. Drinking water concentrations of 2, 4, 8, 16, and 32 ppm sodium selenite were estimated to deliver 0.08, 0.13, 0.2, 0.4, 0.8 (males), and 0.9 (females) mg/kg selenium per day. Water consumption by male rats exposed to 15 ppm sodium selenate or greater and female rats exposed to 7.5 ppm or greater was notably lower than that by control rats (Table 2). In the sodium selenite study, water consumption by male rats in the 32 ppm group and female rats in the 16 and 32 ppm groups was notably lower than that by the controls (Table 3).

TABLE 2 Survival, Weight Gain, Water Consumption, and Compound Consumption Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate

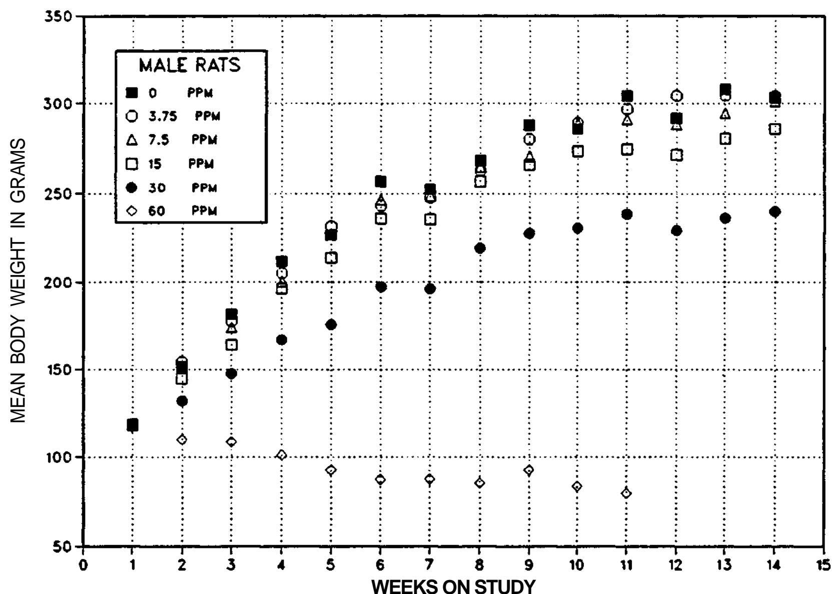
Dose (ppm)	Survival[1]	Mean Body Weight (grams) Initial	Final	Change	Final Weight Relative to Controls[2] (%)	Average Water Consumption[3] (g/day)	Average Dose[3] (mg/kg/day)
MALE							
0	10/10	118	311	193		19.1	
3.75	10/10	119	308	189	99	19.8	0.29
7.5	10/10	120	304	184	98	17.3	0.51
15	10/10	119	288	169	93	14.7	0.92
30	10/10	118	243	125	78	10.7	1.57
60	0/10[4]	117	–	–	–	3.9[5]	2.54[5]
FEMALE							
0	10/10	115	197	82		16.5	
3.75	10/10	116	196	81	100	14.7	0.31
7.5	10/10	105	191	87	97	10.8	0.47
15	10/10	117	178	61	90	9.8	0.88
30	10/10	116	141	24	71	6.4	1.35
60	0/10[6]	117	–	–	–	2.7	1.84

1 Number surviving at 13 weeks/number of animals per group. For groups with no survivors, no final mean body weights or body weight changes are given.
2 (Dose group mean/control group mean) × 100.
3 Average of individual consumption values for Weeks 1-13 for all animals in the base study.
4 Week of death: 4, 4, 5, 5, 5, 7, 7, 7, 8, 11.
5 Consumption values were calculated for Weeks 1-6 only, due to high mortality after week 6.
6 Week of death: 4, 4, 5, 5, 5, 5, 6, 6, 6, 6.

TABLE 3 Survival, Weight Gain, Water Consumption, and Compound Consumption Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite

Dose (ppm)	Survival[1]	Mean Body Weight (grams)			Final Weight Relative to Controls[2] (%)	Average Water Consumption[3] (g/day)	Average Dose[3] (mg/kg/day)
		Initial	Final	Change			
MALE							
0	10/10	141	348	207		22.2	
2	10/10	141	338	197	97	22.0	0.17
4	10/10	140	339	199	97	19.7	0.29
8	10/10	142	332	190	95	18.1	0.54
16	10/10	144	321	177	92	16.1	0.98
32	10/10	142	229	87	66	10.2	1.59
FEMALE							
0	10/10	122	199	78		14.6	
2	10/10	122	207	85	104	15.6	0.17
4	10/10	122	198	76	99	12.7	0.28
8	10/10	122	196	75	99	10.9	0.50
16	10/10	124	188	65	94	9.2	0.86
32	8/10[4]	124	92	−31	46	6.1	1.67

[1] Number surviving at 13 weeks/number of animals per group.
[2] (Dose group mean/control group mean) × 100.
[3] Average of individual consumption values for Weeks 1-13 for all animals in the base study.
[4] Week of death: 8, 10.



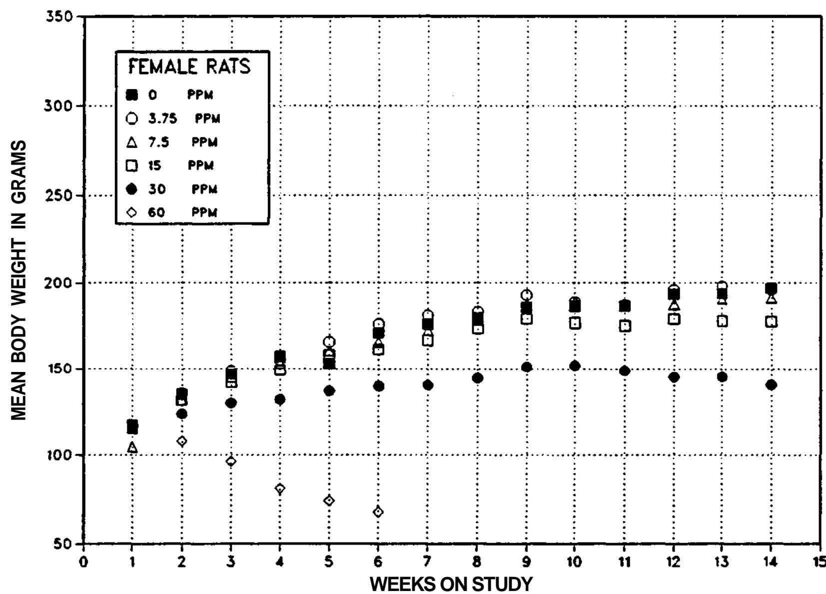


FIGURE 1 **Body Weights of F344/N Rats Administered Sodium Selenate in Drinking Water for 13 Weeks**

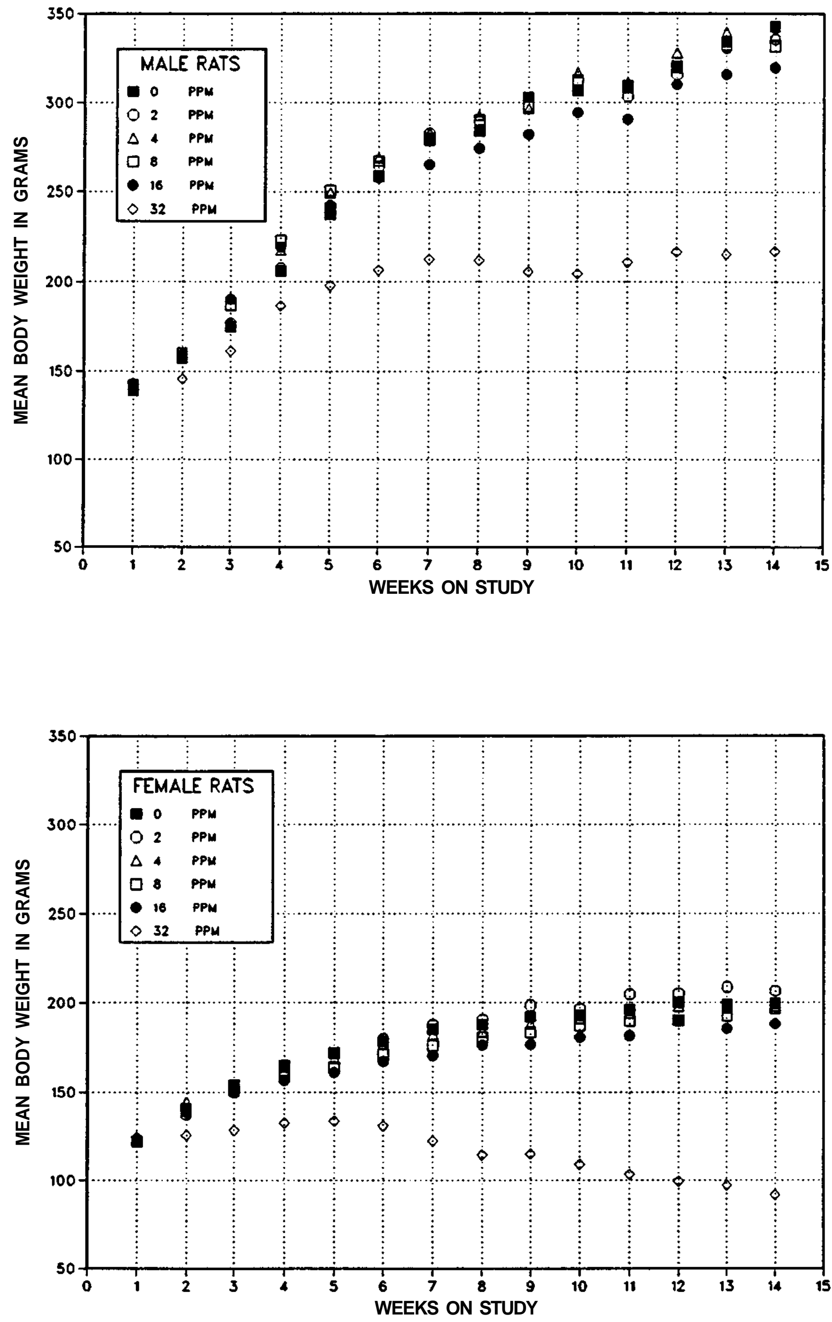


FIGURE 2 Body Weights of F344/N Rats Administered Sodium Selenite in Drinking Water for 13 Weeks

Sodium Selenate: The organ weights of male and female rats in the 15 and 30 ppm groups were significantly different from those of the controls (Appendix C, Table C1). The decreases observed in the absolute weights of the heart, right kidney (males only), liver, lungs (males only), and thymus (females only) and the increases in the relative weights of the brain, lungs (females only), and right testis were considered secondary to depressed body weight gain. The increases in relative kidney weight in males and females in the 15 and 30 ppm groups were likely a physiologic response to dehydration caused by reduced water consumption by these groups.

Hematology, clinical chemistry, and urinalysis data for rats in the 13-week drinking water study of sodium selenate are provided in Appendix D, Table D1. Alterations in multiple endpoints were noted, and changes suggesting a treatment relationship are described below. In general, severity was exposure concentration dependent, and many changes occurred at early time points but moderated or were resolved by the end of the study.

In male rats in the clinical pathology study, mild changes in hematology parameters occurred primarily in the 30 and 60 ppm groups on Days 3, 14, and 42. At these time points, an exposure concentration-related polycythemia occurred, as evidenced by increased erythrocyte (RBC) counts. Increases in hematocrit (Hct) and hemoglobin (Hgb) concentration were also evident but occurred only on Day 3. In males in the 30 ppm group, the RBC count returned to a level similar to that of the controls by Day 70 and remained at that level at the end of the study. No exposure concentration-related hematology changes occurred in base-study male rats evaluated at Week 13; however, Hct, Hgb concentration, and RBC count were increased in base-study females in the 30 ppm group. A microcytic process occurred in male rats in the clinical pathology study, as evidenced by mild decreases in mean cell volume and mean cell hemoglobin in the 30 and 60 ppm groups on Days 3, 14, and 42. This change was also present at Day 70 in the 30 ppm group, but was resolved by the end of the study.

A mild azotemia, evidenced by elevations in serum urea nitrogen concentration, occurred in male rats in the clinical pathology study that were exposed to 7.5 ppm or greater. This azotemia appeared at Day 14 in the 30 and 60 ppm groups and was present in the four highest exposure groups by Day 42. By the end of the study, the azotemia was resolved in the 7.5 and 15 ppm groups but was still evident in the 30 ppm group. Serum alanine aminotransferase (ALT) activity was increased in the 15, 30, and 60 ppm groups on Day 14. This increase in enzyme activity also occurred in the 30 and 60 ppm groups on Day 42 and in the 30 ppm group on Day 70. ALT activity was elevated in almost all

groups of exposed female rats in the base study. An increase in ALT activity would suggest a hepatocellular effect; however, serum sorbitol dehydrogenase (SDH) activity, another biomarker of hepatocellular integrity, was not increased. Bile acid concentration was increased, indicating cholestasis, on Day 42 in male rats in the 30 and 60 ppm groups in the special study. This finding was supported by an increase in 5′-nucleotidase activity in the 30 ppm group on Day 42. Alkaline phosphatase and 5′-nucleotidase activities were decreased in various exposure groups on Days 3 and 14; these decreases occurred in the 30 and 60 ppm groups at both time points. Alkaline phosphatase activity was decreased in all groups of exposed male rats with survivors at the end of the base study.

Male rats in all exposed groups had decreased urine volume and increased urine specific gravity at all time points. On Days 3 and 14, an alkalinuria, evidenced by increased urine pH, was present in treated groups. This changed to an aciduria, evidenced by decreased urine pH, on Days 42 and 70 and at the end of the study.

Treatment-related gross lesions observed at necropsy consisted of decreased thymus, seminal vesicle, and uterus sizes in male and female rats in the 60 ppm groups. These gross observations, as well as the microscopic lesions observed in exposed rats, were considered secondary to decreased water consumption, marked decreases in body weight gain, or changes typically seen in animals that die or are killed moribund. Cellular depletion of the bone marrow, lymph nodes, thymus, and spleen, atrophy or degeneration of the male and female reproductive organs, metaphyseal atrophy of the bone, minimal single-cell necrosis of hepatocytes, and atrophy of acinar structures of the pancreas and salivary glands were typical of the histopathologic findings seen in rats in the 60 ppm groups that died before the end of the study (Appendix A, Table A1). Lymphoid organ changes diagnosed as cellular depletion consisted of decreased numbers of lymphocytes in the thymic cortex and decreased size of the lymphoid follicles and periarteriolar sheaths in the lymph node and spleen. Cellular depletion of the bone marrow consisted of a decrease in the density of erythroid and myeloid cellular components. Atrophy in other glandular organs was based on decreased organ and cell size or absence of normal cytoplasmic granules or secretory product in the ductular lumen. These changes were present in a few rats exposed to 30 ppm that had body weight gains that were markedly lower than those of the controls.

Degeneration of the renal papilla was an exposure concentration- and treatment-related lesion that occurred in the kidneys of male and female rats (Table 4). This papillary lesion varied from minimal to marked in severity. Minimal degeneration consisted of a focal area of edema of the interstitium at the most distal tip of the renal papilla. This was characterized by a slight loss of cytoplasmic and nuclear detail of the interstitial cells, with increased eosinophilia and granularity of the cytoplasm. Epithelial cells lining the distal portion of collecting ducts were swollen, and the cytoplasm often contained large, clear vacuolar spaces. When the degeneration involved a large portion of the distal papilla, the lesion was diagnosed as mild. In rats with moderately severe degeneration, the morphologic changes were more prominent and included necrosis of the interstitial cells and renal epithelium covering the distal end of the papilla. The incidence and average severity of this lesion were slightly greater in females than in males (Table 4). In male rats, papillary lesions were of minimal severity except at the two highest exposure concentrations (30 and 60 ppm), where the degeneration was minimal to mild. Papillary degeneration was not present in male rats in the 3.75 ppm group. Papillary degeneration, which varied in severity from minimal to moderate, was present in most female rats exposed to 15 ppm or greater. Minimal degeneration that occurred in 1 of 10 females in the 3.75 ppm group was similar in morphologic appearance and severity to the papillary degeneration present in one control female rat.

TABLE 4 Incidence and Severity of Kidney Lesions in F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate[1]

	Concentration (ppm)					
	0	3.75	7.5	15	30	60
MALE						
n	8	9	10	9	10	9
Papilla, degeneration	0	0	3 (1.0)	6 (1.0)	6 (1.7)	7 (1.6)
FEMALE						
n	8	10	8	9	7	9
Papilla, degeneration	1 (1.0)	1 (1.0)	5 (1.0)	8 (1.4)	7 (1.9)	6 (2.0)

[1] Although sections from both kidneys were examined microscopically for each rats in each group, the distal papilla was not always present. For each group, n = number of rats with at least one renal papilla present for evaluation. Average severity (in parentheses) is based on the number of animals with lesions: 1=minimal, 2=mild, 3=moderate, and 4=marked.

The number of testicular spermatid heads and the spermatid count per gram of testis were significantly decreased in males in the 3.75 and 15 ppm groups; motility was slightly decreased in males exposed to 30 ppm (Appendix E, Table E1). Exposed females spent more time in diestrus and less time in proestrus, estrus, and metestrus than control females (Table E2).

The livers of all base-study male rats were analyzed for selenium concentration. The following average selenium concentrations (per dry weight of tissue) were detected: 3.75 ppm group, 3.7 ± 0.4 ppm; 7.5 ppm group, 5.4 ± 0.6 ppm; 15 ppm group, 7.9 ± 0.8 ppm; and 30 ppm group, 10.2 ± 0.5 ppm. The selenium concentration in control males was less than the minimum quantifiable level. No livers were examined from rats exposed to 60 ppm sodium selenate due to mortality.

Sodium Selenite: Differences in organ weights occurred primarily in rats in the 32 ppm groups in the sodium selenite study (Tables 5 and C2). The absolute and relative thymus weights of rats exposed to 32 ppm were significantly decreased; relative right kidney weights were increased in rats in the 32 ppm groups. Other statistically significant differences in organ weights were considered related to decreases in body weight gain in exposed rats.

Hematology, clinical chemistry, and urinalysis data for rats in the 13-week drinking water study of sodium selenite are provided in Appendix D, Table D2. Hematology changes similar to those occurring in rats in the sodium selenate study occurred in rats in the sodium selenite study; however, these changes were sporadic and minimal.

Increases in ALT activity occurred in clinical pathology and base-study male rats exposed to 32 ppm and in females exposed to 16 or 32 ppm. This change is similar to that occurring in the sodium selenate study; however, in the sodium selenite study, SDH activity was also elevated in clinical pathology study males at Day 70. 5′-Nucleotidase activity and bile acid concentration were increased in clinical pathology study male rats in the 32 ppm group on Days 42 and 70 and at Week 13. These changes, which were similar to the changes in rats in the sodium selenate study, also occurred at Week 13 in base-study male and female rats exposed to 32 ppm. Additionally, alkaline phosphatase activity was increased sporadically in various groups in the clinical pathology and base studies.

TABLE 5 Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite[1]

	Concentration (ppm)					
	0	2	4	8	16	32
MALE						
n	10	10	10	10	10	10
Necropsy body wt	355 ± 6	346 ± 5	346 ± 4	337 ± 4	323 ± 8**	230 ± 15**
Right kidney						
Absolute	1.245 ± 0.020	1.299 ± 0.030	1.257 ± 0.035	1.221 ± 0.031	1.239 ± 0.047	1.104 ± 0.062*
Relative	3.51 ± 0.05	3.75 ± 0.06	3.63 ± 0.08	3.62 ± 0.06	3.83 ± 0.06*	4.89 ± 0.21**
Liver						
Absolute	13.586 ± 0.432	13.152 ± 0.376	12.761 ± 0.305	13.235 ± 0.394	13.169 ± 0.527	8.365 ± 0.934**
Relative	38.23 ± 0.71	37.95 ± 0.72	36.85 ± 0.73	39.19 ± 0.82	40.65 ± 0.74	35.53 ± 2.13
Thymus						
Absolute	0.353 ± 0.028	0.325 ± 0.015	0.345 ± 0.029	0.335 ± 0.024	0.306 ± 0.023	0.180 ± 0.025**
Relative	0.99 ± 0.08	0.94 ± 0.05	1.00 ± 0.08	1.00 ± 0.08	0.95 ± 0.06	0.76 ± 0.08*
FEMALE						
n	10	10	10	10	10	8
Necropsy body wt	198 ± 3	207 ± 5	198 ± 3	196 ± 3	189 ± 2	92 ± 6**
Right kidney						
Absolute	0.633 ± 0.023	0.709 ± 0.022	0.677 ± 0.024	0.695 ± 0.020	0.706 ± 0.018	0.545 ± 0.026*
Relative	3.20 ± 0.10	3.43 ± 0.06	3.41 ± 0.09	3.53 ± 0.08	3.74 ± 0.08**	6.00 ± 0.30**
Liver						
Absolute	5.954 ± 0.145	6.471 ± 0.180	5.901 ± 0.163	5.684 ± 0.275	5.975 ± 0.126	3.058 ± 0.235**
Relative	30.07 ± 0.44	31.28 ± 0.48	29.79 ± 0.49	28.85 ± 1.12	31.68 ± 0.45	33.02 ± 1.13**
Thymus						
Absolute	0.239 ± 0.011	0.255 ± 0.013	0.239 ± 0.011	0.249 ± 0.010	0.225 ± 0.011	0.052 ± 0.012**
Relative	1.21 ± 0.06	1.24 ± 0.06	1.21 ± 0.05	1.27 ± 0.05	1.19 ± 0.06	0.54 ± 0.08**

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

Decreases in urine volume and increases in urine specific gravity occurred in multiple exposure groups at various time points in the clinical pathology study males. These changes were similar to the urinalysis changes in the sodium selenate study.

Treatment-related gross lesions observed at necropsy consisted of decreased thymus, seminal vesicle, and uterus sizes in male and female rats in the 32 ppm groups. Most microscopic diagnoses of atrophy or cellular depletion in the thymus, lymph nodes, bone marrow, spleen, salivary gland, pancreas, liver, mammary gland, uterus, clitoral gland, and metaphyseal plate of the femur (Appendix A, Table A2) were considered secondary to

the marked decrease in body weight gain in males and the body weight loss in females exposed to 32 ppm. Lymphoid organ changes diagnosed as cellular depletion consisted of decreased numbers of lymphocytes in the thymic cortex and decreased size of the lymphoid follicles and periarteriolar sheaths in the lymph node and spleen. Cellular depletion in the bone marrow consisted of a decrease in the density of erythroid and myeloid cellular components. Atrophy of the bone metaphyseal plate ranged from decreased size and number of metaphyseal trabeculae to the complete absence of the trabeculae, which are normally present in growing, young adult rats. Atrophy in other glandular organs was based on decreased organ and cell size or absence of normal cytoplasmic granules or secretory product in ductular lumen.

