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Fluoride

Fluorine (F) is the most electronegative and reactive of known elements. It rarely occurs free in nature, chemically combining to form fluorides. Fluorides are widely distributed throughout the environment in various anthropogenic and natural forms. Mineral forms of F include cryolite (Na_3AlF_6), fluorite (CaF_2), and fluorapatite ($\text{Ca}_5(\text{PO}_4)_3\text{F}$). Vegetation can accumulate fluoride from soil, water, and the atmosphere.¹⁴⁶ In aqueous environments, F occurs as the free fluoride ion (F^-) and is mobile, especially in alkaline waters.⁹⁵ Unless surface waters are contaminated by a F^- source, ground waters tend to have higher concentrations of F^- than surface waters.

Essentiality

The NRC¹⁴⁷ describes F^- as an “important constituent” of bones and teeth, and, although essentiality has not been proven, small amounts have been added to municipal water supplies to improve dental health for decades. Apparently, even if F is essential, the dietary requirement is so small it is easily met by even highly purified diets. As noted by Ammerman,¹⁴⁸ “Whether or not it is essential for animals may be open to debate... The fact that it is toxic is more easily confirmed.”

Metabolism

Fluoride is readily absorbed by the stomach, rumen, and small intestine. The efficiency of absorption depends upon the solubility of the specific F compound, other dietary components, and the species, sex, and age of the animal.^{147,149} Conditions that result in very low pH favor the formation of hydrogen fluoride (HF), which is lipophilic and thus diffuses easily across lipid membranes. The F^- ion is absorbed in the small intestine via a pH independent process.¹⁴⁷ Soluble fluorides, i.e. the F^- ion in water, are almost 100% absorbed. Less soluble sources such as F compounds in bone meal are relatively poorly absorbed. Ca, Mg, Al, NaCl, and high lipid concentrations are known to depress F uptake.^{147,150}

Two mechanisms are responsible for removal of F^- from the systemic circulation: renal excretion and deposition in calcified tissues. After absorption, most F^- circulates in plasma as ionic F^- . To a lesser extent, it circulates as

CaF_2 or HF, or it is bound to protein.¹⁵⁰⁻¹⁵² Circulating F^- represents a relatively small portion of the total body burden but is the form most easily exchanged with other tissues and/or eliminated via renal filtration.^{151,152} Urinary excretion is the primary route of elimination and is directly related to urinary pH; thus, factors that affect urinary pH influence how much F^- is excreted.^{150,153} Under “normal” circumstances, roughly 50% of ingested F^- is eliminated immediately, and the remainder is incorporated into bony tissues¹⁴⁷; however, these percentages may be significantly modified by physiologic factors such as age, sex, or other factors. Calcified tissues such as teeth and bone have a great affinity for F^- , incorporating it as fluorapatite in place of hydroxyapatite in the calcified matrix.^{147,153} To a certain extent, bone deposition represents a form of detoxication by decreasing the F^- exposure of other tissues. Fluorapatite crystals, however, are less soluble than the hydroxyapatite they replace and thus 1) persist for long periods in bone, and 2) interfere with normal turnover (remodelling) of bone. Therefore, at higher concentrations, bone F^- interferes with normal physiological processes like growth and healing. Since F^- deposition in skeletal tissues is related to the turnover of bone minerals, young, rapidly growing animals are more likely to accumulate it.¹⁴⁷

Toxicity

Animals can ingest potentially toxic doses of F^- from a variety of sources. In the past, forages contaminated by aluminum smelters or grown in naturally high F^- soils, rock phosphate fed nutritional supplements, and/or consumption of naturally high F^- water have resulted in F^- poisoning.^{147,149,154-156} Large doses of soluble F^- can form corrosive HF, interfere with ion gradients in excitable cells, and/or precipitate divalent cations from serum.^{157,158} Thus, acute fluorosis is manifested as gastroenteritis, cardiac arrhythmias, and/or collapse.¹⁵⁷ Chronic or sub-chronic exposure to somewhat lower doses results in kidney damage,^{157,159,160} neurologic damage, or reproductive failure.¹⁶¹⁻¹⁶³ The most sensitive (i.e. occur at the lowest dose) clinical manifestations of F^- toxicosis in livestock and wildlife under real-world conditions are tooth and bone deformities.^{149,164-169} These bony tissue lesions often

result in difficulty grazing, reduced feed intake, ill-thrift, and decreased performance.^{149,166,167} Alternating periods of high and low F⁻ exposure are more toxic than a continuous intake of the same average amount. Nutritional status and the age when exposed to F⁻ also influence tolerance.¹⁷⁰