Degeneration of the renal papilla was an exposure concentration- and treatment-related histopathologic effect that occurred in the kidneys of male and female rats (Table 6). This papillary lesion varied from minimal to marked in severity. Minimal degeneration consisted of a focal area of edema of the interstitium at the most distal tip of the renal papilla. This was characterized by a slight loss of cytoplasmic and nuclear detail of the interstitial cells, with increased eosinophilia and granularity of the cytoplasm. Epithelial cells lining the distal portion of collecting ducts were swollen, and the cytoplasm often contained large, clear vacuolar spaces. When the degeneration involved a large area of the distal portion of the papilla, the lesion was diagnosed as mild. In rats with degeneration of moderate or marked severity, the morphologic features were more prominent and included necrosis of the interstitial cells and renal epithelium covering the distal end of the papilla (Plates 1-4). The incidence and average severity of this lesion were greater in females than in males (Table 6). In male rats, papillary lesions were of minimal severity except at the highest exposure concentration (32 ppm), where the degeneration was mild to moderate. Papillary degeneration was not present in male rats in the 2 ppm group, and the single occurrence in a male in the 4 ppm group was similar in morphology and severity to the minimal focal area of papillary degeneration in the kidney of one control male. Papillary degeneration, which varied in severity from minimal to moderate, was present in most female rats exposed to 8 ppm or greater. Minimal degeneration occurred in 1 of 10 females in the 2 ppm group and 3 of 10 females in the 4 ppm group.

TABLE 6 Incidence and Severity of Kidney Lesions in F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite[1]

	Concentration (ppm)					
	0	2	4	8	16	32
MALE						
n	10	10	10	8	10	8
Papilla, degeneration	1 (1.0)	0	1 (1.0)	2 (1.0)	5 (1.0)	7 (2.3)
FEMALE						
n	10	9	10	7	8	10
Papilla, degeneration	0	1 (1.0)	3 (1.0)	6 (1.3)	8 (1.8)	9 (2.0)

[1] Although both kidneys were examined microscopically for 10 rats in each group, the distal papilla was not always present for evaluation. For each group, n = number of rats with at least one renal papilla present for evaluation. Average severity (in parentheses) is based on the number of animals with lesions: 1=minimal, 2=mild, 3=moderate, and 4=marked.

Epididymal sperm concentration was significantly decreased in all groups of exposed males (Appendix E, Table E3). Female rats in the 16 ppm group differed significantly from the control females in the relative length of time spent in estrous stages, spending more time in diestrus and less time in proestrus and estrus (Table E4).

The livers of all base-study male rats were analyzed for selenium concentration. The following average selenium concentrations (per dry weight of tissue) were detected: 2 ppm group, 3.4 ± 0.2 ppm; 4 ppm group, 4.1 ± 0.5 ppm; 8 ppm group, 5.8 ± 0.4 ppm; 16 ppm group, 7.9 ± 0.8 ppm; and 32 ppm group, 12 ± 1 ppm. The selenium concentration in control males was less than the minimum quantifiable level.

13-Week Drinking Water Studies in $B6C3F_1$ Mice

All male and female mice survived until the end of the sodium selenate and sodium selenite studies (Tables 7 and 8). Final mean body weights of male and female mice and mean body weight gains of males exposed to 15 ppm sodium selenate or greater were lower than those of the controls; the mean body weight gains of female mice in the 30 and 60 ppm groups were also notably lower than the control mean body weight gain (Table 7 and Figure 3). In the sodium selenite study, the final mean body weights of male and female mice and the mean body weight gains of females in the 16 and 32 ppm groups were lower than those of the controls; the mean body weight gain of males in the 32 ppm group was also lower than that of the controls (Table 8 and Figure 4). No clinical signs in either study were considered related to sodium selenate or sodium selenite administration.

In both studies, water consumption by males and females at the three highest exposure levels (15, 30, and 60 ppm sodium selenate; 8, 16, and 32 ppm sodium selenite) was lower than that by the respective controls (Tables 7 and 8). Drinking water concentrations of 3.75, 7.5, 15, 30, and 60 ppm sodium selenate were estimated to deliver 0.3, 0.5, 0.8, 1.5, and 2.6 mg selenium/kg body weight per day. Drinking water concentrations of 2, 4, 8, 16, and 32 ppm sodium selenite were estimated to deliver 0.14, 0.3, 0.5, 0.9, and 1.6 mg/kg selenium per day.

TABLE 7 Survival, Weight Gain, Water Consumption, and Compound Consumption Data for B6C3F$_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate

Dose (ppm)	Survival[1]	Mean Body Weight (grams) Initial	Final	Change	Final Weight Relative to Controls[2] (%)	Average Water Consumption[3] (g/day)	Average Dose[3] (mg/kg/day)
MALE							
0	10/10	24.8	39.7	14.8		4.6	
3.75	10/10	24.6	38.6	14.0	97	4.9	0.55
7.5	10/10	25.1	39.0	13.9	98	4.7	1.07
15	10/10	24.9	36.8	11.9	93	3.9	1.87
30	10/10	24.8	34.3	9.6	87	3.0	2.95
60	10/10	24.6	30.2	5.6	76	2.5	5.45
FEMALE							
0	10/10	20.3	30.8	10.4		5.4	
3.75	10/10	20.1	29.3	9.2	95	6.5	0.92
7.5	10/10	20.3	32.7	12.4	106	4.8	1.29
15	10/10	19.9	28.6	8.7	93	3.8	2.18
30	10/10	19.7	25.7	6.0	83	3.3	4.10
60	10/10	20.2	24.0	3.9	78	2.7	7.17

[1] Number surviving at 13 weeks/number of animals per group.
[2] (Dose group mean/control group mean) × 100.
[3] Average of individual consumption values for Weeks 1-13 for all animals in the base study.

TABLE 8 Survival, Weight Gain, Water Consumption, and Compound Consumption Data for $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite

Dose (ppm)	Survival[1]	Mean Body Weight (grams)			Final Weight Relative to Controls[2] (%)	Average Water Consumption[3] (g/day)	Average Dose[3] (mg/kg/day)
		Initial	Final	Change			
MALE							
0	10/10	23.8	40.8	17.0		4.6	
2	10/10	23.5	40.0	16.5	98	4.5	0.26
4	10/10	23.0	40.7	17.6	100	4.7	0.56
8	10/10	23.2	39.3	16.1	96	3.8	0.91
16	10/10	22.5	37.4	14.9	92	3.2	1.61
32	10/10	22.8	33.8	11.0	83	3.1	3.31
FEMALE							
0	10/10	18.6	31.7	13.0		5.7	
2	10/10	19.2	30.6	11.4	97	5.1	0.37
4	10/10	18.8	31.0	12.1	98	5.7	0.85
8	10/10	19.3	30.3	11.0	96	4.2	1.25
16	10/10	19.2	29.2	10.0	92	3.5	2.19
32	10/10	19.0	25.5	6.5	80	2.8	3.83

[1] Number surviving at 13 weeks/number of animals per group.
[2] (Dose group mean/control group mean) × 100.
[3] Average of individual consumption values for Weeks 1-13 for all animals in the base study.

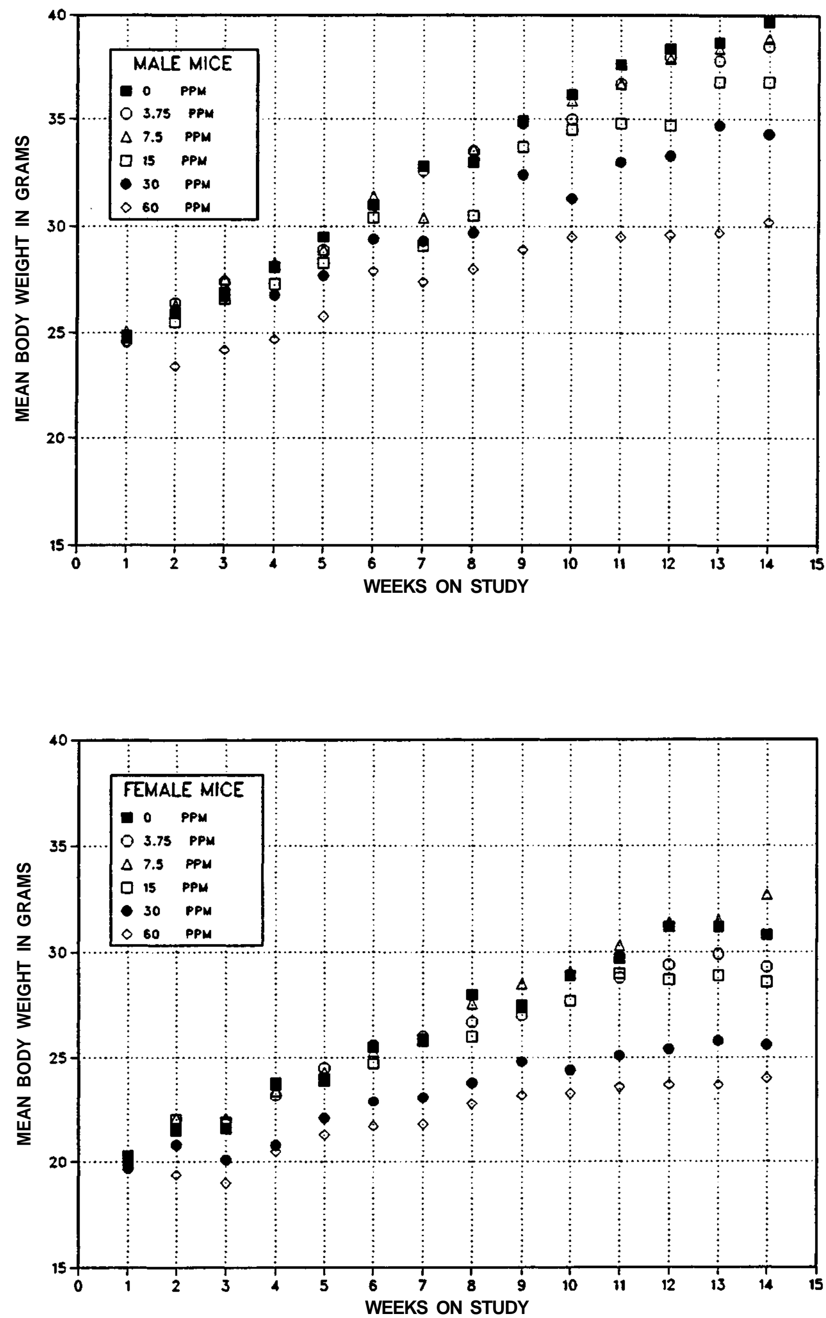
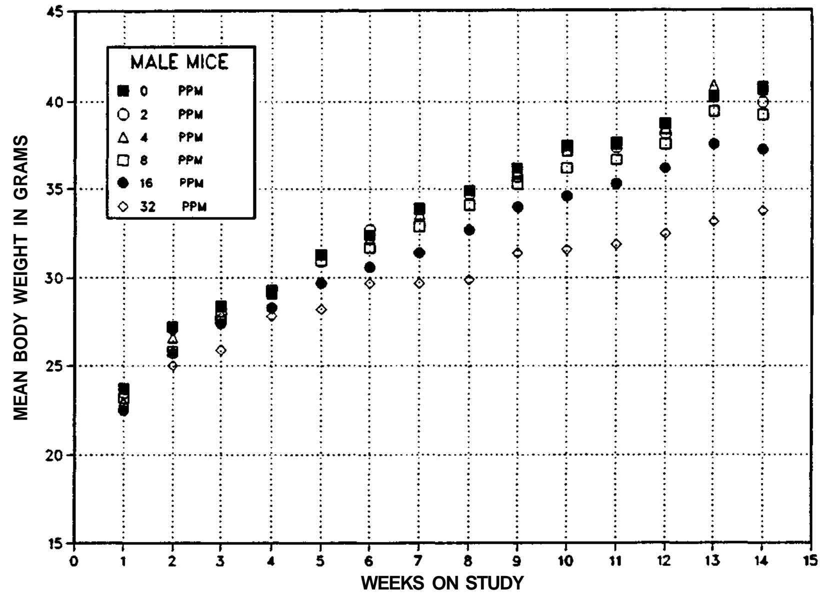


FIGURE 3 **Body Weights of $B6C3F_1$ Mice Administered Sodium Selenate in Drinking Water for 13 Weeks**



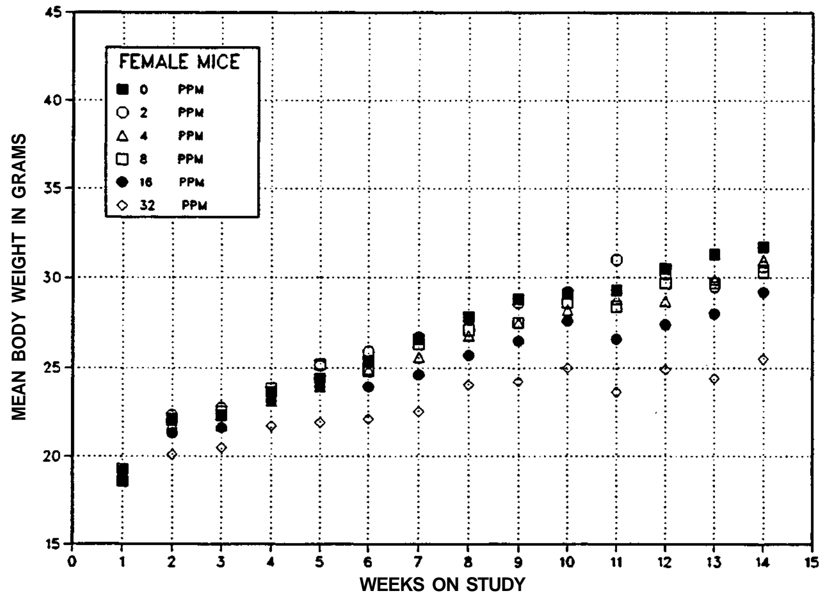


FIGURE 4 Body Weights of $B6C3F_1$ Mice Administered Sodium Selenite in Drinking Water for 13 Weeks

Sodium Selenate: Relative right kidney weight generally increased with increasing exposure concentration in male and female mice, and the increase was significant in all groups except in females exposed to 7.5 ppm; in this group, the absolute right kidney weight was significantly increased (Appendix C, Table C3). Relative right testis weights were also increased in males exposed to 15 ppm or greater. Other differences in organ weights were sporadic or were secondary to decreases in body weight gain.

The results of hematologic analyses for control and exposed male and female mice were similar (Appendix D, Table D3). In male mice, the creatinine level was significantly decreased in the 60 ppm group and alkaline phosphatase activity was significantly decreased in the 30 ppm group. No significant changes in clinical chemistry parameters occurred in female mice.

No gross or microscopic lesions were considered related to treatment.

No significant differences in sperm motility or vaginal cytology parameters occurred in exposed males or females (Appendix E, Tables E5 and E6).

Sodium Selenite: In male and female mice exposed to 32 ppm and in males exposed to 16 ppm sodium selenite, relative right kidney weights were significantly increased (Table C4). Other statistically significant differences in organ weights were considered secondary to decreased body weight gains in exposed mice.

The results of hematologic and clinical chemistry analyses for control and exposed male and female mice were similar (Table D4).

No gross or microscopic lesions were considered related to treatment.

No significant differences in sperm motility parameters occurred in male mice exposed to sodium selenite (Table E7). The estrous cycle length of females in the 32 ppm group was significantly increased (Table E8).

PLATE 1

Kidney of a female rat administered 32 ppm sodium selenite in drinking water for 13 weeks. Marked degeneration (*) present at the tip of the renal papilla. H&E 60x.

PLATE 2

Kidney from a control female rat shows appearance of a normal renal papilla for comparison with the sodium selenite treatment effect shown in Plate 1. H&E 60x.

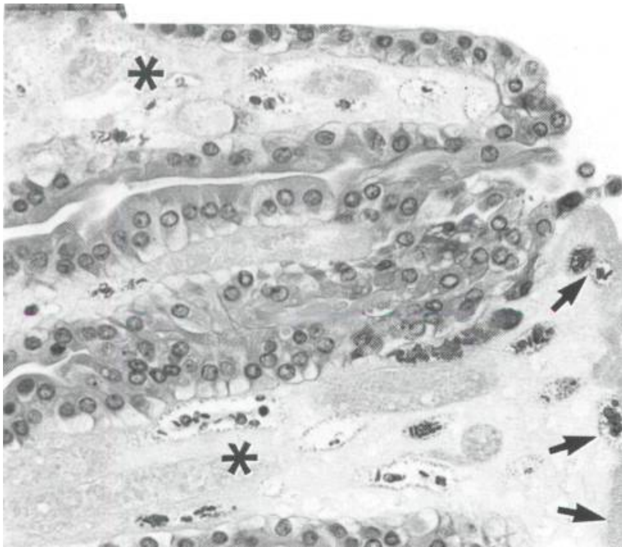


PLATE 3

Detail of the tip of the renal papilla shown in Plate 1. Note the absence of interstitial cell nuclei, edema, and a granular appearance of the interstitium (*) compared to the control rat papilla shown in Plate 4. Note also the minimal focal necrosis of the renal epithelium (arrows) at the tip of the papilla. H&E 250x.

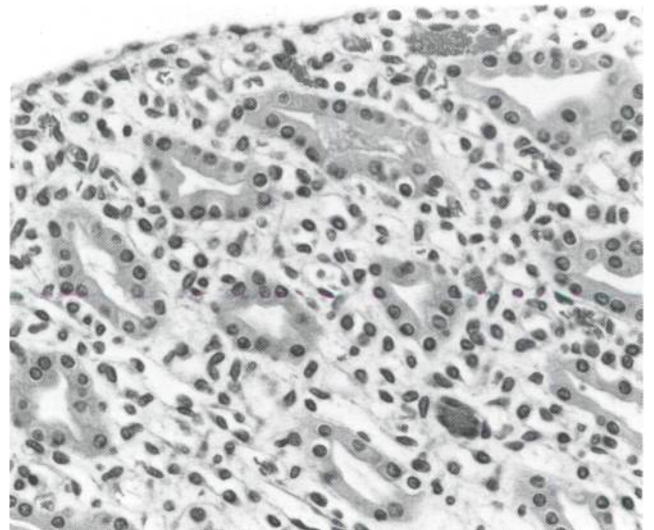


PLATE 4

Detail of the papilla from a control female rat, shown in Plate 2, for comparison with the papilla from a female rat treated with sodium selenite, shown in Plate 3. H&E 250X.

DISCUSSION

Sodium selenate and sodium selenite are used as supplements in poultry and livestock feed to promote growth, and both forms of selenium have been found in chemical waste disposal sites. Because these two selenium compounds are likely to be present in groundwater, 13-week drinking water studies were conducted to compare and characterize their toxic effects in rats and mice.

Very little difference in the toxicity of sodium selenate and sodium selenite was seen. In rats, the compounds caused mortality; reduction in body weight and water consumption; increased incidences of renal papillary degeneration; increases in serum alanine aminotransferase (ALT), sorbitol dehydrogenase (SDH), alkaline phosphatase, and 5′-nucleotidase activities and bile acid concentration; and increased estrous cycle length. In mice, sodium selenate and sodium selenite caused reductions in body weight and water consumption, and sodium selenite also caused increases in estrous cycle length.

Results of these studies showed no differences in sensitivity to selenium between the sexes. The results of early studies suggested that selenium was more toxic to female rats than to males (Smith and Stohlman, 1940; Fitzhugh *et al.*, 1944). In contrast, Tinsley *et al.* (1967) concluded that sodium selenate and sodium selenite were equally toxic to male and female Wistar rats in a chronic study. Schroeder (1967) observed a higher number of deaths in male Long-Evans rats than in females receiving 2 ppm selenium as sodium selenite in the drinking water. However, mortality was not increased in male Sprague-Dawley rats that received 2 ppm selenium as sodium selenite in drinking water (Palmer and Olson, 1974).

In the current studies, no deaths occurred among rats given drinking water containing as much as 30 ppm sodium selenate (0.61 mg/kg selenium per day) or 16 ppm sodium selenite (0.42 mg/kg selenium per day) and mice receiving up to 60 ppm sodium selenate (2.63 mg/kg selenium per day) or 32 ppm sodium selenite (1.63 mg/kg selenium per day); Schroeder (1967) reported a 50% mortality among weanling Long-Evans rats given 2 ppm selenium as sodium selenite for 35 days. In another study, all weanling Sprague-Dawley rats fed diets containing selenium (1 mg Se/kg diet) from sodium selenate or selenite died within 29 days (McAdam and Levander, 1987). These contrasting results may be due in part to the different ages of the animals when the studies began. Rats were 6 weeks old at the beginning of the NTP studies, compared with 3 to 4 weeks at the beginning of the

Schroeder study. Results of a study by Jacobs and Forst (1981b) indicated that the age of rats at the beginning of sodium selenite administration influenced survival. In this study, the survival of 5-week-old rats receiving 4 ppm selenium as sodium selenite in drinking water for 64 weeks was 63%, compared to 94% for the controls. In a second study, the survival of 8-week-old rats receiving the same concentration of sodium selenite for 61 weeks was 95%, compared to 90% for the controls (Jacobs and Forst, 1981b).

Clinical signs of ruffled fur, emaciation, and abnormal posture were observed in rats exposed to the highest concentrations of sodium selenate (60 ppm) and sodium selenite (32 ppm). These clinical signs were due to debilitation resulting from reduced water consumption and were not considered specifically related to the administration of sodium selenate or selenite. No clinical signs attributed to chemical administration were observed in mice.

The majority of the changes observed in the hematology, clinical chemistry, and urinalysis parameters in rats exposed to sodium selenate or selenite were attributed to reduced water intake and resulting dehydration. This is supported by the observed decreases in water consumption and urine output and increases in urine specific gravity.

Increases in erythrocyte (RBC) counts, hematocrit, and hemoglobin concentration would be consistent with the relative polycythemia of dehydration. In female rats in the sodium selenate study, this relative polycythemia was present at Week 13. In male rats, this was a transient effect that was resolved by the end of the study. The decreases in mean cell volume and mean cell hemoglobin indicate a microcytosis that would be consistent with a relative or absolute iron deficiency or with an abnormality in iron utilization (Jain, 1986). Another possibility is RBC fragmentation. However, there was no morphologic evidence on the blood smears to support this hypothesis. It is possible that an iron deficiency-like anemia occurred but was masked by hemoconcentration as a result of severe dehydration. The microcytosis was a transient effect that was resolved by the end of the study. In the sodium selenite study, these hematology effects were minimal and sporadic.

Serum concentrations of urea nitrogen (UN) and creatinine are traditional screening tests used to evaluate renal function (Ragan, 1989). In the current studies, elevated serum UN in exposed rats indicate an azotemia and suggest a compromised renal function. However, there was no concurrent rise in creatinine levels, and the urine specific gravity was elevated, indicating that the exposed rats were able to concentrate their urine. It is likely that the increased UN values were the result of dehydration. Additionally, the reduced

mean body weights of the exposed rats may suggest an alteration in nutritional status, and altered protein catabolism can result in increased UN concentrations without evidence of renal damage (Finco, 1989).

Increases in ALT and SDH activities suggest a liver effect. The specific activities of ALT and SDH are high in the liver, and increases in the serum activity of these enzymes indicate hepatocellular damage (Boyd, 1983). However, except for minimal focal hepatocellular necrosis observed in a few animals that died, no histopathologic liver lesions related to selenium administration were found. The differences observed between ALT and SDH activities and histopathologic responses may be related to a variety of factors, including mechanisms and rates of injury and repair, organ adaptation, health and nutritional status, age of the animal, and exposure concentration (WHO, 1978; Roe, 1988). Furthermore, changes in cell membrane integrity and altered enzyme synthesis, release, catabolism, inactivation or inhibition, and excretion have all been implicated as effectors of serum enzyme activity in disease (Schmidt and Schmidt, 1987, 1989; Pappas, 1989). Therefore, the increases may not be related to direct hepatocellular damage with leakage of enzymes into the circulation. The large standard error observed at Day 70 for ALT and SDH activities in male rats in the 32 ppm group of the sodium selenite study suggests that the animals were not affected equally.

Elevations of serum bile acid concentrations and alkaline phosphatase and 5′-nucleotidase activities indicate cholestasis. In the sodium selenate study, this effect was transient, involving increases in 5′-nucleotidase activity and bile acid concentration. Decreases in alkaline phosphatase activity occurring on Days 3 and 14 of this study would be consistent with decreased feed intake, as supported by the decreased body weight gains. It has been shown that circulating alkaline phosphatase in the normal rat is primarily of intestinal and bone origin (Bianchi-Bosisio Righetti and Kaplan, 1971), and fasting or feed restriction causes decreases in circulating alkaline phosphatase activity (Jenkins and Robinson, 1975; M. B. Thompson - personal communication). In the sodium selenite study, this cholestatic effect occurred in male and female rats exposed to 32 ppm and was persistent throughout the study.

No biologically significant changes in hematology or clinical chemistry parameters occurred in mice receiving up to 60 ppm sodium selenate or 32 ppm sodium selenite in drinking water for 13 weeks.

The kidney and the reproductive system may have been sites of toxicity of sodium selenate or selenite administration. However, these results may have been confounded by the dehydrated and unthrifty conditions of the animals in which the lesions occurred. The kidney lesions observed in exposed rats consisted of minimal to mild renal papillary degeneration. Possible mechanisms for papillary necrosis include direct cellular injury, reduction of renal papillary blood flow, inhibition of prostaglandin synthesis, and free radical formation (Kinkaid-Smith *et al.*, 1968; Sabatini *et al.*, 1983; Black, 1986; Rubin, 1986).

Studies have shown a relationship between water deprivation and renal papillary necrosis. Drug-induced papillary necrosis in horses required water deprivation (Gunson and Soma, 1983; Maxie, 1993). Dehydration has also been contributory to drug-induced papillary necrosis in cats (Wolf *et al.*, 1991). Papillary necrosis in dogs has resulted from dehydration alone (Maxie, 1993). Renal papillary degeneration in rats has been seen in other NTP studies (NTP, 1993, 1994) in which the drinking water was the route of exposure and water consumption was reduced because of poor palatability (Table 9). One of these chemicals, cupric sulfate, was also studied when administered in feed for 13 weeks. Cupric sulfate did not cause papillary degeneration in rats fed concentrations as high as 8,000 ppm (NTP, 1993). Unlike the minimal to mild papillary lesions seen in the cupric sulfate and *t*-butyl alcohol (NTP, 1994) studies with reduced water consumption (Table 9), a number of rats in the sodium selenate and sodium selenite studies had more severe (moderate to marked) papillary lesions which included necrosis of the interstitial cells and uroepithelium at the tip of the papilla. Because selenium is excreted through the kidney, and based on the occurrence of papillary lesions in exposed rats with moderately decreased water consumption, it is possible that there is some effect of sodium selenate and sodium selenite on the development of papillary lesions. For this effect to be seen, a paired water consumption study designed to eliminate the confounding effect of dehydration would be necessary.

TABLE 9 Incidence and Severity of Renal Papillary Lesions in F344/N Rats in NTP Drinking Water Studies

Concentration (ppm)	Papillary Lesion Incidence (Severity)	Water Consumption (mL/day)
2-WEEK CUPRIC SULFATE STUDY		
Male		
0	None	17.9
300	None	17.3
1,000	None	14.7
3,000	3/5 (minimal)	4.8
10,000	1/5 (minimal)	1.0[1]
Female		
0	None	16.3
300	None	15.3
1,000	None	11.3
3,000	3/5 (minimal)	3.2
10,000	None	0.9[1]
13-WEEK *t*-BUTYL ALCOHOL STUDY		
Male		
0	None	20.6
20,000	None	19.3
40,000	2/10 (minimal), 1/10 (mild)	4.3[2]
Female		
0	None	14.6
20,000	1/10 (minimal, focal)	10.6
40,000	1/10 (minimal), 1/10 (mild)	10.3

[1] All animals died early.
[2] Water consumption at Week 12; for Weeks 1-11, water consumption was 8 to 10 mL/day.

The reports on the induction of kidney lesions by selenium compounds are conflicting. In earlier studies in which rats were administered 10 ppm selenium in feed, minimal renal tubule degeneration was reported (Lillie and Smith, 1940). In later studies, however, no kidney lesions were found in rats fed diets that provided up to 11.2 mg/kg selenium as sodium selenite (Halverson *et al.*, 1966) or 2 mg/L selenium as sodium selenate in drinking water for 35 weeks (Schroeder and Mitchener, 1971). In the NTP studies, kidney lesions occurred in rats given sodium selenate or selenite for 13 weeks. These contrasting results could be due to the different strains of rats (Sprague-Dawley or Long-Evans in earlier studies versus Fischer in NTP studies), the different routes of administration (dosed feed versus dosed water), or the different concentrations of sodium selenate or selenite used in the studies.

Although selenium has been reported to affect bone growth (Harr *et al.*, 1967; Campo and Bielen, 1971), the narrowing of the metaphyseal growth plate in the femur of rats in these studies was not considered to be directly related to the toxicity of selenium. Bone lesions were present only in rats in the sodium selenate study that died weeks before the study ended. Reduction of bone growth was attributed to the progressive body weight loss and inanition secondary to the marked reduction in water and feed consumption.

No organs were identified as sites of the toxicity of sodium selenate or selenite in mice administered up to 60 ppm sodium selenate or 32 ppm sodium selenite.

Results of sperm motility and vaginal cytology evaluations indicate that the reproductive system of male and female rats could be considered sites of sodium selenate and sodium selenite toxicity. Sperm motility was decreased in males receiving 30 ppm sodium selenate, and epididymal sperm concentration was decreased in all groups of males exposed to sodium selenite. The two selenium compounds increased the time females spent in diestrus and decreased the time spent in proestrus and estrus; the time females spent in metestrus was decreased by sodium selenate and increased by sodium selenite. Additionally, atrophic lesions were observed in the organs of the reproductive system in male and female rats administered sodium selenate or selenite. These lesions were due to the debilitated conditions of the animals, as indicated by depressed body weights. Reproductive effects such as unsuccessful matings and reduced numbers of pups in the litters of rats exposed to selenium have been observed previously (Rosenfeld and Beath, 1954). Some of the reproductive effects observed in rats and mice receiving sodium selenate or sodium selenite could be due to the depressed body weights of these animals. Chapin *et al.* (1993a,b) studied the influence of feed restriction and body weight depression on the reproductive performance of rats and mice; a 30% depression in the mean body weight of male CD-1® Swiss mice caused a significant decrease in the numbers of epididymal sperm and spermatids. In female mice, a 30% depression in mean body weight increased the length of the estrous cycle and adversely affected reproductive performance. A 30% mean body weight depression in female Sprague-Dawley rats did not affect fertility but caused decreased ovary weight, transiently increased the estrous cycle length, and caused a 20% decrease in the number of corpora lutea. A similar body weight depression in male Sprague-Dawley rats caused a slight decrease in the percent of motile sperm. The effects observed by Chapin *et al.* required a considerable depression (30%) in body weight. In the NTP studies, an increase in estrous cycle length was observed in rats and mice (sodium selenite study only) at concentrations that caused a less than 10% body weight

depression. Therefore it was concluded that the increase in the length of the estrous cycle observed in female rats and mice was related to chemical administration.

Based on mortality in rats, body weight depression, and renal lesions, sodium selenate and sodium selenite were more toxic to rats than to mice. These chemicals caused increases in estrous cycle length in rats; sodium selenite also caused an increase in estrous cycle length in mice. Based on mortality, body weight depression, decreased water consumption, and renal papillary lesions, the estimated no-observed-adverse-effect level (NOAEL) in rats was 0.4 mg selenium/kg body weight for sodium selenate and for sodium selenite. Based on body weight depression and decreased water consumption, the estimated NOAEL in mice was 0.8 mg selenium/kg body weight for sodium selenate and 0.9 mg selenium/kg body weight for sodium selenite.

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APPENDIX A

Summary of Nonneoplastic Lesions in Rats

Table A1 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate A-2

Table A2 Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate A-5

Table A3 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite A-8

Table A4 Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite A-10

TABLE A1 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate[1]

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
DISPOSITION SUMMARY						
Animals initially in study	10	10	10	10	10	10
Early deaths						
Natural death						6
Moribund sacrifice						4
Survivors						
Terminal sacrifice	10	10	10	10	10	
Animals examined microscopically	10	10	10	10	10	10
Alimentary System						
Liver	(10)	(6)	(8)	(10)	(10)	(10)
Fatty change				1 (10%)	1 (10%)	
Hematopoietic cell proliferation, focal	4 (40%)	2 (33%)	4 (50%)	2 (20%)	4 (40%)	
Hepatodiaphragmatic nodule	2 (20%)	3 (50%)	3 (38%)		1 (10%)	
Inflammation, focal		1 (17%)	1 (13%)		1 (10%)	
Necrosis, multifocal					3 (30%)	2 (20%)
Pancreas	(10)				(10)	(9)
Atrophy						6 (67%)
Salivary glands	(10)				(9)	(9)
Atrophy						8 (89%)
Stomach, forestomach	(10)		(3)	(1)	(10)	(10)
Mucosa, erosion, focal			2 (67%)	1 (100%)		
Mucosa, hyperplasia				1 (100%)		
Mucosa, ulcer, focal			1 (33%)			
Stomach, glandular	(10)				(10)	(10)
Mucosa, hemorrhage, focal						2 (20%)
Submucosa, hemorrhage, focal						1 (10%)
Cardiovascular System						
Heart	(10)				(10)	(10)
Cardiomyopathy	5 (50%)				3 (30%)	
Endocrine System						
Adrenal cortex	(10)				(10)	(10)
Hyperplasia						2 (20%)
Vacuolization cytoplasmic	10 (100%)				8 (80%)	
General Body System						
None						

TABLE A1 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate (continued)

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
Genital System						
Epididymis	(10)				(10)	(10)
Lumen, degeneration						9 (90%)
Penis						(1)
Hemorrhage, focal						1 (100%)
Preputial gland	(10)	(1)			(10)	(10)
Atrophy						9 (90%)
Seminal vesicle	(10)				(10)	(10)
Atrophy						10 (100%)
Testes	(10)				(10)	(10)
Germinal epithelium, degeneration						4 (40%)
Hematopoietic System						
Bone marrow	(10)			(10)	(10)	(10)
Femoral, depletion cellular					9 (90%)	9 (90%)
Femoral, pigmentation, hemosiderin						5 (50%)
Lymph node, mandibular	(10)	(10)	(10)	(10)	(9)	(9)
Congestion	3 (30%)	1 (10%)	2 (20%)	2 (20%)		
Hyperplasia, lymphoid	1 (10%)		1 (10%)		1 (11%)	
Lymphocyte, depletion cellular						7 (78%)
Lymph node, mesenteric	(10)	(10)	(10)	(10)	(10)	(6)
Congestion					1 (10%)	
Hyperplasia, lymphoid			1 (10%)			
Lymphocyte, depletion cellular						5 (83%)
Spleen	(10)				(10)	(10)
Lymphocyte, depletion cellular						7 (70%)
Thymus	(10)				(10)	(8)
Depletion lymphoid						8 (100%)
Integumentary System						
None						
Musculoskeletal System						
Bone	(10)			(10)	(10)	(10)
Distal, femur, metaphysis, atrophy					3 (30%)	9 (90%)
Nervous System						
None						
Respiratory System						
None						

TABLE A1 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate (continued)

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
Special Senses System						
Eye						(2)
Infiltration cellular, polymorphonuclear						1 (50%)
Lens, cataract						1 (50%)
Urinary System						
Kidney	(10)	(10)	(10)	(10)	(10)	(10)
Mineralization, focal						1 (10%)
Papilla, degeneration			3 (100%)	6 (100%)	6 (60%)	7 (70%)
Renal tubule, dilatation, focal	1 (10%)				1 (10%)	2 (20%)
Urinary bladder	(10)		(1)		(10)	(10)
Calculus gross observation			1 (100%)			
Calculus microscopic observation only			1 (100%)			

[1] Number of animals examined microscopically at site and number of animals with lesion.

TABLE A2 Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate[1]

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
DISPOSITION SUMMARY						
Animals initially in study	10	10	10	10	10	10
Early deaths						
Natural death						9
Moribund sacrifice						1
Survivors						
Terminal sacrifice	10	10	10	10	10	
Animals examined microscopically	10	10	10	10	10	10
Alimentary System						
Liver	(10)	(8)	(7)	(10)	(10)	(10)
Hematopoietic cell proliferation, focal	7 (70%)	5 (63%)	3 (43%)	2 (20%)	3 (30%)	
Hepatodiaphragmatic nodule		3 (38%)	5 (71%)	1 (10%)	1 (10%)	
Inflammation, focal		2 (25%)		1 (10%)	4 (40%)	
Necrosis, multifocal					2 (20%)	9 (90%)
Hepatocyte, inclusion body intracytoplasmic, focal					1 (10%)	
Mesentery	(1)		(1)			
Fat, necrosis	1 (100%)		1 (100%)			
Pancreas	(10)				(10)	(10)
Atrophy						8 (80%)
Salivary glands	(10)				(10)	(9)
Atrophy						9 (100%)
Stomach, forestomach	(10)	(1)	(1)		(10)	(10)
Submucosa, ectopic tissue, focal		1 (100%)				
Stomach, glandular	(10)				(10)	(10)
Mucosa, hemorrhage, focal						7 (70%)
Cardiovascular System						
None						
Endocrine System						
Pituitary gland	(10)				(10)	(9)
Pars nervosa, developmental malformation					1 (10%)	
Thyroid gland	(10)				(10)	(10)
Ectopic thymus	1 (10%)					
General Body System						
None						

TABLE A2 Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate (continued)

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
Genital System						
Clitoral gland	(10)		(1)	(1)	(10)	(10)
Atrophy						10 (100%)
Ovary	(10)	(1)		(10)	(10)	(9)
Cyst	2 (20%)	1 (100%)		2 (20%)		
Interstitium, atrophy					5 (50%)	9 (100%)
Uterus	(10)	(2)		(9)	(10)	(10)
Endometrium, atrophy					10 (100%)	6 (60%)
Lumen, dilatation		1 (50%)				
Hematopoietic System						
Bone marrow	(10)		(10)	(10)	(10)	(10)
Femoral, depletion cellular				3 (30%)	10 (100%)	10 (100%)
Femoral, inflammation, focal, subacute			1 (10%)			
Femoral, pigmentation, hemosiderin						3 (30%)
Sternal, depletion cellular					1 (10%)	
Lymph node	(1)			(1)	(1)	
Mediastinal, hyperplasia, lymphoid				1 (100%)		
Pancreatic, hyperplasia, lymphoid	1 (100%)				1 (100%)	
Lymph node, mandibular	(10)	(10)	(10)	(10)	(10)	(9)
Congestion		1 (10%)	1 (10%)			
Hyperplasia, lymphoid				2 (20%)	1 (10%)	
Lymphocyte, depletion cellular						8 (89%)
Lymph node, mesenteric	(10)	(10)	(10)	(10)	(10)	(9)
Hyperplasia, lymphoid				2 (20%)	2 (20%)	
Lymphocyte, depletion cellular						9 (100%)
Spleen	(10)				(10)	(10)
Lymphocyte, depletion cellular						10 (100%)
Thymus	(10)				(10)	(9)
Depletion lymphoid						9 (100%)
Integumentary System						
Mammary gland	(10)				(10)	(6)
Atrophy						6 (100%)
Musculoskeletal System						
Bone	(10)		(10)	(10)	(10)	(10)
Distal, femur, metaphysis, atrophy					9 (90%)	10 (100%)
Sternum, developmental malformation					1 (10%)	
Nervous System						
None						

TABLE A2 Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate (continued)

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
Respiratory System						
Lung	(10)	(2)	(1)		(10)	(10)
Edema						1 (10%)
Inflammation, acute, focal		1 (50%)				
Inflammation, focal, subacute			1 (100%)			
Special Senses System						
None						
Urinary System						
Kidney	(10)	(10)	(10)	(10)	(10)	(10)
Mineralization, focal	9 (90%)				4 (40%)	4 (40%)
Papilla, degeneration	1 (10%)	1 (100%)	5 (100%)	8 (100%)	7 (70%)	6 (60%)

[1] Number of animals examined microscopically at site and number of animals with lesion.

TABLE A3 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite[1]

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
DISPOSITION SUMMARY						
Animals initially in study	10	10	10	10	10	10
Survivors						
Terminal sacrifice	10	10	10	10	10	10
Animals examined microscopically	10	10	10	10	10	10
Alimentary System						
Intestine large, rectum	(10)					(10)
Parasite metazoan						1 (10%)
Liver	(10)	(3)	(3)		(2)	(10)
Fatty change	5 (50%)		3 (100%)			
Hematopoietic cell proliferation, focal	2 (20%)				1 (50%)	2 (20%)
Hepatodiaphragmatic nodule	1 (10%)	3 (100%)	3 (100%)		2 (100%)	
Cardiovascular System						
Heart	(10)					(10)
Cardiomyopathy	7 (70%)					6 (60%)
Endocrine System						
Adrenal cortex	(10)					(10)
Zona fasciculata, vacuolization cytoplasmic	10 (100%)					4 (40%)
Pituitary gland	(10)					(10)
Cyst						1 (10%)
General Body System						
None						
Genital System						
None						
Hematopoietic System						
Lymph node, mandibular	(10)		(10)	(10)	(8)	(10)
Congestion	2 (20%)					2 (20%)
Depletion lymphoid						1 (10%)
Lymph node, mesenteric	(10)		(10)	(10)	(10)	(10)
Congestion						5 (50%)
Pigmentation, hemosiderin	10 (100%)				10 (100%)	10 (100%)
Spleen	(10)		(10)	(10)	(10)	(10)
Pigmentation, hemosiderin	10 (100%)				10 (100%)	10 (100%)
Thymus	(10)		(10)	(10)	(10)	(10)
Congestion					1 (10%)	
Depletion lymphoid						4 (40%)

TABLE A3 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite (continued)

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
Integumentary System						
Skin	(10)	(1)				(10)
Pinna, hyperplasia, focal		1 (100%)				
Musculoskeletal System						
None						
Nervous System						
None						
Respiratory System						
Lung	(10)					(10)
Hemorrhage, focal	2 (20%)					1 (10%)
Inflammation, focal, subacute						1 (10%)
Interstitium, inflammation, chronic, focal	1 (10%)					
Pleura, fibrosis, focal	1 (10%)					
Special Senses System						
None						
Urinary System						
Kidney	(10)	(10)	(10)	(10)	(10)	(10)
Hemorrhage, focal						1 (10%)
Inflammation, focal, subacute						1 (10%)
Papilla, degeneration	1 (10%)		1 (10%)	2 (20%)	5 (50%)	7 (70%)
Renal tubule, dilatation, focal	3 (30%)	3 (30%)	3 (30%)	6 (60%)	2 (20%)	5 (50%)
Renal tubule, regeneration	10 (100%)	9 (90%)	9 (90%)	9 (90%)	10 (100%)	8 (80%)
Urinary bladder	(10)	(1)				(10)
Calculus microscopic observation only		1 (100%)				

[1] Number of animals examined microscopically at site and number of animals with lesion.

TABLE A4 Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite[1]

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
DISPOSITION SUMMARY						
Animals initially in study	10	10	10	10	10	10
Early deaths						
Natural death						1
Moribund sacrifice						1
Survivors						
Terminal sacrifice	10	10	10	10	10	8
Animals examined microscopically	10	10	10	10	10	10
Alimentary System						
Liver	(10)	(1)	(3)	(10)	(10)	(10)
Atrophy						10 (100%)
Hematopoietic cell proliferation, focal	6 (60%)		1 (33%)	3 (30%)	3 (30%)	5 (50%)
Hepatodiaphragmatic nodule	2 (20%)	1 (100%)	3 (100%)	2 (20%)		
Necrosis, focal						1 (10%)
Kupffer cell, pigmentation, hemosiderin						6 (60%)
Pancreas	(10)				(10)	(10)
Atrophy						10 (100%)
Salivary glands	(10)			(10)	(10)	(10)
Atrophy					1 (10%)	10 (100%)
Stomach, glandular	(10)					(10)
Submucosa, edema						1 (10%)
Cardiovascular System						
Heart	(10)					(10)
Cardiomyopathy	2 (20%)					
Endocrine System						
Adrenal cortex	(10)					(10)
Hemorrhage						1 (10%)
General Body System						
None						
Genital System						
Clitoral gland	(10)				(10)	(9)
Atrophy						9 (100%)
Inflammation, focal, subacute					1 (10%)	
Ovary	(9)		(1)	(2)	(1)	(10)
Cyst	1 (11%)		1 (100%)	2 (100%)	1 (100%)	
Uterus	(10)		(2)	(10)	(10)	(10)
Endometrium, atrophy					2 (20%)	9 (90%)
Lumen, dilatation	1 (10%)		2 (100%)	4 (40%)	2 (20%)	
Vagina	(10)		(10)	(10)	(10)	(10)
Lumen, concretion, focal				1 (10%)		
Lumen, dilatation, focal				1 (10%)		

TABLE A4 Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite (continued)

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
Hematopoietic System						
Bone marrow	(10)				(10)	(10)
Pigmentation, hemosiderin						2 (20%)
Femoral, depletion cellular						10 (100%)
Lymph node, mandibular	(10)	(1)	(1)		(10)	(10)
Depletion lymphoid						2 (20%)
Hyperplasia, lymphoid			1 (100%)			
Lymph node, mesenteric	(10)	(1)	(1)		(10)	(10)
Congestion						2 (20%)
Depletion lymphoid						1 (10%)
Hyperplasia, lymphoid		1 (100%)				
Pigmentation, hemosiderin	10 (100%)				10 (100%)	10 (100%)
Spleen	(10)				(10)	(10)
Depletion lymphoid						5 (50%)
Fibrosis, focal					1 (10%)	
Pigmentation, hemosiderin	10 (100%)				10 (100%)	10 (100%)
Thymus	(10)				(10)	(7)
Depletion lymphoid						6 (86%)
Integumentary System						
Mammary gland	(10)			(8)	(10)	(9)
Atrophy					4 (40%)	8 (89%)
Musculoskeletal System						
Bone	(10)				(10)	(10)
Distal, femur, metaphysis, atrophy						10
(100%)						
Nervous System						
None						
Respiratory System						
Lung	(10)	(1)				(10)
Hemorrhage, focal	1 (10%)					1 (10%)
Inflammation, focal, subacute	3 (30%)					
Mineralization, focal		1 (100%)				
Special Senses System						
None						
Urinary System						
Kidney	(10)	(10)	(10)	(10)	(10)	(10)
Inflammation, focal, subacute					1 (10%)	
Mineralization, focal	10 (100%)	10 (100%)	10 (100%)	10 (100%)	10 (100%)	8 (80%)
Papilla, degeneration		1 (10%)	3 (30%)	6 (60%)	8 (80%)	9 (90%)
Renal tubule, dilatation, focal			1 (10%)	1 (10%)		4 (40%)

[1] Number of animals examined microscopically at site and number of animals with lesion.