The effect of F⁻ on behavior and brain development was examined in rats by injecting pregnant dams with 0.13 mg/kg BW of sodium fluoride (NaF) subcutaneously on gestational days 14-18 or 17-19.¹⁷¹ Weanlings received either no NaF or NaF in drinking water at 75, 100, or 125 mg F⁻/L for six or 20 weeks, and three 3-month-old adults received water containing 100 mg F⁻/L for six weeks. Rats exposed to F⁻ had sex- and dose-specific behavioral deficits. Males were most sensitive to prenatal exposure; females were more sensitive to weanling and adult exposure. Drinking water containing 125 mg F⁻/L resulted in reduced growth, and 175 mg F⁻/L was lethal. Shan et al.¹⁷² treated rats with differing concentrations of F to investigate the effect of F⁻ on cognitive processes by examining its effects on nicotinic acetylcholine receptors (nAChRs) in the brain. Both 30 and 100 mg F⁻/L in the drinking water produced subtle brain damage indicative of oxidative stress. Paul et al.¹⁷³ administered NaF by oral intubation daily at 20 or 40 mg/kg BW to adult female rats for 60 days and measured spontaneous motor activity, motor coordination, cholinesterase activity in blood and brain, and the protein content of muscle, liver, and serum. Sodium fluoride treatment suppressed spontaneous motor activity and tissue and serum protein concentrations in a dose-dependent manner. Wang et al.¹⁷⁴ found decreased total phospholipid concentrations and ubiquinone in rat livers due to oxidative stress after seven months of consuming water containing 30 or 100 mg F⁻/L.

Rats were offered drinking water containing 225 mg F⁻/L as NaF for 60 days.¹⁷⁵ A second group of rats was also gavaged with calcium carbonate (CaCO₃). The NaF-treated rats exhibited decreased food and water intake, reduced body weight gain, and impaired nervous function. Fluoride-induced dental lesions, inhibition of acetylcholinesterase and N⁺ K⁺ ATPase activity, and decreased serum protein improved after NaF withdrawal. Calcium treatment lessened the impact of F by decreasing serum F concentrations.¹⁷⁵ Rats given drinking water with either 30 or 100 mg F⁻/L as NaF for seven months had decreased kidney proteins and BW gains, and dental fluorosis.¹⁵⁹ Ten or 30 mg F⁻/L administered to male rats via drinking water for three to six months did not cause

any overt clinical effects but did produce biochemical indications of liver damage.¹⁷⁶ Oral administration of NaF in water at 5 or 10 mg (2.25 or 4.5 mg F⁻)/kg BW/day for 30 days to adult male rats resulted in reduced body weight.¹⁶³ Testicular cholesterol and serum testosterone levels were not affected, but sperm motility and count were decreased resulting in a significant decline in fertility. Heindel et al.¹⁷⁷ studied fetal development in rats and rabbits fed up to 300 or 400 mg NaF (135 or 180 mg F⁻)/L drinking water, respectively, during gestation. Although there were no teratogenic effects at any dose, dams lost weight after drinking water with concentrations greater than 150 mg NaF/L (rat) or 200 mg NaF/L (rabbit).