APPENDIX B

Summary of Nonneoplastic Lesions in Mice

Table B1 Summary of the Incidence of Nonneoplastic Lesions in Male B6C3F$_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate B-2

Table B2 Summary of the Incidence of Nonneoplastic Lesions in Female B6C3F$_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate B-4

Table B3 Summary of the Incidence of Nonneoplastic Lesions in Male B6C3F$_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite B-6

Table B4 Summary of the Incidence of Nonneoplastic Lesions in Female B6C3F$_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite B-8

TABLE B1 Summary of the Incidence of Nonneoplastic Lesions in Male $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate[1]

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
DISPOSITION SUMMARY						
Animals initially in study	10	10	10	10	10	10
Survivors						
Terminal sacrifice	10	10	10	10	10	10
Animals examined microscopically	10	7	8	7	7	10
Alimentary System						
Liver	(10)					(10)
Hematopoietic cell proliferation, focal	2 (20%)					3 (30%)
Mesentery		(1)				
Necrosis		1 (100%)				
Fat, developmental malformation		1 (100%)				
Cardiovascular System						
None						
Endocrine System						
None						
General Body System						
None						
Genital System						
None						
Hematopoietic System						
Lymph node	(10)					(10)
Lymphocyte, depletion cellular						1 (10%)
Spleen	(10)	(1)				(10)
Pigmentation, hemosiderin		1 (100%)				
Integumentary System						
None						
Musculoskeletal System						
None						
Nervous System						
None						

TABLE B1 Summary of the Incidence of Nonneoplastic Lesions in Male B6C3F1 Mice in the 13-Week Drinking Water Study of Sodium Selenate (continued)

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
Respiratory System						
None						
Special Senses System						
Harderian gland				(1)		
Hyperplasia				1 (100%)		
Urinary System						
Urinary bladder	(10)	(2)	(1)	(2)		(10)
Calculus gross observation		2 (100%)	1 (100%)	1 (50%)		2 (20%)
Calculus microscopic observation only	2 (20%)	2 (100%)	1 (100%)	1 (50%)		4 (40%)

[1] Number of animals examined microscopically at site and number of animals with lesion.

TABLE B2 Summary of the Incidence of Nonneoplastic Lesions in Female B6C3F$_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate[1]

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
DISPOSITION SUMMARY						
Animals initially in study	10	10	10	10	10	10
Survivors						
Terminal sacrifice	10	10	10	10	10	10
Animals examined microscopically	10	8	7	3	10	10
Alimentary System						
Liver	(10)		(1)		(10)	(10)
Developmental malformation	1 (10%)		1 (100%)			
Hematopoietic cell proliferation, focal	5 (50%)				3 (30%)	4 (40%)
Salivary glands	(10)				(10)	(10)
Inflammation, focal, subacute	2 (20%)					3 (30%)
Cardiovascular System						
None						
Endocrine System						
None						
General Body System						
None						
Genital System						
Ovary	(9)	(1)				(10)
Pigmentation, melanin		1 (100%)				
Uterus	(10)			(1)	(10)	(10)
Endometrium, edema	1 (10%)				1 (10%)	3 (30%)
Lumen, dilatation	1 (10%)				1 (10%)	
Hematopoietic System						
Lymph node, mandibular	(10)					(10)
Hyperplasia, lymphoid						1 (10%)
Lymph node, mesenteric	(10)					(10)
Lymphocyte, depletion cellular						1 (10%)
Spleen	(10)					(10)
Pigmentation, hemosiderin	1 (10%)					
Integumentary System						
None						

TABLE B2 Summary of the Incidence of Nonneoplastic Lesions in Female $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate (continued)

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
Musculoskeletal System						
None						
Nervous System						
None						
Respiratory System						
Lung	(10)	(1)				(10)
Congestion		1 (100%)				
Hemorrhage, focal	1 (10%)					2 (20%)
Special Senses System						
None						
Urinary System						
Kidney	(10)				(10)	(10)
Inflammation, focal, subacute						3 (30%)
Inflammation, subacute	3 (30%)					

[1] Number of animals examined microscopically at site and number of animals with lesion.

TABLE B3 Summary of the Incidence of Nonneoplastic Lesions in Male B6C3F$_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite[1]

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
DISPOSITION SUMMARY						
Animals initially in study	10	10	10	10	10	10
Survivors						
Terminal sacrifice	10	10	10	10	10	10
Animals examined microscopically	10					10
Alimentary System						
Liver	(10)					(10)
Hematopoietic cell proliferation	1 (10%)					1 (10%)
Cardiovascular System						
None						
Endocrine System						
Parathyroid gland	(8)					(5)
Unilateral, cyst	1 (13%)					
Thyroid gland	(10)					(10)
Inflammation, focal, subacute						1 (10%)
General Body System						
None						
Genital System						
None						
Hematopoietic System						
Bone marrow	(10)					(10)
Pigmentation, hemosiderin						1 (10%)
Integumentary System						
None						
Musculoskeletal System						
None						
Nervous System						
None						

TABLE B3 Summary of the Incidence of Nonneoplastic Lesions in Male $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite (continued)

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
Respiratory System						
Lung	(10)					(10)
Hemorrhage, focal	1 (10%)					5 (50%)
Special Senses System						
None						
Urinary System						
Kidney	(10)					(10)
Pelvis, inflammation, focal						1 (10%)
Urinary bladder	(10)					(10)
Lumen, concretion	1 (10%)					

[1] Number of animals examined microscopically at site and number of animals with lesion.

TABLE B4 Summary of the Incidence of Nonneoplastic Lesions in Female B6C3F$_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite[1]

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
DISPOSITION SUMMARY						
Animals initially in study	10	10	10	10	10	10
Survivors						
Terminal sacrifice	10	10	10	10	10	10
Animals examined microscopically	10		2	1		10
Alimentary System						
Liver	(10)		(1)			(10)
Hematopoietic cell proliferation	5 (50%)		1 (100%)			4 (40%)
Hepatodiaphragmatic nodule			1 (100%)			
Salivary glands	(10)					(10)
Inflammation, subacute	2 (20%)					2 (20%)
Cardiovascular System						
None						
Endocrine System						
None						
General Body System						
None						
Genital System						
Ovary	(10)		(1)			(10)
Cyst			1 (100%)			
Uterus	(10)			(1)		(10)
Endometrium, hyperplasia				1 (100%)		
Lumen, dilatation	1 (10%)					
Hematopoietic System						
None						
Integumentary System						
None						
Musculoskeletal System						
None						
Nervous System						
None						

TABLE B4 Summary of the Incidence of Nonneoplastic Lesions in Female $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite (continued)

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
Respiratory System						
Lung	(10)					(10)
Hemorrhage, focal	1 (10%)					3 (30%)
Special Senses System						
None						
Urinary System						
None						

[1] Number of animals examined microscopically at site and number of animals with lesion.

APPENDIX C

Organ Weights and Organ-Weight-to-Body-Weight Ratios

Table C1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate C-2

Table C2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite C-3

Table C3 Organ Weights and Organ-Weight-to-Body-Weight Ratios for $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate C-4

Table C4 Organ Weights and Organ-Weight-to-Body-Weight Ratios for $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite C-5

TABLE C1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate[1]

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
MALE						
n	10	10	10	10	10	0
Necropsy body wt	319 ± 4	309 ± 4	303 ± 4*	290 ± 6**	246 ± 7**	–
Brain						
Absolute	1.818 ± 0.068	1.898 ± 0.017	1.866 ± 0.018	1.847 ± 0.017	1.731 ± 0.062	–
Relative	5.70 ± 0.23	6.14 ± 0.07	6.17 ± 0.08	6.39 ± 0.10*	7.09 ± 0.33**	–
Heart						
Absolute	0.933 ± 0.048	0.937 ± 0.018	0.888 ± 0.017	0.873 ± 0.042	0.759 ± 0.016**	–
Relative	2.92 ± 0.15	3.03 ± 0.07	2.93 ± 0.02	3.00 ± 0.10	3.10 ± 0.08	–
Right kidney						
Absolute	1.095 ± 0.016	1.078 ± 0.018	1.081 ± 0.026	1.023 ± 0.024*	0.984 ± 0.031**	–
Relative	3.43 ± 0.06	3.49 ± 0.05	3.57 ± 0.08	3.53 ± 0.04	4.00 ± 0.08**	–
Liver						
Absolute	12.062 ± 0.250	10.941 ± 0.347	11.038 ± 0.494	11.379 ± 0.414	9.481 ± 0.367**	–
Relative	37.76 ± 0.59	35.30 ± 0.76	36.37 ± 1.39	39.15 ± 0.66	38.46 ± 0.58	–
Lungs						
Absolute	1.777 ± 0.073	1.717 ± 0.043	1.775 ± 0.036	1.766 ± 0.086	1.430 ± 0.081**	–
Relative	5.55 ± 0.19	5.57 ± 0.19	5.86 ± 0.10	6.07 ± 0.21	5.82 ± 0.29	–
Right testis						
Absolute	1.444 ± 0.062	1.423 ± 0.018	1.393 ± 0.022	1.402 ± 0.027	1.363 ± 0.029	–
Relative	4.53 ± 0.21	4.61 ± 0.07	4.60 ± 0.07	4.84 ± 0.05	5.56 ± 0.13**	–
Thymus						
Absolute	0.268 ± 0.010	0.261 ± 0.025	0.249 ± 0.015	0.230 ± 0.014	0.220 ± 0.015	–
Relative	0.84 ± 0.04	0.85 ± 0.08	0.83 ± 0.05	0.80 ± 0.06	0.89 ± 0.05	–
FEMALE						
n	10	10	10	10	10	0
Necropsy body wt	199 ± 5	195 ± 4	192 ± 3	182 ± 2**	141 ± 4**	–
Brain						
Absolute	1.726 ± 0.021	1.701 ± 0.052	1.664 ± 0.058	1.671 ± 0.066	1.649 ± 0.051	–
Relative	8.74 ± 0.18	8.77 ± 0.35	8.69 ± 0.33	9.20 ± 0.35	11.77 ± 0.50**	–
Heart						
Absolute	0.592 ± 0.022	0.658 ± 0.035	0.601 ± 0.012	0.571 ± 0.030	0.458 ± 0.013**	–
Relative	2.98 ± 0.09	3.37 ± 0.13	3.14 ± 0.06	3.14 ± 0.16	3.24 ± 0.06	–
Right kidney						
Absolute	0.700 ± 0.010	0.684 ± 0.010	0.703 ± 0.012	0.720 ± 0.019	0.658 ± 0.015	–
Relative	3.54 ± 0.08	3.52 ± 0.06	3.67 ± 0.07	3.96 ± 0.09**	4.67 ± 0.08**	–
Liver						
Absolute	6.219 ± 0.152	6.377 ± 0.222	6.339 ± 0.141	6.241 ± 0.214	4.478 ± 0.175**	–
Relative	31.41 ± 0.70	32.67 ± 0.75	33.05 ± 0.62	34.35 ± 1.06*	31.65 ± 0.62	–
Lungs						
Absolute	1.192 ± 0.039	1.168 ± 0.045	1.262 ± 0.069	1.218 ± 0.059	1.055 ± 0.035	–
Relative	6.05 ± 0.25	6.01 ± 0.25	6.56 ± 0.29	6.70 ± 0.31	7.50 ± 0.25**	–
Thymus						
Absolute	0.217 ± 0.006	0.256 ± 0.011	0.236 ± 0.008	0.223 ± 0.012	0.161 ± 0.007**	–
Relative	1.10 ± 0.04	1.32 ± 0.06*	1.23 ± 0.04	1.23 ± 0.06	1.14 ± 0.04	–

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

TABLE C2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite[1]

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
MALE						
n	10	10	10	10	10	10
Necropsy body wt	355 ± 6	346 ± 5	346 ± 4	337 ± 4	323 ± 8**	230 ± 15**
Brain						
Absolute	1.991 ± 0.016	2.007 ± 0.024	1.942 ± 0.015	1.962 ± 0.013	1.939 ± 0.016	1.843 ± 0.031**
Relative	5.62 ± 0.09	5.80 ± 0.07	5.62 ± 0.10	5.82 ± 0.04	6.03 ± 0.14	8.36 ± 0.58**
Heart						
Absolute	1.137 ± 0.044	1.115 ± 0.035	1.066 ± 0.028	1.089 ± 0.032	1.069 ± 0.042	0.790 ± 0.037**
Relative	3.20 ± 0.08	3.22 ± 0.08	3.08 ± 0.09	3.23 ± 0.09	3.31 ± 0.09	3.52 ± 0.18
Right kidney						
Absolute	1.245 ± 0.020	1.299 ± 0.030	1.257 ± 0.035	1.221 ± 0.031	1.239 ± 0.047	1.104 ± 0.062*
Relative	3.51 ± 0.05	3.75 ± 0.06	3.63 ± 0.08	3.62 ± 0.06	3.83 ± 0.06*	4.89 ± 0.21**
Liver						
Absolute	13.586 ± 0.432	13.152 ± 0.376	12.761 ± 0.305	13.235 ± 0.394	13.169 ± 0.527	8.365 ± 0.934**
Relative	38.23 ± 0.71	37.95 ± 0.72	36.85 ± 0.73	39.19 ± 0.82	40.65 ± 0.74	35.53 ± 2.13
Lungs						
Absolute	1.875 ± 0.096	1.839 ± 0.055	1.706 ± 0.135	1.810 ± 0.079	1.910 ± 0.104	1.755 ± 0.201
Relative	5.27 ± 0.22	5.32 ± 0.16	4.96 ± 0.43	5.36 ± 0.20	5.91 ± 0.28	7.88 ± 1.02**
Right testis						
Absolute	1.490 ± 0.022	1.497 ± 0.020	1.480 ± 0.025	1.480 ± 0.013	1.472 ± 0.024	1.354 ± 0.042**
Relative	4.21 ± 0.07	4.33 ± 0.05	4.28 ± 0.07	4.39 ± 0.02	4.57 ± 0.07	6.09 ± 0.35**
Thymus						
Absolute	0.353 ± 0.028	0.325 ± 0.015	0.345 ± 0.029	0.335 ± 0.024	0.306 ± 0.023	0.180 ± 0.025**
Relative	0.99 ± 0.08	0.94 ± 0.05	1.00 ± 0.08	1.00 ± 0.08	0.95 ± 0.06	0.76 ± 0.08*
FEMALE						
n	10	10	10	10	10	8
Necropsy body wt	198 ± 3	207 ± 5	198 ± 3	196 ± 3	189 ± 2	92 ± 6**
Brain						
Absolute	1.785 ± 0.014	1.660 ± 0.073	1.695 ± 0.070	1.780 ± 0.009	1.724 ± 0.054	1.553 ± 0.064**
Relative	9.04 ± 0.14	8.06 ± 0.40	8.56 ± 0.33	9.08 ± 0.16	9.15 ± 0.28	17.42 ± 1.32**
Heart						
Absolute	0.699 ± 0.027	0.721 ± 0.033	0.634 ± 0.029	0.649 ± 0.019	0.628 ± 0.019	0.350 ± 0.015**
Relative	3.53 ± 0.13	3.48 ± 0.12	3.20 ± 0.13	3.30 ± 0.08	3.33 ± 0.08	3.82 ± 0.10
Right kidney						
Absolute	0.633 ± 0.023	0.709 ± 0.022	0.677 ± 0.024	0.695 ± 0.020	0.706 ± 0.018	0.545 ± 0.026*
Relative	3.20 ± 0.10	3.43 ± 0.06	3.41 ± 0.09	3.53 ± 0.08	3.74 ± 0.08**	6.00 ± 0.30**
Liver						
Absolute	5.954 ± 0.145	6.471 ± 0.180	5.901 ± 0.163	5.684 ± 0.275	5.975 ± 0.126	3.058 ± 0.235**
Relative	30.07 ± 0.44	31.28 ± 0.48	29.79 ± 0.49	28.85 ± 1.12	31.68 ± 0.45	33.02 ± 1.13**
Lungs						
Absolute	1.116 ± 0.045	1.164 ± 0.049	1.186 ± 0.034	1.091 ± 0.033	1.124 ± 0.051	0.867 ± 0.059**
Relative	5.65 ± 0.24	5.65 ± 0.26	6.01 ± 0.20	5.55 ± 0.15	5.95 ± 0.23	9.47 ± 0.60**
Thymus						
Absolute	0.239 ± 0.011	0.255 ± 0.013	0.239 ± 0.011	0.249 ± 0.010	0.225 ± 0.011	0.052 ± 0.012**
Relative	1.21 ± 0.06	1.24 ± 0.06	1.21 ± 0.05	1.27 ± 0.05	1.19 ± 0.06	0.54 ± 0.08**

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

TABLE C3 Organ Weights and Organ-Weight-to-Body-Weight Ratios for $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate[1]

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
MALE						
n	10	10	10	10	10	10
Necropsy body wt	39.4 ± 1.0	38.4 ± 0.9	38.9 ± 0.9	36.6 ± 0.7*	33.9 ± 0.6**	30.1 ± 0.6**
Brain						
Absolute	0.430 ± 0.004	0.427 ± 0.014	0.440 ± 0.007	0.431 ± 0.004	0.420 ± 0.012	0.428 ± 0.005
Relative	10.95 ± 0.22	11.19 ± 0.48	11.34 ± 0.25	11.83 ± 0.25	12.42 ± 0.45**	14.25 ± 0.26**
Heart						
Absolute	0.154 ± 0.005	0.164 ± 0.008	0.153 ± 0.005	0.157 ± 0.006	0.146 ± 0.006	0.140 ± 0.007
Relative	3.91 ± 0.11	4.27 ± 0.19	3.93 ± 0.08	4.32 ± 0.16	4.30 ± 0.13	4.64 ± 0.22**
Right kidney						
Absolute	0.278 ± 0.013	0.290 ± 0.007	0.295 ± 0.007	0.295 ± 0.008	0.288 ± 0.003	0.283 ± 0.009
Relative	7.03 ± 0.24	7.54 ± 0.10*	7.60 ± 0.21*	8.07 ± 0.12**	8.51 ± 0.13**	9.37 ± 0.14**
Liver						
Absolute	1.599 ± 0.065	1.586 ± 0.061	1.569 ± 0.054	1.537 ± 0.041	1.453 ± 0.040	1.360 ± 0.037**
Relative	40.63 ± 1.41	41.38 ± 1.53	40.32 ± 1.08	42.03 ± 0.92	42.82 ± 0.79	45.17 ± 0.80**
Lungs						
Absolute	0.333 ± 0.018	0.283 ± 0.018	0.335 ± 0.024	0.312 ± 0.015	0.307 ± 0.011	0.261 ± 0.016**
Relative	8.46 ± 0.44	7.41 ± 0.48	8.65 ± 0.63	8.51 ± 0.32	9.06 ± 0.34	8.67 ± 0.51
Right testis						
Absolute	0.115 ± 0.004	0.118 ± 0.006	0.124 ± 0.004	0.119 ± 0.003	0.120 ± 0.002	0.113 ± 0.002
Relative	2.92 ± 0.10	3.07 ± 0.12	3.19 ± 0.11	3.25 ± 0.09*	3.53 ± 0.05**	3.77 ± 0.09**
Thymus						
Absolute	0.048 ± 0.003	0.043 ± 0.003	0.042 ± 0.004	0.049 ± 0.004	0.040 ± 0.004	0.044 ± 0.003
Relative	1.23 ± 0.08	1.12 ± 0.09	1.08 ± 0.10	1.34 ± 0.12	1.20 ± 0.11	1.45 ± 0.08
FEMALE						
n	10	10	10	10	10	10
Necropsy body wt	30.7 ± 0.7	29.5 ± 0.7	32.3 ± 0.6	28.5 ± 0.8*	25.2 ± 0.4**	23.8 ± 0.6**
Brain						
Absolute	0.451 ± 0.005	0.444 ± 0.010	0.449 ± 0.007	0.455 ± 0.006	0.433 ± 0.006	0.426 ± 0.007*
Relative	14.74 ± 0.34	15.14 ± 0.45	13.94 ± 0.31	16.09 ± 0.44**	17.20 ± 0.23**	17.95 ± 0.28**
Heart						
Absolute	0.119 ± 0.005	0.122 ± 0.004	0.127 ± 0.004	0.125 ± 0.004	0.113 ± 0.003	0.115 ± 0.003
Relative	3.89 ± 0.15	4.15 ± 0.13	3.92 ± 0.12	4.41 ± 0.11**	4.50 ± 0.11**	4.85 ± 0.10**
Right kidney						
Absolute	0.185 ± 0.010	0.203 ± 0.005	0.211 ± 0.006*	0.203 ± 0.004	0.194 ± 0.005	0.181 ± 0.009
Relative	6.05 ± 0.36	6.90 ± 0.19*	6.55 ± 0.18	7.17 ± 0.10**	7.70 ± 0.18**	7.61 ± 0.30**
Liver						
Absolute	1.242 ± 0.065	1.249 ± 0.044	1.245 ± 0.050	1.217 ± 0.040	1.023 ± 0.038**	1.031 ± 0.030**
Relative	40.63 ± 2.24	42.51 ± 1.44	38.50 ± 1.19	42.83 ± 1.18	40.64 ± 1.43	43.35 ± 0.72
Lungs						
Absolute	0.356 ± 0.021	0.347 ± 0.022	0.344 ± 0.019	0.332 ± 0.017	0.261 ± 0.011**	0.276 ± 0.018**
Relative	11.57 ± 0.65	11.81 ± 0.75	10.68 ± 0.61	11.71 ± 0.59	10.39 ± 0.44	11.56 ± 0.62
Thymus						
Absolute	0.048 ± 0.003	0.051 ± 0.003	0.057 ± 0.004	0.054 ± 0.004	0.043 ± 0.003	0.040 ± 0.004
Relative	1.57 ± 0.10	1.74 ± 0.09	1.76 ± 0.11	1.91 ± 0.13	1.70 ± 0.12	1.70 ± 0.17

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

TABLE C4 Organ Weights and Organ-Weight-to-Body-Weight Ratios for $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite[1]

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
MALE						
n	10	10	10	10	10	10
Necropsy body wt	40.8 ± 0.7	40.1 ± 0.9	40.8 ± 0.9	39.5 ± 0.9	37.7 ± 1.2*	34.6 ± 0.6**
Brain						
Absolute	0.438 ± 0.003	0.426 ± 0.005	0.436 ± 0.003	0.431 ± 0.006	0.427 ± 0.005	0.433 ± 0.005
Relative	10.77 ± 0.20	10.67 ± 0.25	10.76 ± 0.25	10.96 ± 0.21	11.41 ± 0.36	12.55 ± 0.15**
Heart						
Absolute	0.153 ± 0.005	0.158 ± 0.008	0.155 ± 0.006	0.144 ± 0.003	0.143 ± 0.006	0.155 ± 0.005
Relative	3.75 ± 0.13	3.93 ± 0.15	3.79 ± 0.09	3.66 ± 0.09	3.80 ± 0.17	4.48 ± 0.11**
Right kidney						
Absolute	0.274 ± 0.010	0.289 ± 0.009	0.287 ± 0.006	0.281 ± 0.006	0.299 ± 0.010	0.298 ± 0.006
Relative	6.70 ± 0.21	7.23 ± 0.23	7.06 ± 0.13	7.14 ± 0.15	7.94 ± 0.12**	8.62 ± 0.15**
Liver						
Absolute	1.576 ± 0.046	1.616 ± 0.086	1.582 ± 0.059	1.558 ± 0.049	1.465 ± 0.048	1.456 ± 0.053
Relative	38.69 ± 1.10	40.15 ± 1.54	38.80 ± 1.10	39.48 ± 0.83	38.95 ± 1.10	42.18 ± 1.52
Lungs						
Absolute	0.271 ± 0.019	0.248 ± 0.011	0.264 ± 0.017	0.308 ± 0.031	0.280 ± 0.012	0.264 ± 0.019
Relative	6.66 ± 0.45	6.21 ± 0.28	6.53 ± 0.49	7.82 ± 0.77	7.42 ± 0.21	7.69 ± 0.66
Right testis						
Absolute	0.122 ± 0.002	0.115 ± 0.003	0.109 ± 0.008	0.121 ± 0.003	0.120 ± 0.003	0.121 ± 0.002
Relative	2.99 ± 0.06	2.89 ± 0.08	2.68 ± 0.19	3.06 ± 0.06	3.22 ± 0.12	3.50 ± 0.07**
Thymus						
Absolute	0.052 ± 0.007	0.053 ± 0.003	0.059 ± 0.004	0.053 ± 0.004	0.052 ± 0.005	0.050 ± 0.004
Relative	1.28 ± 0.17	1.32 ± 0.08	1.44 ± 0.08	1.35 ± 0.13	1.35 ± 0.09	1.44 ± 0.10
FEMALE						
n	10	10	10	10	10	10
Necropsy body wt	31.5 ± 1.4	30.4 ± 1.1	30.9 ± 0.5	29.9 ± 0.5	29.2 ± 1.0	25.3 ± 0.5**
Brain						
Absolute	0.442 ± 0.005	0.442 ± 0.005	0.456 ± 0.007	0.431 ± 0.016	0.439 ± 0.005	0.441 ± 0.004
Relative	14.25 ± 0.59	14.71 ± 0.60	14.78 ± 0.33	14.44 ± 0.58	15.18 ± 0.41	17.48 ± 0.30**
Heart						
Absolute	0.120 ± 0.003	0.120 ± 0.005	0.127 ± 0.002	0.118 ± 0.004	0.115 ± 0.002	0.111 ± 0.004
Relative	3.85 ± 0.13	3.95 ± 0.08	4.11 ± 0.11	3.97 ± 0.16	3.99 ± 0.12	4.38 ± 0.11**
Right kidney						
Absolute	0.180 ± 0.005	0.170 ± 0.011	0.196 ± 0.006	0.179 ± 0.006	0.183 ± 0.005	0.185 ± 0.004
Relative	5.77 ± 0.15	5.62 ± 0.32	6.34 ± 0.16	6.00 ± 0.21	6.31 ± 0.18	7.31 ± 0.06**
Liver						
Absolute	1.229 ± 0.047	1.222 ± 0.057	1.275 ± 0.080	1.190 ± 0.035	1.100 ± 0.056	1.040 ± 0.021*
Relative	39.22 ± 0.80	40.08 ± 0.85	41.03 ± 2.11	40.03 ± 1.73	37.65 ± 1.40	41.17 ± 1.00
Lungs						
Absolute	0.248 ± 0.012	0.274 ± 0.019	0.257 ± 0.014	0.248 ± 0.016	0.224 ± 0.014	0.222 ± 0.009
Relative	8.01 ± 0.55	9.04 ± 0.63	8.27 ± 0.35	8.25 ± 0.43	7.67 ± 0.41	8.74 ± 0.25
Thymus						
Absolute	0.057 ± 0.004	0.053 ± 0.004	0.056 ± 0.004	0.057 ± 0.004	0.060 ± 0.003	0.052 ± 0.004
Relative	1.81 ± 0.09	1.74 ± 0.13	1.82 ± 0.13	1.90 ± 0.14	2.06 ± 0.13	2.06 ± 0.18

[1] Organ weights and body weights are given in grams; relative organ weights (organ-weight-to-body-weight ratios) are given as mg organ weight/g body weight (mean ± standard error).

* Significantly different ($P \leq 0.05$) from the control group by Williams' test.

** Significantly different ($P \leq 0.01$) from the control group by Williams' test.

APPENDIX D

Hematology, Clinical Chemistry, and Urinalysis Results

Table D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate D-2

Table D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite D-8

Table D3 Hematology and Clinical Chemistry Data for $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate D-14

Table D4 Hematology and Clinical Chemistry Data for $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite D-16

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate[1]

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
MALE						
Special Clinical Pathology Study						
Hematology						
n						
Day 3	10	10	10	10	9	10
Day 14	10	10	10	9	10	10
Day 42	9	9	10	8	10	5
Day 70	9	10	10	10	10	0
Week 13	10	10	8	10	10	0
Hematocrit (%)						
Day 3	43.0 ± 0.5	42.0 ± 0.4	43.0 ± 0.6	43.0 ± 0.6	44.3 ± 0.6	45.9 ± 0.5**
Day 14	47.7 ± 0.9	47.2 ± 0.4	49.2 ± 0.7	48.6 ± 1.0	45.5 ± 0.7	45.9 ± 2.1
Day 42	46.1 ± 0.4	46.2 ± 0.6	46.3 ± 0.6	45.7 ± 1.0	45.0 ± 0.5	51.0 ± 3.3
Day 70	46.1 ± 1.1	47.1 ± 0.7	47.8 ± 0.5	47.9 ± 0.5	45.3 ± 1.3	–
Week 13	46.8 ± 0.8	45.6 ± 0.8	46.9 ± 0.7	47.0 ± 0.7	46.3 ± 0.8	–
Hemoglobin (g/dL)						
Day 3	13.7 ± 0.1	13.6 ± 0.1	13.8 ± 0.2	13.8 ± 0.2	14.2 ± 0.1*	14.7 ± 0.2**
Day 14	15.3 ± 0.2	14.9 ± 0.1	15.5 ± 0.2	15.4 ± 0.3	14.5 ± 0.2	15.0 ± 0.7
Day 42	15.6 ± 0.2	15.4 ± 0.1	15.6 ± 0.1	15.5 ± 0.2	15.1 ± 0.1	17.3 ± 1.3
Day 70	15.3 ± 0.3	15.6 ± 0.1	15.6 ± 0.1	15.6 ± 0.1	14.9 ± 0.4	–
Week 13	15.4 ± 0.2	15.1 ± 0.1	15.2 ± 0.1	15.4 ± 0.1	15.2 ± 0.1	–
Erythrocytes (10^6/µL)						
Day 3	6.92 ± 0.07	6.97 ± 0.09	6.97 ± 0.12	7.09 ± 0.09	7.46 ± 0.11**	7.76 ± 0.14**
Day 14	7.76 ± 0.13	7.68 ± 0.08	7.95 ± 0.12	8.19 ± 0.18	8.27 ± 0.14*	9.01 ± 0.34**
Day 42	8.36 ± 0.10	8.41 ± 0.11	8.23 ± 0.13	8.32 ± 0.17	8.79 ± 0.11*	10.20 ± 0.69**
Day 70	8.72 ± 0.20	8.86 ± 0.13	8.88 ± 0.11	9.00 ± 0.08	8.77 ± 0.27	–
Week 13	8.51 ± 0.18	8.24 ± 0.14	8.23 ± 0.12	8.41 ± 0.10	8.46 ± 0.18	–
Reticulocytes (10^6/µL)						
Day 3	0.53 ± 0.04	0.45 ± 0.03	0.44 ± 0.04	0.42 ± 0.03	0.46 ± 0.03	0.43 ± 0.04
Day 14	0.36 ± 0.02	0.33 ± 0.03	0.35 ± 0.03	0.38 ± 0.03[2]	0.36 ± 0.03	0.32 ± 0.05
Day 42	0.12 ± 0.02	0.14 ± 0.02	0.13 ± 0.01	0.15 ± 0.03	0.13 ± 0.01	0.07 ± 0.01
Day 70	0.22 ± 0.03	0.18 ± 0.02	0.22 ± 0.02	0.22 ± 0.02	0.21 ± 0.02	–
Week 13	0.09 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.10 ± 0.01	–
Nucleated erythrocytes (10^3/µL)						
Day 3	0.06 ± 0.02	0.06 ± 0.02	0.08 ± 0.03	0.03 ± 0.02	0.03 ± 0.01	0.03 ± 0.01
Day 14	0.06 ± 0.03	0.07 ± 0.03	0.07 ± 0.03	0.03 ± 0.01	0.07 ± 0.02	0.06 ± 0.03
Day 42	0.05 ± 0.02	0.02 ± 0.02	0.09 ± 0.03	0.07 ± 0.02	0.04 ± 0.02	0.08 ± 0.03
Day 70	0.04 ± 0.03	0.04 ± 0.02	0.05 ± 0.02	0.00 ± 0.00	0.04 ± 0.02	–
Week 13	0.04 ± 0.02	0.01 ± 0.01	0.00 ± 0.00[3]	0.02 ± 0.01	0.01 ± 0.01	–
Mean cell volume (fL)						
Day 3	62.1 ± 0.4	60.3 ± 0.5*	61.7 ± 0.5	60.6 ± 0.5	59.4 ± 0.3**	59.1 ± 0.6**
Day 14	61.5 ± 0.5	61.5 ± 0.4	62.1 ± 0.4	59.3 ± 0.9	54.9 ± 0.3**	51.0 ± 0.8**
Day 42	54.9 ± 0.4	55.0 ± 0.3	56.3 ± 0.3	55.1 ± 0.1	51.2 ± 0.5**	50.2 ± 1.4*
Day 70	53.1 ± 0.3	53.2 ± 0.1	53.7 ± 0.3	53.4 ± 0.3	51.8 ± 0.4*	–
Week 13	55.3 ± 0.6	55.3 ± 0.6	57.1 ± 0.3*	55.7 ± 0.5	54.6 ± 0.4	–

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate (continued)

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
MALE (continued)						
Mean cell hemoglobin (pg)						
Day 3	19.8 ± 0.2	19.5 ± 0.2	19.8 ± 0.2	19.5 ± 0.1	19.1 ± 0.2**	18.9 ± 0.2**
Day 14	19.7 ± 0.1	19.4 ± 0.1	19.5 ± 0.1	18.8 ± 0.2**	17.6 ± 0.1**	16.6 ± 0.3**
Day 42	18.7 ± 0.2	18.4 ± 0.2	18.9 ± 0.3	18.7 ± 0.2	17.2 ± 0.3**	17.0 ± 0.7*
Day 70	17.5 ± 0.2	17.6 ± 0.2	17.6 ± 0.1	17.3 ± 0.1	17.0 ± 0.1*	–
Week 13	18.2 ± 0.4	18.3 ± 0.2	18.4 ± 0.3	18.4 ± 0.2	18.0 ± 0.3	–
Mean cell hemoglobin concentration (g/dL)						
Day 3	31.9 ± 0.2	32.4 ± 0.3	32.1 ± 0.2	32.2 ± 0.2	32.1 ± 0.4	32.0 ± 0.3
Day 14	32.1 ± 0.2	31.5 ± 0.2	31.6 ± 0.2	31.6 ± 0.2	31.9 ± 0.2	32.6 ± 0.2
Day 42	34.0 ± 0.2	33.4 ± 0.4	33.7 ± 0.4	33.9 ± 0.4	33.7 ± 0.3	33.9 ± 0.9
Day 70	33.1 ± 0.3	33.0 ± 0.3	32.7 ± 0.2	32.5 ± 0.2	32.8 ± 0.3	–
Week 13	33.0 ± 0.4	33.1 ± 0.4	32.3 ± 0.4	32.9 ± 0.5	32.9 ± 0.5	–
Leukocytes (10^3/µL)						
Day 3	6.91 ± 0.11	6.72 ± 0.25	6.88 ± 0.49	7.75 ± 0.30	6.87 ± 0.30	7.26 ± 0.63
Day 14	8.08 ± 0.47	8.28 ± 0.44	8.81 ± 0.47	9.04 ± 0.56	8.13 ± 0.57	8.21 ± 0.67
Day 42	6.72 ± 0.33	7.41 ± 0.44	7.12 ± 0.34	7.89 ± 0.51	7.89 ± 0.63	5.48 ± 1.15
Day 70	7.98 ± 0.77	7.13 ± 0.33	7.12 ± 0.38	8.18 ± 0.57	7.50 ± 0.40	–
Week 13	5.79 ± 0.45	6.72 ± 0.50	5.54 ± 0.23	6.44 ± 0.49	6.77 ± 0.31	–
Segmented neutrophils (10^3/µL)						
Day 3	0.70 ± 0.06	0.87 ± 0.13	0.90 ± 0.11	0.93 ± 0.12	0.78 ± 0.06	0.78 ± 0.12
Day 14	0.98 ± 0.13	0.89 ± 0.14	0.90 ± 0.12	1.00 ± 0.16	1.02 ± 0.10	1.17 ± 0.20
Day 42	1.03 ± 0.08	1.15 ± 0.09	1.11 ± 0.14	1.15 ± 0.14	1.22 ± 0.16	1.36 ± 0.24
Day 70	1.44 ± 0.23	1.26 ± 0.13	1.20 ± 0.11	1.08 ± 0.08	1.55 ± 0.25	–
Week 13	1.37 ± 0.15	1.64 ± 0.24	1.11 ± 0.13	1.47 ± 0.21	1.59 ± 0.15	–
Lymphocytes (10^3/µL)						
Day 3	5.85 ± 0.12	5.40 ± 0.16	5.50 ± 0.38	6.32 ± 0.27	5.81 ± 0.21	6.09 ± 0.46
Day 14	6.71 ± 0.46	6.98 ± 0.48	7.44 ± 0.37	7.59 ± 0.44	6.89 ± 0.48	6.77 ± 0.46
Day 42	5.44 ± 0.30	5.93 ± 0.39	5.80 ± 0.25	6.41 ± 0.43	6.21 ± 0.52	3.95 ± 0.90
Day 70	6.03 ± 0.69	5.48 ± 0.27	5.43 ± 0.35	6.74 ± 0.53	5.59 ± 0.32	–
Week 13	4.07 ± 0.38	4.58 ± 0.28	4.02 ± 0.22	4.63 ± 0.37	4.87 ± 0.18	–
Monocytes (10^3/µL)						
Day 3	0.33 ± 0.05	0.36 ± 0.07	0.37 ± 0.06	0.44 ± 0.05	0.21 ± 0.04	0.30 ± 0.08
Day 14	0.37 ± 0.04	0.35 ± 0.06	0.40 ± 0.05	0.36 ± 0.06	0.21 ± 0.05	0.23 ± 0.06
Day 42	0.23 ± 0.08	0.27 ± 0.07	0.24 ± 0.05	0.28 ± 0.05	0.38 ± 0.05	0.18 ± 0.06
Day 70	0.38 ± 0.12	0.35 ± 0.04	0.39 ± 0.06	0.31 ± 0.05	0.25 ± 0.05	–
Week 13	0.33 ± 0.06	0.38 ± 0.06	0.30 ± 0.03	0.26 ± 0.04	0.27 ± 0.06	–
Eosinophils (10^3/µL)						
Day 3	0.02 ± 0.01	0.06 ± 0.02	0.08 ± 0.02	0.04 ± 0.02	0.03 ± 0.02	0.03 ± 0.01
Day 14	0.02 ± 0.01	0.06 ± 0.03	0.06 ± 0.01	0.08 ± 0.03	0.01 ± 0.01	0.04 ± 0.02
Day 42	0.02 ± 0.01	0.06 ± 0.02	0.01 ± 0.01	0.08 ± 0.04	0.06 ± 0.03	0.01 ± 0.01
Day 70	0.09 ± 0.03	0.03 ± 0.01	0.08 ± 0.02	0.04 ± 0.03	0.09 ± 0.03	–
Week 13	0.02 ± 0.01	0.11 ± 0.04*	0.09 ± 0.03	0.07 ± 0.03	0.04 ± 0.02	–

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate (continued)

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
MALE (continued)						
Clinical Chemistry						
n						
Day 3	10	10	10	10	10	10
Day 14	10	10	10	9	10	10
Day 42	10	10	10	10	10	5
Day 70	10	10	10	10	10	0
Week 13	10	10	9	10	10	0
Urea nitrogen (mg/dL)						
Day 3	19.1 ± 0.4	18.3 ± 0.6	18.2 ± 0.3	18.3 ± 0.5	17.5 ± 0.3*	16.1 ± 0.6**
Day 14	20.8 ± 0.8	18.7 ± 0.5	19.0 ± 0.7	21.7 ± 0.6	26.0 ± 0.6**	32.9 ± 1.9**
Day 42	11.9 ± 0.5	12.9 ± 0.8	14.0 ± 0.7*	16.0 ± 0.8**	24.7 ± 1.4**	45.4 ± 7.3**
Day 70	17.6 ± 0.6	18.8 ± 0.7	19.6 ± 0.4*	21.8 ± 1.3**	29.3 ± 1.3**	–
Week 13	15.3 ± 0.8	14.6 ± 0.8	13.9 ± 0.6	16.9 ± 0.8	23.1 ± 1.2**	–
Creatinine (mg/dL)						
Day 3	0.54 ± 0.02	0.54 ± 0.02	0.50 ± 0.02	0.52 ± 0.01	0.50 ± 0.00*	0.49 ± 0.02*
Day 14	0.44 ± 0.02	0.40 ± 0.02	0.46 ± 0.02	0.46 ± 0.02	0.41 ± 0.02	0.40 ± 0.02
Day 42	0.57 ± 0.02	0.56 ± 0.02	0.53 ± 0.02	0.57 ± 0.02	0.57 ± 0.02	0.58 ± 0.04
Day 70	0.62 ± 0.04	0.55 ± 0.02	0.60 ± 0.02	0.58 ± 0.03	0.58 ± 0.04	–
Week 13	0.48 ± 0.02	0.55 ± 0.03	0.51 ± 0.02	0.51 ± 0.02	0.49 ± 0.02	–
Alanine aminotransferase (IU/L)						
Day 3	36 ± 1	33 ± 1	33 ± 1	34 ± 1	34 ± 1	34 ± 1
Day 14	30 ± 1	31 ± 1	32 ± 1	39 ± 2**	42 ± 2**	76 ± 11**
Day 42	38 ± 2	37 ± 1	36 ± 1	38 ± 2	64 ± 9**	201 ± 30**[4]
Day 70	43 ± 2	38 ± 1	38 ± 1	40 ± 3	71 ± 12*	–
Week 13	47 ± 3	44 ± 3	35 ± 2*	38 ± 2	49 ± 2	–
Alkaline phosphatase (IU/L)						
Day 3	742 ± 11	676 ± 10**	670 ± 23**	615 ± 17**	565 ± 17**	536 ± 14**
Day 14	432 ± 13	410 ± 5	414 ± 12	407 ± 13	371 ± 9**	285 ± 18**
Day 42	207 ± 3	204 ± 4	196 ± 4	190 ± 6	212 ± 7	182 ± 21
Day 70	180 ± 7	155 ± 4*	166 ± 5	160 ± 5	183 ± 5	–
Week 13	129 ± 3	116 ± 2*	118 ± 6	115 ± 2*	125 ± 4	–
Sorbitol dehydrogenase (IU/L)						
Day 3	5 ± 0	4 ± 0*	5 ± 0	5 ± 0	4 ± 0**	4 ± 0*[3]
Day 14	5 ± 1	6 ± 0	6 ± 0	5 ± 1	5 ± 1	6 ± 2
Day 42	6 ± 0	7 ± 0	7 ± 0	6 ± 1	7 ± 1	11 ± 2[5]
Day 70	6 ± 1	7 ± 0	6 ± 0	6 ± 1	7 ± 1	–
Week 13	4 ± 0	4 ± 0	4 ± 0	4 ± 0	4 ± 0	–
5′-Nucleotidase (IU/L)						
Day 3	18 ± 1	17 ± 0	17 ± 0	18 ± 0	16 ± 0**	14 ± 0**[3]
Day 14	29 ± 1	26 ± 1	25 ± 1	27 ± 2	24 ± 0**	24 ± 1*
Day 42	23 ± 1	25 ± 1	24 ± 2	26 ± 1	27 ± 1**	28 ± 3[4]
Day 70	36 ± 2	31 ± 2	33 ± 1	32 ± 2	37 ± 2	–
Week 13	15 ± 1	14 ± 1	14 ± 0	15 ± 0	15 ± 1	–
Bile acids (µmol/L)						
Day 3	13.5 ± 1.7	15.2 ± 2.5	12.5 ± 0.9	12.2 ± 1.2	13.0 ± 1.8	13.8 ± 1.9[3]
Day 14	25.4 ± 2.9	21.6 ± 1.8	21.0 ± 1.3	23.0 ± 2.4[6]	20.2 ± 1.7	23.2 ± 4.2
Day 42	17.2 ± 3.1	28.6 ± 4.1	21.8 ± 1.7	23.9 ± 3.2	38.9 ± 8.7*	64.5 ± 11.2**[4]
Day 70	25.5 ± 5.2	18.9 ± 1.5	18.3 ± 1.5	19.4 ± 1.2	24.4 ± 3.2	–
Week 13	14.3 ± 2.9[3]	22.6 ± 8.4[7]	14.0 ± 4.5[8]	10.7 ± 2.3[7]	22.4 ± 6.2	–

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate (continued)