Certain elements are known to interfere with the uptake of F, a fact some have attempted to exploit therapeutically. Rats received drinking water treated with equivalent amounts of F as aluminum fluoride (AlF₃, 0.5 mg/L) or NaF (2.1 mg/L) for 52 weeks to evaluate the interaction of Al with F.¹⁷⁸ AlF₃ reduced the neuronal density of the brain neocortex compared to the NaF and control rats. Brain and kidney Al concentrations were higher in both AlF₃- and NaF-treated groups than in controls. Rabbits were fed drinking water containing various combinations of either F⁻ (1-50 mg/L as NaF) or Al (100-500 mg/L as AlCl₃) for 10 weeks. Although none of the treatments resulted in significant weight loss, Al treatment decreased F⁻ accumulation in bone. Surprisingly, F⁻, by itself, increased bone Al concentrations, suggesting Al or an Al-F complex play a role in osteofluorosis.¹⁷⁹ Kessibi et al.¹⁸⁰ gavaged sheep with 0, 1.9, or 4.7 mg F⁻/kg BW, with or without 13.5 mg Al/kg, for 33 months. In all treated animals, the general health status declined and osteodental signs appeared while F⁻ levels increased in teeth, bones, and organs. In sheep given 4.7 mg F⁻/kg BW, lesions were observed in kidney and liver. Aluminum sulfate ((Al₂(SO₄)₃) alleviated some, but not all, of the effects of 1.9 mg F⁻/kg BW.

Rats and mice were fed no NaF in drinking water or at 11, 45, or 79 mg F⁻/L for up to two years in a carcinogenesis bioassay.¹⁸¹ Body weights and survival rates of F⁻ treated rats and mice were similar to controls. Osteosarcomas occurred in a small, statistically, and historically insignificant number of male rats at the highest dose, while there was no evidence of carcinogenic activity in female rats or mice of either sex. Rats on the highest two dosages also exhibited some increased osteo- and dental fluorosis.¹⁸¹ Deer mice captured and fed 38, 1,065, 1,355, or 1,936 ppm dietary F⁻ for eight weeks

lost weight and many died at the highest dose.¹⁸² The toxicological response and metabolism of F⁻ by three species of wild mammals (two species of voles and wood mouse) were compared to laboratory mice.¹⁸³ Animals were given no NaF or 40 or 80 mg F/L as NaF in their drinking water for up to 84 days. Forty and 80 mg F/L treatments caused mortalities in the voles, probably as a result of the greater water intake of this species. Severe dental lesions were apparent in all animals surviving the 80 mg F/L treatment.

Osteo-dental fluorosis was observed in cattle, buffalo, sheep, and goats from several villages in India where the mean F⁻ concentration in drinking water ranged between 1.5 to 4.0 mg/L.¹⁶⁴ Forage F⁻ concentrations were not measured, but the situation described suggests only background concentrations were present. The prevalence and severity of skeletal fluorosis increased with increasing F⁻ concentration and age. Cattle and buffalo near a phosphate plant in India developed dental and bony lesions due to fluorosis.¹⁸⁴ Lesions were more common in older animals than younger and in buffalo than in cattle. Environmental F⁻ concentrations were: 534 mg F/kg in fodder, 1.2 mg F/L in pond water, and 0.5 mg F/L in ground water, which, assuming standard consumption of forage and water, would have provided approximately 14 mg F/kg BW. Two ranches, one with drinking water containing up to 10.5 mg F/L, the other with 3 mg/L, were compared in Argentina.¹⁸⁵ While both had similar forage F⁻ values (~15-25 ppm), cattle from the former exhibited excessive dental erosion. Neeley and Harbaugh¹⁸⁶ studied a Texas dairy herd drinking 4-5 mg F/L before and after management changes that resulted in increased F⁻ intake from 0.52 mg/kg BW to 1.69 mg/kg BW, primarily as a result of increased water consumption. Most animals exhibited dental fluorosis both before and after the change, but breeding efficiency and production increased after the change, probably as the result of better nutrition and management. Rand and Schmidt¹⁸⁷ followed several Arizona herds' drinking water containing 16 mg F/L and consuming forage containing up to 25 ppm F⁻. They concluded 1 mg F/kg BW can be tolerated for 5-10 years with only minor cosmetic effects, but 2 mg F/kg BW will result in accelerated tooth wear and signs of osteofluorosis. After the Lonquimay volcano erupted in Chile, animals were exposed to water concentrations less than 2 mg F/L and as much as 48 ppm F⁻ in forage. Two years later cattle were still developing fluorosis.¹⁸⁸ Cattle fed a contaminated supplement that provided between 0.7-1.6 mg F/kg BW/day for a year developed bone lesions and dental fluorosis.¹⁸⁹