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
MALE (continued)						
Urinalysis						
n						
Day 7	10	10	10	10	10	10
Day 14	9	10	10	10	10	10
Day 42	10	10	10	10	10	3
Day 70	10	10	10	10	10	0
Week 13	10	10	9	10	10	0
Alkaline phosphatase (mU/hr)						
Day 7	1 ± 0	1 ± 0	2 ± 1	1 ± 0	1 ± 0	1 ± 0
Day 14	3 ± 1	1 ± 0[3]	1 ± 0*	1 ± 0*	1 ± 0*	1 ± 0**
Day 42	5 ± 1	4 ± 1	2 ± 0	2 ± 0	2 ± 0	1 ± 1[9]
Day 70	3 ± 1[3]	2 ± 0	1 ± 0	1 ± 0	1 ± 0	–
Week 13	3 ± 1	2 ± 0	1 ± 0	2 ± 0	1 ± 0	–
N-acetyl-β-D-glucosaminidase (mU/hr)						
Day 7	4 ± 0	4 ± 0	4 ± 0	3 ± 0*	3 ± 0**	2 ± 0**
Day 14	5 ± 0	5 ± 0	5 ± 0	4 ± 0*	3 ± 0**	1 ± 0**
Day 42	6 ± 0	6 ± 0	5 ± 0	5 ± 0	5 ± 0	6 ± 2[9]
Day 70	4 ± 0	4 ± 0	4 ± 0	4 ± 0	5 ± 0	–
Week 13	5 ± 0	5 ± 0	4 ± 0*	4 ± 0	4 ± 0	–
Volume (mL/16 hr)						
Day 7	5.1 ± 0.3	4.2 ± 0.1**	3.3 ± 0.3**	2.8 ± 0.1**	2.6 ± 0.2**	1.6 ± 0.2**
Day 14	8.1 ± 0.8	4.8 ± 0.3**	4.4 ± 0.2**	3.8 ± 0.2**	3.0 ± 0.2**	1.8 ± 0.2**
Day 42	7.8 ± 0.6	5.2 ± 0.3**	4.1 ± 0.2**	4.0 ± 0.3**	3.6 ± 0.2**	1.7 ± 0.6**
Day 70	6.7 ± 0.9	3.2 ± 0.2**	3.4 ± 0.4**	3.4 ± 0.3**	3.2 ± 0.2**	–
Week 13	8.7 ± 0.4	4.8 ± 0.5**	3.4 ± 0.4**	3.8 ± 0.3**	3.3 ± 0.3**	–
Specific gravity						
Day 7	1.048 ± 0.001	1.067 ± 0.002**	1.081 ± 0.003**	1.092 ± 0.003**	1.088 ± 0.002**	1.111 ± 0.003**
Day 14	1.044 ± 0.005	1.071 ± 0.003**	1.092 ± 0.003**	1.089 ± 0.002**	1.097 ± 0.003**	1.125 ± 0.004**
Day 42	1.039 ± 0.003	1.061 ± 0.004**	1.061 ± 0.003**	1.070 ± 0.004**	1.083 ± 0.002**	1.104 ± 0.006**
Day 70	1.035 ± 0.006	1.066 ± 0.004**	1.071 ± 0.003**	1.077 ± 0.002**	1.080 ± 0.003**	–
Week 13	1.030 ± 0.001	1.058 ± 0.003**	1.064 ± 0.006**	1.076 ± 0.003**	1.082 ± 0.002**	–
pH						
Day 7	6.35 ± 0.08	6.80 ± 0.11**	6.75 ± 0.13*	6.95 ± 0.05**	7.35 ± 0.22**	7.15 ± 0.17**
Day 14	6.94 ± 0.10	6.75 ± 0.08	6.90 ± 0.07	6.95 ± 0.12	7.50 ± 0.15**	8.20 ± 0.20**
Day 42	6.95 ± 0.05	6.80 ± 0.08	6.60 ± 0.07**	6.50 ± 0.00**	6.65 ± 0.11**	6.50 ± 0.50*
Day 70	7.00 ± 0.11	6.75 ± 0.11	6.50 ± 0.11**	6.50 ± 0.11**	6.60 ± 0.18*	–
Week 13	6.85 ± 0.08	6.35 ± 0.11**	6.11 ± 0.07**	6.20 ± 0.08**	6.50 ± 0.24**	–

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate (continued)

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
MALE (continued)						
Base Study						
n	10	10	10	10	10	0
Hematology						
Hematocrit (%)	46.0 ± 0.6	47.4 ± 0.7	46.0 ± 0.4	46.3 ± 0.5	45.1 ± 0.7	–
Hemoglobin (g/dL)	15.1 ± 0.1	15.5 ± 0.2	15.1 ± 0.1	15.2 ± 0.1	14.9 ± 0.1	–
Erythrocytes (10^6/µL)	9.01 ± 0.11	9.28 ± 0.13	8.95 ± 0.07	9.01 ± 0.12	8.81 ± 0.09	–
Reticulocytes (10^6/µL)	0.21 ± 0.02	0.18 ± 0.02	0.18 ± 0.02	0.19 ± 0.02	0.17 ± 0.01	–
Nucleated erythrocytes (10^3/µL)	0.03 ± 0.02	0.02 ± 0.01	0.04 ± 0.02	0.01 ± 0.01	0.03 ± 0.01	–
Mean cell volume (fL)	50.9 ± 0.2	50.9 ± 0.2	51.5 ± 0.4	51.4 ± 0.3	51.0 ± 0.4	–
Mean cell hemoglobin (pg)	16.7 ± 0.1	16.6 ± 0.1	16.8 ± 0.1	16.9 ± 0.2	16.9 ± 0.1	–
Mean cell hemoglobin concentration (g/dL)	32.8 ± 0.3	32.7 ± 0.2	32.8 ± 0.2	32.9 ± 0.3	33.0 ± 0.4	–
Leukocytes (10^3/µL)	6.37 ± 0.20	6.71 ± 0.33	6.62 ± 0.36	7.28 ± 0.34	5.99 ± 0.23	–
Segmented neutrophils (10^3/µL)	1.12 ± 0.13	1.15 ± 0.19	1.23 ± 0.11	1.02 ± 0.12	1.06 ± 0.07	–
Lymphocytes (10^3/µL)	4.88 ± 0.28	5.16 ± 0.32	5.06 ± 0.33	5.80 ± 0.31	4.62 ± 0.20	–
Monocytes (10^3/µL)	0.30 ± 0.04	0.34 ± 0.07	0.26 ± 0.02	0.36 ± 0.08	0.24 ± 0.02	–
Eosinophils (10^3/µL)	0.03 ± 0.01	0.03 ± 0.01	0.05 ± 0.01	0.09 ± 0.03	0.05 ± 0.02	–
Clinical Chemistry						
Urea nitrogen (mg/dL)	26.3 ± 1.1	24.3 ± 1.2	26.2 ± 1.9	27.0 ± 1.7	27.5 ± 1.3	–
Creatinine (mg/dL)	0.61 ± 0.02	0.63 ± 0.02	0.63 ± 0.02	0.62 ± 0.01	0.59 ± 0.02	–
Alanine aminotransferase (IU/L)	68 ± 4	55 ± 3	54 ± 5*	51 ± 2*	80 ± 13	–
Alkaline phosphatase (IU/L)	271 ± 7	223 ± 10**	256 ± 10*	234 ± 5**	223 ± 6**	–
Sorbitol dehydrogenase (IU/L)	6 ± 0	6 ± 0	6 ± 1*	5 ± 0**	6 ± 1**	–
5′-Nucleotidase (IU/L)	31 ± 1	28 ± 1	29 ± 2	28 ± 1	29 ± 2	–
Bile acids (µmol/L)	22.9 ± 2.3	27.5 ± 4.7	19.6 ± 2.2	20.2 ± 1.7	31.3 ± 4.1	–

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate (continued)

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
FEMALE						
Hematology						
n	10	9	10	10	9	0
Hematocrit (%)	43.9 ± 0.6	45.2 ± 0.3	44.9 ± 0.4	44.9 ± 0.6	46.4 ± 0.7*	–
Hemoglobin (g/dL)	14.4 ± 0.1	14.8 ± 0.1*	14.8 ± 0.1*	14.6 ± 0.2	15.2 ± 0.1**	–
Erythrocytes (10^6/µL)	8.16 ± 0.16	8.36 ± 0.09	8.08 ± 0.10	8.22 ± 0.13	8.78 ± 0.16*	–
Reticulocytes (10^6/µL)	0.15 ± 0.01	0.16 ± 0.01	0.16 ± 0.01[3]	0.16 ± 0.02	0.15 ± 0.01	–
Nucleated erythrocytes (10^3/µL)	0.04 ± 0.02	0.07 ± 0.03	0.04 ± 0.02	0.07 ± 0.02	0.02 ± 0.02	–
Mean cell volume (fL)	53.7 ± 0.6	54.2 ± 0.4	55.5 ± 0.3	54.6 ± 0.4	52.8 ± 0.5	–
Mean cell hemoglobin (pg)	17.7 ± 0.3	17.7 ± 0.2	18.3 ± 0.2	17.8 ± 0.2	17.4 ± 0.2	–
Mean cell hemoglobin concentration (g/dL)	32.8 ± 0.3	32.7 ± 0.2	33.0 ± 0.3	32.6 ± 0.3	32.9 ± 0.3	–
Leukocytes (10^3/µL)	6.88 ± 0.30	7.33 ± 0.49	7.79 ± 0.66	8.47 ± 0.59*	8.00 ± 0.55	–
Segmented neutrophils (10^3/µL)	1.43 ± 0.17	1.45 ± 0.20	1.67 ± 0.34	1.85 ± 0.24	1.34 ± 0.11	–
Lymphocytes (10^3/µL)	5.06 ± 0.25	5.42 ± 0.39	5.57 ± 0.34	5.98 ± 0.52	6.14 ± 0.47	–
Monocytes (10^3/µL)	0.28 ± 0.05	0.36 ± 0.05	0.47 ± 0.04*	0.47 ± 0.04*	0.45 ± 0.08*	–
Eosinophils (10^3/µL)	0.08 ± 0.02	0.09 ± 0.02	0.07 ± 0.02	0.12 ± 0.02	0.05 ± 0.02	–
Clinical Chemistry						
n	10	10	10	10	10	0
Urea nitrogen (mg/dL)	26.1 ± 0.6	25.0 ± 0.8	27.6 ± 1.2	26.9 ± 1.0	28.8 ± 1.2	–
Creatinine (mg/dL)	0.59 ± 0.02	0.66 ± 0.03	0.61 ± 0.03	0.58 ± 0.03	0.52 ± 0.01*	–
Alanine aminotransferase (IU/L)	40 ± 1	44 ± 1**	40 ± 2	52 ± 4**	88 ± 7**	–
Alkaline phosphatase (IU/L)	219 ± 9	232 ± 7	230 ± 11	243 ± 9	243 ± 9	–
Sorbitol dehydrogenase (IU/L)	6 ± 1	6 ± 1	7 ± 1	6 ± 1	6 ± 1	–
5′-Nucleotidase (IU/L)	30 ± 2	37 ± 2	32 ± 2	31 ± 2	30 ± 2	–
Bile acids (µmol/L)	34.6 ± 7.1	24.6 ± 5.4	21.8 ± 3.5	23.3 ± 3.7	30.2 ± 6.0	–

[1] Data are given as mean ± standard error. Statistical tests were performed on unrounded data.
[2] n=8.
[3] n=9.
[4] n=4.
[5] n=3.
[6] n=10.
[7] n=7.
[8] n=6.
[9] n=2.
* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test.
** Significantly different ($P \leq 0.01$) from the control group by Dunn's or Shirley's test.

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite[1]

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
MALE						
Special Clinical Pathology Study						
Hematology						
n						
Day 3	10	10	10	10	10	10
Day 14	9	9	10	10	10	10
Day 42	9	10	9	8	9	10
Day 70	10	8	9	9	10	9
Week 13	9	10	10	10	10	9
Hematocrit (%)						
Day 3	43.0 ± 0.6	44.2 ± 0.6	43.7 ± 0.5	43.8 ± 0.8	44.5 ± 0.7	44.8 ± 0.4
Day 14	46.9 ± 0.7	46.0 ± 0.4	46.8 ± 0.4	45.7 ± 0.5	46.2 ± 0.4	45.9 ± 0.6
Day 42	49.1 ± 0.7	48.8 ± 0.5	49.6 ± 0.3	49.8 ± 0.6	49.6 ± 0.6	49.5 ± 0.4
Day 70	48.9 ± 0.7	47.3 ± 0.4	48.2 ± 0.6	47.2 ± 0.6	47.1 ± 0.8	49.1 ± 0.6
Week 13	48.4 ± 0.6	49.3 ± 0.4	49.9 ± 0.3*	48.5 ± 0.4	49.3 ± 0.6	51.3 ± 1.0**
Hemoglobin (g/dL)						
Day 3	14.2 ± 0.1	14.5 ± 0.2	14.4 ± 0.1	14.6 ± 0.1	14.7 ± 0.1*	14.7 ± 0.1**
Day 14	15.2 ± 0.1	14.8 ± 0.1	15.0 ± 0.1	14.7 ± 0.1	14.8 ± 0.1	14.8 ± 0.1
Day 42	15.9 ± 0.2	15.8 ± 0.1	15.9 ± 0.2	16.1 ± 0.1	16.0 ± 0.2	16.0 ± 0.1
Day 70	15.7 ± 0.2	15.5 ± 0.1	15.8 ± 0.2	15.5 ± 0.1	15.6 ± 0.3	15.9 ± 0.3
Week 13	15.7 ± 0.1	15.7 ± 0.1	16.0 ± 0.1*	15.8 ± 0.1	15.8 ± 0.2	16.4 ± 0.4
Erythrocytes (10^6/µL)						
Day 3	7.17 ± 0.12	7.41 ± 0.11	7.23 ± 0.09	7.31 ± 0.13	7.43 ± 0.13	7.54 ± 0.08*
Day 14	7.55 ± 0.11	7.35 ± 0.06	7.43 ± 0.09	7.39 ± 0.10	7.22 ± 0.10	7.46 ± 0.07
Day 42	8.93 ± 0.10	9.02 ± 0.11	9.16 ± 0.10	9.27 ± 0.12	9.17 ± 0.12	9.29 ± 0.10
Day 70	9.33 ± 0.16	9.02 ± 0.08	9.08 ± 0.14	9.01 ± 0.13	8.90 ± 0.17	9.37 ± 0.08
Week 13	9.00 ± 0.14	9.18 ± 0.06	9.26 ± 0.08	9.02 ± 0.07	9.02 ± 0.10	9.36 ± 0.18
Reticulocytes (10^6/µL)						
Day 3	0.27 ± 0.03	0.29 ± 0.02	0.31 ± 0.02	0.31 ± 0.02	0.31 ± 0.03	0.27 ± 0.02
Day 14	0.36 ± 0.03	0.32 ± 0.02	0.32 ± 0.01	0.36 ± 0.03	0.43 ± 0.02	0.43 ± 0.03
Day 42	0.14 ± 0.02	0.14 ± 0.02	0.19 ± 0.03	0.20 ± 0.02	0.16 ± 0.02	0.14 ± 0.02
Day 70	0.15 ± 0.02	0.19 ± 0.01	0.18 ± 0.02	0.18 ± 0.02	0.16 ± 0.02	0.19 ± 0.01
Week 13	0.18 ± 0.02	0.19 ± 0.02	0.16 ± 0.02	0.15 ± 0.02	0.15 ± 0.02	0.17 ± 0.02
Nucleated erythrocytes (10^3/µL)						
Day 3	0.02 ± 0.01	0.02 ± 0.01	0.04 ± 0.02	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Day 14	0.08 ± 0.03	0.06 ± 0.02	0.06 ± 0.02	0.05 ± 0.02	0.02 ± 0.01	0.07 ± 0.03[2]
Day 42	0.07 ± 0.03	0.06 ± 0.02	0.02 ± 0.02	0.05 ± 0.02	0.01 ± 0.01	0.02 ± 0.01
Day 70	0.12 ± 0.06	0.03 ± 0.02	0.04 ± 0.02	0.07 ± 0.03	0.08 ± 0.03	0.08 ± 0.02
Week 13	0.06 ± 0.02	0.07 ± 0.03	0.03 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.04 ± 0.02
Mean cell volume (fL)						
Day 3	60.0 ± 0.3	59.8 ± 0.4	60.5 ± 0.2	59.7 ± 0.3	59.9 ± 0.4	59.5 ± 0.3
Day 14	62.1 ± 0.6	62.6 ± 0.5	63.0 ± 0.5	62.0 ± 0.4	64.0 ± 0.7	61.6 ± 0.6
Day 42	54.8 ± 0.4	54.1 ± 0.3	54.2 ± 0.3	53.8 ± 0.4	54.1 ± 0.6	53.3 ± 0.5*
Day 70	52.6 ± 0.4	52.4 ± 0.4	53.1 ± 0.3	52.4 ± 0.5	53.0 ± 0.3	52.4 ± 0.6
Week 13	53.8 ± 0.4	53.5 ± 0.3	53.8 ± 0.6	53.8 ± 0.4	54.5 ± 0.4	55.0 ± 0.6

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite (continued)

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
MALE (continued)						
Mean cell hemoglobin (pg)						
Day 3	19.8 ± 0.2	19.5 ± 0.2	19.9 ± 0.1	19.9 ± 0.2	19.7 ± 0.3	19.6 ± 0.2
Day 14	20.1 ± 0.2	20.1 ± 0.2	20.2 ± 0.2	19.8 ± 0.1	20.6 ± 0.2	19.9 ± 0.1
Day 42	17.8 ± 0.1	17.6 ± 0.1	17.4 ± 0.1*	17.4 ± 0.1**	17.5 ± 0.2*	17.3 ± 0.1**
Day 70	16.8 ± 0.1	17.1 ± 0.1	17.4 ± 0.2	17.3 ± 0.2	17.6 ± 0.2*	17.0 ± 0.3
Week 13	17.4 ± 0.2	17.1 ± 0.1	17.3 ± 0.1	17.5 ± 0.1	17.5 ± 0.1	17.5 ± 0.2
Mean cell hemoglobin concentration (g/dL)						
Day 3	33.1 ± 0.3	32.7 ± 0.4	32.9 ± 0.2	33.3 ± 0.4	33.0 ± 0.4	32.9 ± 0.2
Day 14	32.4 ± 0.3	32.1 ± 0.2	32.1 ± 0.2	32.1 ± 0.1	32.1 ± 0.2	32.3 ± 0.4
Day 42	32.4 ± 0.2	32.5 ± 0.2	32.1 ± 0.3	32.3 ± 0.1	32.3 ± 0.2	32.4 ± 0.1
Day 70	32.1 ± 0.2	32.7 ± 0.2	32.7 ± 0.3	32.9 ± 0.3	33.1 ± 0.4	32.5 ± 0.3
Week 13	32.4 ± 0.3	31.8 ± 0.3	32.1 ± 0.2	32.6 ± 0.2	32.0 ± 0.2	32.1 ± 0.4
Leukocytes (10^3/µL)						
Day 3	8.45 ± 0.65	9.32 ± 0.57	8.82 ± 0.63	8.97 ± 0.64	10.13 ± 0.59	9.23 ± 0.40
Day 14	8.52 ± 0.34	8.60 ± 0.50	8.37 ± 0.44	8.65 ± 0.31	8.53 ± 0.30	8.10 ± 0.34
Day 42	7.00 ± 0.32	7.90 ± 0.31	8.17 ± 0.33*	7.78 ± 0.47	8.04 ± 0.23	8.06 ± 0.30*
Day 70	8.04 ± 0.53	7.64 ± 0.38	9.00 ± 0.57	7.27 ± 0.31	7.53 ± 0.45	8.21 ± 0.70
Week 13	6.06 ± 0.24	6.52 ± 0.53	7.55 ± 0.52	6.92 ± 0.28	7.22 ± 0.39	6.70 ± 0.37
Segmented neutrophils (10^3/µL)						
Day 3	0.88 ± 0.09	1.15 ± 0.12	1.16 ± 0.11	1.07 ± 0.17	0.95 ± 0.16	0.91 ± 0.13
Day 14	1.27 ± 0.15	1.25 ± 0.12	1.19 ± 0.08	1.29 ± 0.11	1.11 ± 0.10	1.25 ± 0.11[2]
Day 42	1.13 ± 0.12	0.96 ± 0.10	0.77 ± 0.10	1.21 ± 0.15	1.16 ± 0.09	1.49 ± 0.13
Day 70	1.70 ± 0.23	1.39 ± 0.15	1.64 ± 0.17	1.40 ± 0.14	1.72 ± 0.19	2.22 ± 0.20*
Week 13	1.38 ± 0.05	0.95 ± 0.09**	1.11 ± 0.07	1.22 ± 0.08	1.32 ± 0.13	1.53 ± 0.18
Lymphocytes (10^3/µL)						
Day 3	7.20 ± 0.59	7.60 ± 0.50	7.24 ± 0.55	7.33 ± 0.55	8.60 ± 0.51	7.81 ± 0.30
Day 14	6.66 ± 0.28	6.92 ± 0.53	6.83 ± 0.43	6.91 ± 0.32	6.90 ± 0.31	6.47 ± 0.30[2]
Day 42	5.43 ± 0.28	6.42 ± 0.29	6.98 ± 0.29**	6.14 ± 0.44	6.36 ± 0.26	6.12 ± 0.33
Day 70	5.94 ± 0.32	5.72 ± 0.37	6.89 ± 0.50	5.43 ± 0.26	5.39 ± 0.34	5.48 ± 0.47
Week 13	4.38 ± 0.22	5.34 ± 0.47	6.05 ± 0.50*	5.40 ± 0.28	5.51 ± 0.37	4.81 ± 0.25
Monocytes (10^3/µL)						
Day 3	0.31 ± 0.06	0.49 ± 0.11	0.41 ± 0.09	0.54 ± 0.11	0.52 ± 0.09	0.43 ± 0.06
Day 14	0.46 ± 0.08	0.36 ± 0.07	0.28 ± 0.05	0.37 ± 0.06	0.44 ± 0.06	0.26 ± 0.05[2]
Day 42	0.36 ± 0.07	0.44 ± 0.05	0.29 ± 0.07	0.37 ± 0.05	0.42 ± 0.05	0.36 ± 0.08
Day 70	0.35 ± 0.04	0.43 ± 0.08	0.41 ± 0.10	0.39 ± 0.06	0.38 ± 0.06	0.41 ± 0.08
Week 13	0.24 ± 0.03	0.18 ± 0.03	0.28 ± 0.04	0.23 ± 0.05	0.30 ± 0.04	0.26 ± 0.06
Eosinophils (10^3/µL)						
Day 3	0.05 ± 0.02	0.03 ± 0.02	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.05 ± 0.03
Day 14	0.08 ± 0.03	0.03 ± 0.02	0.02 ± 0.01	0.04 ± 0.02	0.04 ± 0.02	0.03 ± 0.02[2]
Day 42	0.04 ± 0.02	0.04 ± 0.02	0.10 ± 0.04	0.05 ± 0.02	0.03 ± 0.01	0.07 ± 0.03
Day 70	0.03 ± 0.02	0.09 ± 0.03	0.04 ± 0.03	0.02 ± 0.01	0.04 ± 0.03	0.09 ± 0.02
Week 13	0.04 ± 0.01	0.04 ± 0.02	0.09 ± 0.03	0.05 ± 0.02	0.06 ± 0.02	0.07 ± 0.03

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite (continued)

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
MALE (continued)						
Clinical Chemistry						
n						
Day 3	10	10	10	10	10	10
Day 14	10	10	10	10	10	10
Day 42	10	10	10	9	10	10
Day 70	10	10	10	10	10	9
Week 13	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 3	16.3 ± 0.7	17.1 ± 0.5	17.8 ± 0.4	17.8 ± 0.5	17.9 ± 0.5	18.4 ± 0.4*
Day 14	19.7 ± 0.6	18.8 ± 0.8	20.1 ± 0.5	20.3 ± 0.6	21.0 ± 0.6	24.1 ± 0.9**
Day 42	18.9 ± 0.4	19.8 ± 1.0	20.0 ± 0.7	20.4 ± 0.5	20.8 ± 0.6	23.8 ± 1.3**
Day 70	16.1 ± 0.7	16.9 ± 0.6	18.0 ± 1.0	18.3 ± 0.7*	20.0 ± 0.9**	26.8 ± 1.4**
Week 13	21.0 ± 1.1	20.8 ± 0.7	21.4 ± 0.5	20.5 ± 0.7	20.7 ± 0.7	24.7 ± 2.1
Creatinine (mg/dL)						
Day 3	0.48 ± 0.01	0.48 ± 0.02[2]	0.52 ± 0.02	0.51 ± 0.02	0.48 ± 0.02	0.51 ± 0.01
Day 14	0.52 ± 0.02	0.49 ± 0.01	0.51 ± 0.02	0.47 ± 0.02	0.48 ± 0.02	0.48 ± 0.01
Day 42	0.52 ± 0.03	0.54 ± 0.02	0.54 ± 0.02	0.57 ± 0.03	0.56 ± 0.02	0.48 ± 0.03
Day 70	0.57 ± 0.03	0.61 ± 0.02	0.64 ± 0.03	0.62 ± 0.01	0.56 ± 0.02	0.51 ± 0.03
Week 13	0.80 ± 0.03	0.80 ± 0.02	0.78 ± 0.02	0.81 ± 0.04	0.79 ± 0.03	0.81 ± 0.05
Alanine aminotransferase (IU/L)						
Day 3	30 ± 1	33 ± 1	30 ± 1	30 ± 1	31 ± 1	28 ± 1
Day 14	32 ± 2	31 ± 1	31 ± 2	30 ± 1	35 ± 2	45 ± 4**
Day 42	40 ± 1	38 ± 1	41 ± 2	43 ± 3	34 ± 1	53 ± 6
Day 70	35 ± 2	32 ± 1	36 ± 2	33 ± 2	33 ± 1	183 ± 51**
Week 13	48 ± 2	48 ± 2	46 ± 2	43 ± 1	44 ± 2	75 ± 8*
Alkaline phosphatase (IU/L)						
Day 3	406 ± 15	401 ± 9	411 ± 7	419 ± 6*	419 ± 10	415 ± 6
Day 14	333 ± 9	321 ± 15	342 ± 12	348 ± 9	383 ± 14*	377 ± 14*
Day 42	345 ± 9	345 ± 11	340 ± 10	335 ± 9	324 ± 12	341 ± 11
Day 70	157 ± 6	149 ± 4	154 ± 5	146 ± 2	149 ± 8	212 ± 12*
Week 13	283 ± 9	263 ± 10	273 ± 10	264 ± 6	254 ± 5	293 ± 18
Sorbitol dehydrogenase (IU/L)						
Day 3	4 ± 0	4 ± 0[2]	4 ± 0	5 ± 0*	4 ± 0	5 ± 0
Day 14	4 ± 0	4 ± 0	4 ± 0	4 ± 0	4 ± 0	5 ± 0
Day 42	5 ± 0	5 ± 0[2]	6 ± 0	7 ± 1	5 ± 0	6 ± 0
Day 70	4 ± 0	5 ± 0	5 ± 1	5 ± 1*	5 ± 1	20 ± 8**[3]
Week 13	6 ± 0	6 ± 0	6 ± 0	5 ± 0	5 ± 0	6 ± 0
5′-Nucleotidase (IU/L)						
Day 3	29 ± 1	30 ± 1	30 ± 1	30 ± 1	28 ± 0	30 ± 1
Day 14	15 ± 0	13 ± 1	15 ± 1	13 ± 0	16 ± 1	18 ± 1
Day 42	17 ± 1	17 ± 1[2]	17 ± 0	17 ± 1	17 ± 0	22 ± 1**
Day 70	14 ± 0	15 ± 1	17 ± 1**	17 ± 1**	16 ± 0*	37 ± 7**[3]
Week 13	18 ± 1	17 ± 1	18 ± 1	17 ± 0	18 ± 0	23 ± 1*
Bile acids (µmol/L)						
Day 3	10.5 ± 0.9	12.3 ± 1.7[2]	10.8 ± 1.0	11.3 ± 1.5	10.7 ± 3.0	8.1 ± 1.0
Day 14	13.9 ± 3.0	14.5 ± 1.4	11.3 ± 2.3	8.8 ± 0.7	12.7 ± 0.8	19.7 ± 3.1
Day 42	9.9 ± 2.5[2]	10.3 ± 2.1[2]	15.7 ± 2.6	8.6 ± 1.6	8.9 ± 2.2	28.2 ± 4.4**
Day 70	9.7 ± 1.2	12.1 ± 2.2	11.4 ± 1.7	7.1 ± 0.5[2]	9.2 ± 2.0	43.4 ± 12.1*[4]
Week 13	11.4 ± 1.9	12.0 ± 1.8	14.7 ± 2.6	11.7 ± 1.5	11.1 ± 2.8	39.7 ± 6.5**

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite (continued)

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
MALE (continued)						
Urinalysis						
n						
Day 14	9	10	10	10	10	10
Other	10	10	10	10	10	10
Alkaline phosphatase (mU/hr)						
Day 14	2 ± 1	2 ± 0	3 ± 1	2 ± 1	1 ± 0	1 ± 0
Day 42	5 ± 1	4 ± 0	2 ± 0**	2 ± 0**	3 ± 0*	2 ± 1*
Day 70	4 ± 0	3 ± 0*	2 ± 0**	2 ± 0**	3 ± 0**	2 ± 0**
Week 13	3 ± 1	2 ± 0	2 ± 0	2 ± 0	2 ± 0	1 ± 0*
N-acetyl-β-D-glucosaminidase (mU/hr)						
Day 14	6 ± 0	6 ± 1	5 ± 0	5 ± 0	5 ± 0*	3 ± 0**
Day 42	6 ± 1	5 ± 0	5 ± 0	5 ± 0	4 ± 0*	4 ± 0*
Day 70	6 ± 0	4 ± 1*	4 ± 0**	5 ± 0**	5 ± 0*	4 ± 0**[2]
Week 13	6 ± 1	5 ± 0	5 ± 0	5 ± 0	5 ± 0	3 ± 0**
Volume (mL/16 hr)						
Day 14	6.8 ± 0.3	7.0 ± 0.5	4.8 ± 0.4	4.3 ± 0.4**	5.1 ± 0.4	3.8 ± 0.4**
Day 42	8.5 ± 0.8	4.7 ± 0.3**	3.8 ± 0.3**	3.7 ± 0.3**	3.2 ± 0.2**	2.9 ± 0.2**
Day 70	8.5 ± 0.9	5.0 ± 0.5**	3.9 ± 0.3**	3.9 ± 0.3**	4.0 ± 0.2**	3.4 ± 0.3**
Week 13	6.1 ± 0.6	4.3 ± 0.4*	3.4 ± 0.2**	3.6 ± 0.2**	4.0 ± 0.3**	3.0 ± 0.2**
Specific gravity						
Day 14	1.062 ± 0.003[5]	1.060 ± 0.002	1.064 ± 0.001	1.066 ± 0.002	1.064 ± 0.002	1.057 ± 0.004
Day 42	1.031 ± 0.003	1.047 ± 0.002**	1.060 ± 0.003**	1.067 ± 0.002**	1.066 ± 0.003**	1.075 ± 0.004**
Day 70	1.035 ± 0.004	1.061 ± 0.004**	1.065 ± 0.003**	1.066 ± 0.003**	1.066 ± 0.002**	1.078 ± 0.005**
Week 13	1.044 ± 0.005	1.056 ± 0.006	1.065 ± 0.004**	1.063 ± 0.002**	1.063 ± 0.003**	1.073 ± 0.005**
pH						
Day 14	6.60 ± 0.10[5]	6.50 ± 0.07	6.50 ± 0.07	6.65 ± 0.08	6.85 ± 0.08	6.90 ± 0.07*
Day 42	7.00 ± 0.00	6.85 ± 0.08	6.90 ± 0.07	6.90 ± 0.07	6.95 ± 0.05	7.20 ± 0.08
Day 70	6.90 ± 0.07	7.35 ± 0.17	6.50 ± 0.13	6.50 ± 0.07	6.55 ± 0.19	7.10 ± 0.23
Week 13	6.80 ± 0.08	6.80 ± 0.08	6.30 ± 0.11*	6.45 ± 0.05	6.70 ± 0.08	7.55 ± 0.26
Base Study						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)	46.9 ± 0.4	46.9 ± 0.3	48.1 ± 0.3*	46.8 ± 0.3	47.9 ± 0.6	49.8 ± 1.6*
Hemoglobin (g/dL)	15.3 ± 0.1	15.4 ± 0.2	15.5 ± 0.1	15.4 ± 0.1	15.4 ± 0.1	16.0 ± 0.5
Erythrocytes (10^6/µL)	9.31 ± 0.08	9.36 ± 0.06	9.44 ± 0.09	9.24 ± 0.07	9.33 ± 0.11	9.66 ± 0.24
Reticulocytes (10^6/µL)	0.22 ± 0.01	0.18 ± 0.01	0.17 ± 0.02*	0.17 ± 0.02*	0.18 ± 0.02	0.15 ± 0.02**
Nucleated erythrocytes (10^3/µL)	0.01 ± 0.01	0.00 ± 0.00	0.03 ± 0.02	0.05 ± 0.02	0.08 ± 0.02**	0.03 ± 0.02
Mean cell volume (fL)	50.4 ± 0.2	50.1 ± 0.3	51.1 ± 0.3	50.8 ± 0.2	51.3 ± 0.3*	51.8 ± 0.5*
Mean cell hemoglobin (pg)	16.4 ± 0.1	16.5 ± 0.2	16.4 ± 0.1	16.6 ± 0.1	16.6 ± 0.1	16.5 ± 0.1
Mean cell hemoglobin concentration (g/dL)	32.7 ± 0.2	32.9 ± 0.3	32.2 ± 0.2	32.9 ± 0.3	32.2 ± 0.2	32.1 ± 0.2*

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite (continued)

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
MALE (continued)						
Leukocytes (10^3/µL)	7.50 ± 0.32	7.15 ± 0.42	7.14 ± 0.35	7.36 ± 0.40	7.30 ± 0.54	6.03 ± 0.43**
Segmented neutrophils (10^3/µL)	1.52 ± 0.18	1.03 ± 0.15	1.19 ± 0.10	1.47 ± 0.16	1.32 ± 0.09	1.43 ± 0.14
Lymphocytes (10^3/µL)	5.37 ± 0.24	5.68 ± 0.37	5.47 ± 0.35	5.31 ± 0.39	5.54 ± 0.56	4.20 ± 0.35*
Monocytes (10^3/µL)	0.53 ± 0.07	0.35 ± 0.05*	0.40 ± 0.06	0.44 ± 0.07	0.29 ± 0.04*	0.34 ± 0.04*
Eosinophils (10^3/µL)	0.06 ± 0.02	0.08 ± 0.02	0.06 ± 0.02	0.09 ± 0.03	0.09 ± 0.03	0.05 ± 0.02
Clinical Chemistry						
Urea nitrogen (mg/dL)	21.8 ± 0.5	21.1 ± 0.4	21.7 ± 0.8	22.8 ± 0.6	22.8 ± 0.6	24.0 ± 1.7
Creatinine (mg/dL)	0.69 ± 0.02	0.64 ± 0.02	0.68 ± 0.03	0.68 ± 0.02	0.62 ± 0.01**	0.59 ± 0.02**
Alanine aminotransferase (IU/L)	72 ± 9[2]	55 ± 2	61 ± 2	71 ± 7	61 ± 3	162 ± 58*
Alkaline phosphatase (IU/L)	235 ± 9	256 ± 12	226 ± 15	238 ± 6	226 ± 10	248 ± 16
Sorbitol dehydrogenase (IU/L)	10 ± 2	7 ± 1	9 ± 1	11 ± 2	8 ± 1	11 ± 2
5′-Nucleotidase (IU/L)	33 ± 2	32 ± 2	32 ± 2	35 ± 2	35 ± 2	41 ± 3*
Bile acids (µmol/L)	22.5 ± 2.7	17.4 ± 2.7	12.9 ± 1.3*	16.1 ± 1.5	13.2 ± 1.4*	27.8 ± 3.1
FEMALE						
Hematology						
n	10	10	10	9	10	8
Hematocrit (%)	46.5 ± 1.1	47.5 ± 0.5	46.9 ± 0.9	47.5 ± 0.8	47.4 ± 1.0	50.4 ± 1.7
Hemoglobin (g/dL)	15.1 ± 0.1	15.4 ± 0.1	15.3 ± 0.2	15.2 ± 0.1	15.3 ± 0.1	16.2 ± 0.5*
Erythrocytes (10^6/µL)	8.54 ± 0.17	8.70 ± 0.07	8.54 ± 0.15	8.64 ± 0.10	8.68 ± 0.15	9.36 ± 0.30**
Reticulocytes (10^6/µL)	0.12 ± 0.01	0.13 ± 0.02	0.17 ± 0.02	0.16 ± 0.02	0.15 ± 0.02	0.14 ± 0.03
Nucleated erythrocytes (10^3/µL)	0.01 ± 0.01	0.02 ± 0.01	0.03 ± 0.02	0.02 ± 0.02	0.04 ± 0.02	0.08 ± 0.03*
Mean cell volume (fL)	54.3 ± 0.4	54.8 ± 0.3	54.9 ± 0.3	55.0 ± 0.4	54.5 ± 0.3	53.9 ± 0.6
Mean cell hemoglobin (pg)	17.7 ± 0.2	17.7 ± 0.1	17.9 ± 0.2	17.6 ± 0.2	17.6 ± 0.2	17.3 ± 0.2
Mean cell hemoglobin concentration (g/dL)	32.5 ± 0.6	32.5 ± 0.3	32.7 ± 0.4	32.0 ± 0.4	32.3 ± 0.5	32.2 ± 0.5
Leukocytes (10^3/µL)	5.61 ± 0.45	5.90 ± 0.22	7.03 ± 0.40*	6.48 ± 0.31*	7.09 ± 0.37*	6.78 ± 0.52*
Segmented neutrophils (10^3/µL)	1.35 ± 0.22	1.33 ± 0.08	1.35 ± 0.10[2]	1.21 ± 0.16	1.56 ± 0.17	1.24 ± 0.19
Lymphocytes (10^3/µL)	3.91 ± 0.20	4.21 ± 0.19	4.87 ± 0.23**	4.85 ± 0.28*	5.06 ± 0.32**	5.17 ± 0.48**
Monocytes (10^3/µL)	0.29 ± 0.06	0.27 ± 0.04	0.43 ± 0.09	0.33 ± 0.07	0.41 ± 0.07	0.30 ± 0.09
Eosinophils (10^3/µL)	0.06 ± 0.02	0.07 ± 0.02	0.09 ± 0.03	0.05 ± 0.01	0.04 ± 0.02	0.05 ± 0.03

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite (continued)

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
FEMALE (continued)						
Clinical Chemistry						
n	10	10	10	10	10	8
Urea nitrogen (mg/dL)	20.0 ± 1.0	22.4 ± 0.6*	20.3 ± 0.5	21.8 ± 0.7	20.6 ± 0.4	36.6 ± 2.7**[4]
Creatinine (mg/dL)	0.60 ± 0.03	0.63 ± 0.02	0.59 ± 0.02	0.60 ± 0.02	0.55 ± 0.02	0.54 ± 0.06
Alanine aminotransferase (IU/L)	44 ± 2	47 ± 2	46 ± 2	43 ± 1	56 ± 3**	204 ± 36**
Alkaline phosphatase (IU/L)	191 ± 5	190 ± 5	208 ± 8	234 ± 10**	250 ± 7**	256 ± 18**
Sorbitol dehydrogenase (IU/L)	5 ± 1	6 ± 1	5 ± 1	4 ± 1	5 ± 0	9 ± 1
5′-Nucleotidase (IU/L)	30 ± 1	31 ± 1	32 ± 1	32 ± 1	32 ± 1	36 ± 1**
Bile acids (µmol/L)	23.3 ± 4.5	26.3 ± 3.7	14.6 ± 1.8	16.4 ± 2.6	17.9 ± 1.9	57.6 ± 8.5*

[1] Data are given as mean ± standard error. Statistical tests were performed on unrounded data.
[2] n=9.
[3] n=8.
[4] n=7.
[5] n=10.
* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test.
** Significantly different ($P \leq 0.01$) from the control group by Dunn's or Shirley's test.

TABLE D3 Hematology and Clinical Chemistry Data for $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate[1]

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
MALE						
Hematology						
n	10	9	10	10	10	10
Hematocrit (%)	48.4 ± 0.6	48.7 ± 0.6	48.6 ± 0.5	49.0 ± 0.4	49.2 ± 0.4	49.2 ± 0.7
Hemoglobin (g/dL)	16.0 ± 0.1	15.9 ± 0.1	15.8 ± 0.2	15.9 ± 0.1	16.0 ± 0.1	15.9 ± 0.1
Erythrocytes (10^6/µL)	10.50 ± 0.11	10.26 ± 0.14	10.29 ± 0.16	10.44 ± 0.11	10.49 ± 0.08	10.47 ± 0.13
Reticulocytes (10^6/µL)	0.21 ± 0.01	0.20 ± 0.01	0.20 ± 0.02	0.17 ± 0.01	0.23 ± 0.02	0.18 ± 0.01
Nucleated erythrocytes (10^3/µL)	0.02 ± 0.02	0.04 ± 0.01	0.02 ± 0.01	0.05 ± 0.02	0.03 ± 0.02	0.02 ± 0.01
Mean cell volume (fL)	46.3 ± 0.3	47.6 ± 0.4	47.3 ± 0.5	46.9 ± 0.4	46.9 ± 0.2	47.1 ± 0.3
Mean cell hemoglobin (pg)	15.2 ± 0.1	15.5 ± 0.2	15.4 ± 0.3	15.3 ± 0.1	15.3 ± 0.1	15.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.0 ± 0.4	32.6 ± 0.4	32.6 ± 0.4	32.5 ± 0.2	32.6 ± 0.3	32.2 ± 0.4
Leukocytes (10^3/µL)	4.45 ± 0.32	4.07 ± 0.35	3.72 ± 0.38	5.43 ± 0.26	4.81 ± 0.42	3.51 ± 0.34
Segmented neutrophils (10^3/µL)	0.42 ± 0.03	0.36 ± 0.04	0.36 ± 0.05	0.53 ± 0.07	0.46 ± 0.05	0.38 ± 0.07
Lymphocytes (10^3/µL)	3.84 ± 0.31	3.50 ± 0.32	3.19 ± 0.33	4.66 ± 0.19	4.15 ± 0.37	3.02 ± 0.28
Monocytes (10^3/µL)	0.09 ± 0.02	0.13 ± 0.03	0.09 ± 0.02	0.14 ± 0.03	0.16 ± 0.02	0.07 ± 0.02
Eosinophils (10^3/µL)	0.07 ± 0.02	0.03 ± 0.02	0.05 ± 0.02	0.07 ± 0.02	0.02 ± 0.01	0.02 ± 0.01
Clinical Chemistry						
n	9	5	8	10	9	9
Urea nitrogen (mg/dL)	30.4 ± 2.4[2]	29.2 ± 1.2	31.0 ± 1.5	26.7 ± 1.2[3]	26.1 ± 0.7	26.0 ± 1.2[4]
Creatinine (mg/dL)	0.45 ± 0.03[4]	0.45 ± 0.05[4]	0.46 ± 0.02[2]	0.43 ± 0.03[5]	0.40 ± 0.00[4]	0.30 ± 0.00*[6]
Alanine aminotransferase (IU/L)	49 ± 7	68 ± 12[7]	63 ± 12[8]	45 ± 7[7]	40 ± 4	53 ± 9[7]
Alkaline phosphatase (IU/L)	70 ± 2	66 ± 2[9]	68 ± 2[9]	68 ± 3	60 ± 2**	66 ± 3
Sorbitol dehydrogenase (IU/L)	14 ± 2[5]	13 ± 0[4]	13 ± 1[5]	13 ± 0[4]	13 ± 1[3]	15 ± 0[6]
5′-Nucleotidase (IU/L)	47 ± 2[3]	47 ± 2	47 ± 2	42 ± 2[10]	42 ± 2	42 ± 2[2]
FEMALE						
Hematology						
n	10	10	10	10	10	9
Hematocrit (%)	48.0 ± 0.6	48.8 ± 0.6	49.0 ± 0.6	48.1 ± 0.4	46.6 ± 0.4	48.7 ± 0.9
Hemoglobin (g/dL)	15.9 ± 0.1	15.8 ± 0.1	16.0 ± 0.2	16.0 ± 0.1	15.6 ± 0.1	16.0 ± 0.2
Erythrocytes (10^6/µL)	9.99 ± 0.16	10.09 ± 0.14	10.22 ± 0.13	10.02 ± 0.07	9.54 ± 0.14*	10.04 ± 0.20
Reticulocytes (10^6/µL)	0.22 ± 0.01	0.24 ± 0.02	0.22 ± 0.01	0.23 ± 0.02	0.24 ± 0.02	0.24 ± 0.02
Nucleated erythrocytes (10^3/µL)	0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Mean cell volume (fL)	47.9 ± 0.5	48.4 ± 0.4	47.9 ± 0.4	48.1 ± 0.5	48.7 ± 0.6	49.2 ± 0.5
Mean cell hemoglobin (pg)	15.9 ± 0.3	15.7 ± 0.2	15.6 ± 0.2	16.0 ± 0.1	16.4 ± 0.2	16.2 ± 0.3

TABLE D3 Hematology and Clinical Chemistry Data for B6C3F$_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate (continued)

	0 ppm	3.75 ppm	7.5 ppm	15 ppm	30 ppm	60 ppm
FEMALE (continued)						
Mean cell hemoglobin concentration (g/dL)	33.1 ± 0.4	32.5 ± 0.3	32.6 ± 0.3	33.2 ± 0.3	33.5 ± 0.3	32.9 ± 0.4
Leukocytes (10^3/µL)	2.77 ± 0.23	3.35 ± 0.23	2.96 ± 0.36	3.18 ± 0.26	2.84 ± 0.17	2.87 ± 0.31
Segmented neutrophils (10^3/µL)	0.21 ± 0.02	0.34 ± 0.06	0.21 ± 0.04	0.23 ± 0.04	0.22 ± 0.03	0.20 ± 0.04
Lymphocytes (10^3/µL)	2.46 ± 0.22	2.85 ± 0.22	2.64 ± 0.32	2.81 ± 0.25	2.54 ± 0.17	2.54 ± 0.26
Monocytes (10^3/µL)	0.07 ± 0.02	0.08 ± 0.03	0.08 ± 0.02	0.08 ± 0.02	0.04 ± 0.01	0.08 ± 0.02
Eosinophils (10^3/µL)	0.03 ± 0.01	0.03 ± 0.01	0.01 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.02 ± 0.01
Clinical Chemistry						
n	9	3	6	7	6	4
Urea nitrogen (mg/dL)	25.3 ± 1.7[3]	30.0 ± 1.8[4]	26.7 ± 2.2	26.0 ± 1.7	25.8 ± 1.5	29.2 ± 2.1[2]
Creatinine (mg/dL)	0.38 ± 0.04[2]	0.37 ± 0.07	0.36 ± 0.02[2]	0.33 ± 0.02[10]	0.34 ± 0.02[2]	0.37 ± 0.03[5]
Alanine aminotransferase (IU/L)	40 ± 4	36 ± 3[10]	40 ± 6[3]	45 ± 8[10]	41 ± 6[7]	39 ± 2
Alkaline phosphatase (IU/L)	121 ± 4	118 ± 4[3]	125 ± 6[7]	118 ± 2	134 ± 5[3]	127 ± 7
Sorbitol dehydrogenase (IU/L)	11 ± 1[2]	12 ± 1	11 ± 0[4]	12 ± 0[5]	12 ± 0[2]	–[11]
5′-Nucleotidase (IU/L)	71 ± 5[4]	60 ± 3	77 ± 3	64 ± 3[4]	68 ± 8	–
Bile acids (µmol/L)	18.5 ± 1.5[6]	13.0 ± 0.6	19.0 ± 1.0[6]	16.0[12]	14.3 ± 3.1[4]	–

[1] Data are given as mean ± standard error. Statistical tests were performed on unrounded data.
[2] n=5.
[3] n=7.
[4] n=4.
[5] n=3.
[6] n=2.
[7] n=8.
[8] n=9.
[9] n=10.
[10] n=6.
[11] Not measured for this exposure group.
[12] n=1.
* Significantly different ($P \leq 0.05$) from the control group by Shirley's test.
** Significantly different ($P \leq 0.01$) from the control group by Shirley's test.