Merriman and Hobbs¹⁹⁰ conducted an extensive five-year study of the interactions between soil and water F⁻ and nutrition in cattle. Cattle on pastures with average forage concentrations of 143 ppm F developed dental fluorosis. Fluoride in soil, water, and grasses reportedly did not affect gain, but the experimental design was too small to reliably detect differences in performance. Suttie et al.¹⁹¹ fed dairy calves 1.5 or 3 mg F/kg BW, either continuously or in a six-month rotation, for six years. Bone F⁻ was related to total intake and urinary F⁻ remained high during the "off" period, but dental lesions were related to the F⁻ concentration when teeth were being formed. None of the treatments "affected growth or reproduction," but only a small number of animals was studied. The physiologic effects of forage contaminated by fumes from an aluminum smelter and NaF-treated forage were examined in cattle.¹⁹² Gains were significantly less on diets containing more than 200 ppm F⁻ as NaF. Cattle receiving 70-100 ppm F⁻ exhibited decreased reproductive efficiency indirectly attributed to dental fluorosis.

Cattle were fed 134 ppm dietary F⁻ as soft phosphate or CaF₂, or 67 ppm F⁻ as NaF for 91 days to compare the bioavailability and toxicity of the different sources of F. Feed consumption, average daily gains, and feed conversion were not influenced by source of F⁻¹⁹³; however, the study was too short to detect dental effects, and no controls were included. Shupe et al.¹⁹⁴ summarized 30 years of experimental and observational studies in cattle, sheep, horses, deer, elk, and bison exposed to differing F⁻ concentrations. They concluded that excessive dietary F⁻ during tooth formation damages teeth, and the abnormal wear of these teeth results in impaired performance. Offspring from F⁻-damaged animals showed no signs of fluorosis. Short-term exposure of dairy heifers to 2.5 mg F/kg BW during 13-15 or 16-18 months of age resulted in severe dental fluorosis, even though the *total* F intake was not excessive.¹⁹⁵ Eckerlin et al.¹⁹⁶ and Maylin et al.¹⁹⁷ described a farm where F⁻-contaminated concentrate contributed approximately 12.8 to 56 ppm F⁻ to the diet. Cows had depressed milk production, while their calves exhibited dental and osteofluorosis and had severely stunted growth.

Holsteins were raised and maintained for 7.5 years on forage containing 12, 27, 49, or 93 ppm F⁻ as NaF.¹⁹⁸ Initially, F had no effect on feed intake, digestion coefficients, or nutrient absorption. However, after the cows had been through two lactations, cattle consuming the higher two F⁻ diets consumed and digested less. The "tolerance level" for dietary F was concluded to be between

27-49 ppm of the total diet. McLaren and Merriman¹⁹⁹ monitored beef cattle maintained on “high” (125 ppm) or “low” (37 ppm) F pastures and “good” (80-100% of NRC recommendations) or “poor” nutrition in a 2x2 factorial experiment. They concluded neither F⁻ concentrations nor plane of nutrition had any effect on the “general health” of the animals. Sixteen dairy heifers were fed hay containing 10 or 62 ppm F⁻ or 10 ppm hay supplemented with CaF₂ at 69 ppm F⁻ or NaF at 68 ppm F⁻, for 588 days.²⁰⁰ The F⁻ diets resulted in dosages of 1.14, 1.32, or 1.29 mg F/kg, respectively. Calcium fluoride was less toxic than contaminated hay or NaF. Fluoride caused no adverse effects on soft tissues but did cause significant damage to teeth and bones. Van Rensburg and de Vos²⁰¹ fed cows 5-12 mg F/L in drinking water, with or without superphosphate, through four breeding seasons. By the second season the 8 and 12 mg F/L groups exhibited prolonged post-parturition anestrus, and fertility declined in those two groups during the third season. By the fourth season toxic effects were apparent in the 5 mg F/L group as well.