TABLE D4 Hematology and Clinical Chemistry Data for $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite[1]

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
MALE						
Hematology						
n	8	8	10	9	5	10
Hematocrit (%)	52.7 ± 1.1	51.7 ± 0.9	52.8 ± 1.1	53.9 ± 1.9	51.9 ± 1.6	53.4 ± 0.8
Hemoglobin (g/dL)	17.2 ± 0.2	16.9 ± 0.2	17.3 ± 0.3	17.9 ± 0.5	16.8 ± 0.3	17.3 ± 0.3
Erythrocytes (10^6/µL)	10.91 ± 0.21	10.68 ± 0.15	10.78 ± 0.24	11.24 ± 0.33	10.60 ± 0.30	11.00 ± 0.18
Reticulocytes (10^6/µL)	0.24 ± 0.03	0.29 ± 0.02	0.28 ± 0.02	0.24 ± 0.02	0.32 ± 0.04	0.28 ± 0.02
Mean cell volume (fL)	48.4 ± 0.3	48.5 ± 0.3	49.0 ± 0.3	47.9 ± 0.6	49.0 ± 0.5	48.5 ± 0.2
Mean cell hemoglobin (pg)	15.9 ± 0.2	15.8 ± 0.1	16.1 ± 0.1	15.9 ± 0.1	15.8 ± 0.2	15.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)	32.7 ± 0.4	32.7 ± 0.3	32.8 ± 0.3	33.3 ± 0.7	32.3 ± 0.6	32.5 ± 0.3
Leukocytes (10^3/µL)	2.35 ± 0.21	2.23 ± 0.38	2.30 ± 0.25	2.22 ± 0.29	2.44 ± 0.53	2.46 ± 0.34
Segmented neutrophils (10^3/µL)	0.29 ± 0.02	0.33 ± 0.06	0.27 ± 0.04	0.33 ± 0.08	0.37 ± 0.10	0.24 ± 0.03
Lymphocytes (10^3/µL)	1.98 ± 0.19	1.81 ± 0.31	1.95 ± 0.22	1.80 ± 0.19	1.99 ± 0.42	2.11 ± 0.30
Monocytes (10^3/µL)	0.02 ± 0.01	0.03 ± 0.01	0.04 ± 0.01	0.06 ± 0.03	0.05 ± 0.01	0.06 ± 0.02
Eosinophils (10^3/µL)	0.03 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.03 ± 0.01
Clinical Chemistry						
n	7	3	7	7	7	7
Urea nitrogen (mg/dL)	28.1 ± 2.8	32.3 ± 1.8[2]	29.4 ± 1.5[3]	28.4 ± 1.5	29.3 ± 1.3	26.1 ± 1.0
Creatinine (mg/dL)	0.53 ± 0.03	0.60 ± 0.04[4]	0.53 ± 0.03	0.44 ± 0.04	0.45 ± 0.05[5]	0.50 ± 0.00[6]
Alanine aminotransferase (IU/L)	50 ± 12	51 ± 10	55 ± 11	92 ± 25[7]	66 ± 38[5]	24 ± 2[5]
Alkaline phosphatase (IU/L)	70 ± 2[4]	76 ± 1	74 ± 5[8]	69 ± 6[8]	–[9]	64[10]
Sorbitol dehydrogenase (IU/L)	17 ± 1	11 ± 2	15 ± 2[8]	15 ± 1[6]	12[10]	13[10]
5′-Nucleotidase (IU/L)	48 ± 2[6]	58[10]	57 ± 7[6]	49 ± 6[6]	–	–
FEMALE						
Hematology						
n	10	10	9	10	10	10
Hematocrit (%)	51.2 ± 0.6	52.6 ± 1.2	52.2 ± 2.2	51.9 ± 0.8	51.1 ± 0.8	51.9 ± 0.4
Hemoglobin (g/dL)	17.0 ± 0.2	17.5 ± 0.3	17.4 ± 0.7	17.2 ± 0.3	16.7 ± 0.2	17.1 ± 0.1
Erythrocytes (10^6/µL)	10.39 ± 0.14	10.75 ± 0.25	10.68 ± 0.50	10.57 ± 0.18	10.29 ± 0.17	10.54 ± 0.09
Reticulocytes (10^6/µL)	0.20 ± 0.02	0.21 ± 0.03	0.21 ± 0.03	0.20 ± 0.02	0.21 ± 0.02	0.23 ± 0.02
Mean cell volume (fL)	49.3 ± 0.2	49.0 ± 0.2	49.0 ± 0.4	49.0 ± 0.3	49.6 ± 0.2	49.2 ± 0.2
Mean cell hemoglobin (pg)	16.4 ± 0.1	16.3 ± 0.1	16.3 ± 0.2	16.3 ± 0.1	16.2 ± 0.1	16.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.2 ± 0.2	33.2 ± 0.2	33.2 ± 0.3	33.2 ± 0.2	32.7 ± 0.2	32.9 ± 0.2
Leukocytes (10^3/µL)	2.26 ± 0.14	2.28 ± 0.18	2.96 ± 0.20	2.58 ± 0.24	2.84 ± 0.27	2.44 ± 0.21

TABLE D4 Hematology and Clinical Chemistry Data for $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite (continued)

	0 ppm	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
FEMALE (continued)						
Segmented neutrophils (10^3/µL)	0.25 ± 0.04	0.18 ± 0.03	0.22 ± 0.03	0.28 ± 0.05	0.21 ± 0.03	0.22 ± 0.05
Lymphocytes (10^3/µL)	1.94 ± 0.14	2.02 ± 0.16	2.60 ± 0.16*	2.23 ± 0.20	2.53 ± 0.24	2.13 ± 0.17
Monocytes (10^3/µL)	0.05 ± 0.02	0.04 ± 0.01	0.09 ± 0.03	0.04 ± 0.01	0.08 ± 0.01	0.07 ± 0.03
Eosinophils (10^3/µL)	0.01 ± 0.00	0.03 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.00
Clinical Chemistry						
n	10	4	4	3	3	4
Urea nitrogen (mg/dL)	25.0 ± 1.4	21.8 ± 1.9[8]	25.9 ± 1.4[11]	22.0 ± 1.0[7]	25.0 ± 2.3[2]	29.0 ± 0.8[11]
Creatinine (mg/dL)	0.50 ± 0.00[8]	0.50 ± 0.03[8]	0.51 ± 0.04[2]	0.58 ± 0.08[4]	0.47 ± 0.07	0.43 ± 0.05
Alanine aminotransferase (IU/L)	36 ± 1[6]	46 ± 14	52 ± 12[8]	22 ± 0[5]	62 ± 17	49 ± 11
Alkaline phosphatase (IU/L)	115 ± 3[6]	121 ± 10	108 ± 2	125 ± 4	104 ± 19[5]	121[10]
Sorbitol dehydrogenase (IU/L)	13 ± 4[5]	10 ± 3	13 ± 1	11 ± 3	8 ± 6[5]	13[10]

[1] Data are given as mean ± standard error. Statistical tests were performed on unrounded data.
[2] n=7.
[3] n=10.
[4] n=4.
[5] n=2.
[6] n=3.
[7] n=6.
[8] n=5.
[9] Not measured for this exposure group.
[10] n=1.
[11] n=9.
* Significantly different ($P \leq 0.05$) from the control group by Dunn's test.

APPENDIX E

Reproductive Tissue Evaluations and Estrous Cycle Characterization

Table E1 Summary of Reproductive Tissue Evaluations in Male F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate E-2

Table E2 Summary of Estrous Cycle Characterization in Female F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate E-2

Table E3 Summary of Reproductive Tissue Evaluations in Male F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite E-3

Table E4 Summary of Estrous Cycle Characterization in Female F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite E-3

Table E5 Summary of Reproductive Tissue Evaluations in Male $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate E-4

Table E6 Summary of Estrous Cycle Characterization in Female $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate E-4

Table E7 Summary of Reproductive Tissue Evaluations in Male $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite E-5

Table E8 Summary of Estrous Cycle Characterization in Female $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite E-5

TABLE E1 Summary of Reproductive Tissue Evaluations in Male F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate[1]

Study Parameters	0 ppm	3.75 ppm	15 ppm	30 ppm
n	10	10	10	10
Weights (g)				
Necropsy body weight	319 ± 4	309 ± 4	290 ± 6**	246 ± 7**
Left epididymis	0.425 ± 0.007	0.438 ± 0.007	0.416 ± 0.009	0.409 ± 0.010
Left cauda epididymis	0.171 ± 0.003	0.174 ± 0.007	0.168 ± 0.008	0.164 ± 0.007
Left testis	1.50 ± 0.02	1.51 ± 0.02	1.48 ± 0.03	1.43 ± 0.03
Spermatid measurements				
Spermatid heads (10^7/g testis)	10.91 ± 0.41	9.14 ± 0.26**	9.36 ± 0.40*	10.44 ± 0.39
Spermatid heads (10^7/testis)	16.29 ± 0.54	13.77 ± 0.45*	13.77 ± 0.55**	14.87 ± 0.54
Spermatid count (mean/10^{-4} mL suspension)	81.43 ± 2.68	68.83 ± 2.25*	68.83 ± 2.77**	74.35 ± 2.69
Epididymal spermatozoal measurements				
Motility (%)	97.89 ± 0.13	97.66 ± 0.16	97.65 ± 0.11	96.73 ± 0.27**
Concentration (10^6/g cauda epididymal tissue)	757 ± 23	778 ± 41	736 ± 22	746 ± 32

[1] Data are presented as mean ± standard error. Differences from the control group for epididymal, cauda epididymal, and testis weights and spermatozoal concentration are not significant by Dunn's or Shirley's test.
* Significantly different ($P \leq 0.05$) from the control group by Dunn's test.
** Significantly different ($P \leq 0.01$) from the control group by Williams' (necropsy body weight only), Dunn's, or Shirley's test.

TABLE E2 Summary of Estrous Cycle Characterization in Female F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenate[1]

Study Parameters	0 ppm	3.75 ppm	15 ppm	30 ppm
n	8	8	5	3
Necropsy body weight (g)	199 ± 5	195 ± 4	182 ± 2**	141 ± 4**
Estrous cycle length (days)	6.56 ± 0.58[2]	6.38 ± 0.42[2]	7.80 ± 0.66[3]	8.33 ± 0.67[4]
Estrous stages[5] (% of cycle)				
Diestrus	29.2	40.0	59.2	73.3
Proestrus	13.3	10.8	12.5	3.3
Estrus	49.2	40.8	22.5	16.7
Metestrus	8.3	8.3	5.8	6.7

[1] Necropsy body weight and estrous cycle length data are presented as mean ± standard error; for necropsy body weights, n=10 for all groups. Differences from the control group for estrous cycle length are not significant by Shirley's test.
[2] Estrous cycle longer than 12 days or unclear in 2 of 10 rats.
[3] Estrous cycle longer than 12 days or unclear in 5 of 10 rats.
[4] Estrous cycle longer than 12 days or unclear in 7 of 10 rats.
[5] Evidence shows that females exposed to sodium selenate differ significantly ($P<0.01$, Wilk's Criterion) from the control females in the relative length of time spent in the estrous stages. Exposed females spent more time in diestrus and less time in proestrus, estrus, and metestrus than control females.
** Significantly different ($P \leq 0.01$) from the control group by Williams' test.

TABLE E3 Summary of Reproductive Tissue Evaluations in Male F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite[1]

Study Parameters	0 ppm	4 ppm	8 ppm	16 ppm
n	10	10	10	10
Weights (g)				
Necropsy body weight	355 ± 6	346 ± 4	337 ± 4	323 ± 8**
Left epididymis	0.449 ± 0.006	0.436 ± 0.007	0.439 ± 0.012	0.434 ± 0.008
Left cauda epididymis	0.194 ± 0.003	0.182 ± 0.003	0.184 ± 0.006	0.191 ± 0.005
Left testis	1.53 ± 0.02	1.51 ± 0.04	1.52 ± 0.03	1.51 ± 0.03
Spermatid measurements				
Spermatid heads (10^7/g testis)	10.22 ± 0.44	11.02 ± 0.27	10.68 ± 0.40	10.57 ± 0.71
Spermatid heads (10^7/testis)	15.58 ± 0.64	16.63 ± 0.59	16.23 ± 0.59	16.02 ± 1.15
Spermatid count (mean/10^{-4} mL suspension)	77.88 ± 3.22	83.13 ± 2.93	81.13 ± 2.96	80.08 ± 5.73
Epididymal spermatozoal measurements				
Motility (%)	98.99 ± 0.15	99.35 ± 0.11	99.30 ± 0.10	99.19 ± 0.11
Concentration (10^6/g cauda epididymal tissue)	737 ± 21	656 ± 24*	604 ± 22**	613 ± 18**

[1] Data are presented as mean ± standard error. Differences from the control group for epididymal, cauda epididymal, and testis weights, spermatid measurements, and spermatozoal motility are not significant by Dunn's test.
* Significantly different ($P \leq 0.05$) from the control group by Shirley's test.
** Significantly different ($P \leq 0.01$) from the control group by Williams' (necropsy body weight only) or Shirley's test.

TABLE E4 Summary of Estrous Cycle Characterization in Female F344/N Rats in the 13-Week Drinking Water Study of Sodium Selenite[1]

Study Parameters	0 ppm	4 ppm	8 ppm	16 ppm
n	8	9	9	7
Necropsy body weight (g)	198 ± 3	198 ± 3	196 ± 3	189 ± 2
Estrous cycle length (days)	5.75 ± 0.30	6.56 ± 0.33	6.22 ± 0.52	7.29 ± 0.75
Estrous stages[2] (% of cycle)				
Diestrus	34.2	44.2	46.7	58.3
Proestrus	16.7	10.8	15.0	8.3
Estrus	38.3	36.7	25.8	20.8
Metestrus	10.8	8.3	12.5	12.5

[1] Necropsy body weight and estrous cycle length data are presented as mean ± standard error; for necropsy body weights, n=10 for all groups. Differences from the control group for necropsy body weight are not significant by Williams' test. Differences from the control group for estrous cycle length are not significant by Dunn's test.
[2] Evidence shows that females in the 16 ppm group differ significantly ($P<0.05$, Wilk's Criterion) from the control females in the relative length of time spent in the estrous stages.

TABLE E5 Summary of Reproductive Tissue Evaluations in Male B6C3F$_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate[1]

Study Parameters	0 ppm	3.75 ppm	15 ppm	60 ppm
n	10	10	10	10
Weights (g)				
Necropsy body weight	39.4 ± 1.0	38.4 ± 0.9	36.6 ± 0.7*	30.1 ± 0.6**
Left epididymis	0.044 ± 0.001	0.050 ± 0.003	0.050 ± 0.003	0.041 ± 0.001
Left cauda epididymis	0.015 ± 0.001	0.017 ± 0.001	0.017 ± 0.001	0.014 ± 0.001
Left testis	0.114 ± 0.002	0.121 ± 0.003	0.115 ± 0.002	0.113 ± 0.001
Spermatid measurements				
Spermatid heads (10^7/g testis)	16.53 ± 1.15	17.60 ± 0.95	16.45 ± 0.80	15.60 ± 1.04
Spermatid heads (10^7/testis)	1.89 ± 0.13	2.14 ± 0.14	1.90 ± 0.11	1.75 ± 0.11
Spermatid count (mean/10^{-4} mL suspension)	58.95 ± 4.03	67.03 ± 4.37	59.28 ± 3.60	54.73 ± 3.36
Epididymal spermatozoal measurements				
Motility (%)	97.11 ± 0.14	96.97 ± 0.20	97.02 ± 0.21	96.09 ± 0.42
Concentration (10^6/g cauda epididymal tissue)	1,544 ± 72	1,313 ± 57	1,380 ± 59	1,351 ± 122

[1] Data are presented as mean ± standard error. Differences from the control group for epididymal, cauda epididymal, and testis weights and spermatid and spermatozoal measurements are not significant by Dunn's or Shirley's test.
* Significantly different ($P \leq 0.05$) from the control group by Williams' test.
** Significantly different ($P \leq 0.01$) from the control group by Williams' test.

TABLE E6 Summary of Estrous Cycle Characterization in Female B6C3F$_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenate[1]

Study Parameters	0 ppm	3.75 ppm	15 ppm	60 ppm
n	10	10	9	8
Necropsy body weight (g)	30.7 ± 0.7	29.5 ± 0.7	28.5 ± 0.8*[2]	23.8 ± 0.6**[2]
Estrous cycle length (days)	4.70 ± 0.17	4.60 ± 0.12	5.11 ± 0.51[3]	5.88 ± 0.67[4]
Estrous stages (% of cycle)				
Diestrus	31.7	31.7	22.5	36.7
Proestrus	20.0	20.8	19.2	17.5
Estrus	37.5	38.3	44.2	36.7
Metestrus	10.8	9.2	14.2	9.2

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

TABLE E7 Summary of Reproductive Tissue Evaluations in Male $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite[1]

Study Parameters	0 ppm	2 ppm	8 ppm	32 ppm
n	10	10	10	10
Weights (g)				
Necropsy body weight	40.8 ± 0.7	40.1 ± 0.9	39.5 ± 0.9	34.6 ± 0.6**
Left epididymis	0.051 ± 0.001	0.048 ± 0.002	0.045 ± 0.002	0.047 ± 0.001
Left cauda epididymis	0.017 ± 0.001	0.017 ± 0.001	0.016 ± 0.001	0.016 ± 0.001
Left testis	0.117 ± 0.001	0.110 ± 0.002	0.117 ± 0.003	0.113 ± 0.002
Spermatid measurements				
Spermatid heads (10^7/g testis)	19.38 ± 1.06	22.88 ± 1.14	19.03 ± 0.44	22.30 ± 1.08
Spermatid heads (10^7/testis)	2.26 ± 0.12	2.53 ± 0.14	2.21 ± 0.04	2.50 ± 0.10
Spermatid count (mean/10^{-4} mL suspension)	70.60 ± 3.67	78.98 ± 4.44	69.08 ± 1.36	78.15 ± 3.11
Epididymal spermatozoal measurements				
Motility (%)	98.21 ± 0.44	98.24 ± 0.41	98.80 ± 0.21	98.00 ± 0.73
Concentration (10^6/g cauda epididymal tissue)	1,562 ± 59	1,612 ± 128	1,620 ± 135	1,551 ± 65

[1] Data are presented as mean ± standard error. Differences from the control group for epididymal, cauda epididymal, and testis weights and spermatid and spermatozoal measurements are not significant by Dunn's or Shirley's test.
** Significantly different ($P \leq 0.01$) from the control group by Williams' test.

TABLE E8 Summary of Estrous Cycle Characterization in Female $B6C3F_1$ Mice in the 13-Week Drinking Water Study of Sodium Selenite[1]

Study Parameters	0 ppm	2 ppm	8 ppm	32 ppm
n	10	10	10	8
Necropsy body weight (g)	31.5 ± 1.4	30.4 ± 1.1	29.9 ± 0.5	25.3 ± 0.5**[2]
Estrous cycle length (days)	4.50 ± 0.07	4.55 ± 0.12	5.05 ± 0.45	5.81 ± 0.54*
Estrous stages (% of cycle)				
Diestrus	30.8	29.2	30.0	23.3
Proestrus	19.2	20.8	19.2	16.7
Estrus	33.3	35.8	37.5	51.7
Metestrus	16.7	14.2	13.3	8.3

[1] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. By multivariate analysis of variance, exposed groups do not differ significantly from the control group in the relative length of time spent in the estrous stages.
[2] n=10.
* Significantly different ($P \leq 0.05$) from the control group by Shirley's test.
** Significantly different ($P \leq 0.01$) from the control group by Williams' test.

NTP TECHNICAL REPORTS ON TOXICITY STUDIES PRINTED AS OF JULY 1994

Toxicity Report Number	Chemical	Route of Exposure	Publication Number
1	Hexachloro-1,3-butadiene	Dosed Feed	91-3120
2	*n*-Hexane	Inhalation	91-3121
3	Acetone	Drinking Water	91-3122
4	1,2-Dichloroethane	Drinking Water, Gavage	91-3123
5	Cobalt Sulfate Heptahydrate	Inhalation	91-3124
6	Pentachlorobenzene	Dosed Feed	91-3125
7	1,2,4,5-Tetrachlorobenzene	Dosed Feed	91-3126
8	D &C Yellow No. 11	Dosed Feed	91-3127
9	*o*-Cresol *m*-Cresol *p*-Cresol	Dosed Feed	92-3128
10	Ethylbenzene	Inhalation	92-3129
11	Antimony Potassium Tartrate	Drinking Water, I. P. Inject.	92-3130
12	Castor Oil	Dosed Feed	92-3131
13	Trinitrofluorenone	Dermal, Dosed Feed	92-3132
14	*p*-Chloro-α, α, α-Trifluoro toluene	Gavage (corn oil, α-CD)	92-3133
15	*t*-Butyl Perbenzoate	Gavage	92-3134
16	Glyphosate	Dosed Feed	92-3135
17	Black Newsprint Ink	Dermal	92-3340
18	Methyl Ethyl Ketone Peroxide	Dermal	92-3341
19	Formic Acid	Inhalation	92-3342
20	Diethanolamine	Drinking Water, Dermal	92-3343
21	2 -Hydroxy-4-Methoxybenzophenone	Dosed Feed, Drinking Water	92-3344
22	N, N-Dimethylformamide	Inhalation	93-3345
23	*o*-Nitrotoluene *m*-Nitrotoluene *p*-Nitrotoluene	Dosed Feed	92-3346
24	1,6-Hexanediamine	Inhalation	93-3347
25	Glutaraldehyde	Inhalation	93-3348
26	Ethylene Glycol Ethers	Drinking Water	93-3349
27	Riddelliine	Gavage	94-3350
28	Tetrachlorophthalic Anhydride	Gavage	93-3351
29	Cupric Sulfate	Drinking Water, Dosed Feed	93-3352

* U.S. GOVERNMENT PRINTING OFFICE: 1994 300-970/00017

NTP TECHNICAL REPORTS ON TOXICITY STUDIES PRINTED AS OF JULY 1994 (continued)

Toxicity Report Number	Chemical	Route of Exposure	Publication Number
32	Methylene Bis(thiocyanate)	Gavage	94-3381
33	2-Chloronitrobenzene 4-Chloro nitrobenzene	Inhalation	93-3382
35	Chemical Mixture of 25 Groundwater Contaminants	Drinking Water	93-3384
36	Pesticide/Fertilizer Mixtures	Drinking Water	93-3385
37	Sodium Cyanide	Drinking Water	94-3386