Sheep were maintained on 2, 5, or 10 mg F/L drinking water from natural sources for four years.²⁰² The highest dose affected wool production, probably as a result of limited food consumption caused by dental fluorosis. Pregnant ewes drinking 10 mg F/L water did not transmit toxic quantities of F⁻ to the fetus or to the lamb through milk. Sheep fed a commercial, non-defluorinated, rock phosphate lick to provide 2 mg F/kg BW showed signs of fluorosis.²⁰³ Thirty-seven % of the commercial flock was affected, as opposed to only 17% of the breeding animals of the same age that were in better nutritional condition. Cattle and sheep raised on South African farms where water F⁻ ranged from 4-26 mg/L and forage from 5.3-22.4 ppm experienced severe osteo- and dental fluorosis.²⁰⁴ Assuming normal consumption of forage and water, the dose received was between 2-4 mg F/kg BW. A ranch in New Mexico experiencing dental fluorosis was discovered to have water sources varying from 0.09-3.32 mg F/L. Interestingly, the higher concentrations occurred in wells only used during part of the year, and a child drinking from the highest well had dental fluorosis as well.²⁰⁵

Horses and swine are believed to be less susceptible to fluorosis than cattle and sheep, but there is little clinical and no experimental data to support the contention.¹⁴⁷ Horses grazed in F⁻ contaminated areas developed similar fluorotic signs as cattle and sheep.²⁰⁶ Swine received no NaF or were fed 200 or 1,000 ppm dietary F⁻ as NaF

for 45 days in an experiment to determine the effects of F⁻ on bone growth.²⁰⁷ The higher concentrations of F⁻ produced dose-related decreases in bone growth, feed consumption, and overall growth. Bones from F⁻-treated pigs were less dense and exhibited growth plate abnormalities.

Fluoride toxicosis was diagnosed in elk, deer, and bison on the basis of lesions and F⁻ concentrations in teeth and bones collected by hunters in Utah, Wyoming, and Idaho. Vegetation and water samples collected from areas where fluorotic animals were discovered contained 5.5-430 ppm F⁻ and 0.5-24 mg F/L, respectively.²⁰⁸ The investigators concluded that geographic areas where domestic livestock have chronic fluorosis are also problematic areas for wildlife, which implies wildlife are roughly equally sensitive to F. Suttie et al.²⁰⁹ studied deer near a new aluminum smelter where forage concentrations ranged from 1-30 ppm F⁻. All deer had increased dental F⁻ and some mild cosmetic fluorosis, but none exhibited excessive tooth wear. Tissue F⁻ concentrations in deer diagnosed with fluorosis on the basis of dental lesions near an aluminum smelter were similar to those reported for cattle.²¹⁰ Suttie et al. fed 25 or 50 ppm F⁻ as NaF to whitetail deer fawns.²¹¹ Fluorotic lesions were similar to those in cattle fed the same amount, but cattle seem to develop more bony lesions and fewer dental lesions than deer. Vikoren et al.²¹² surveyed several hundred jawbones from moose, red deer, and roe deer near aluminum smelters where forage concentrations averaged 30 ppm F⁻, and they also looked at a small number of sheep in the same area. Although the overall incidence of fluorosis was low, tissue concentrations were similar in sheep and cervids, and the threshold bone F⁻ concentration for disease in cervids was similar to what was previously reported in domestic species.

Summary

Fluoride generates considerable controversy in human health, largely as a result of the common practice of fluoridating municipal water supplies. We were not, however, able to find any convincing experimental studies that suggested the dramatic effects associated with acute exposure to relatively large doses of F⁻ carried over to low level, long-term exposure. Although there are a few reports of dental fluorosis in people at slightly lower concentrations, the current primary drinking water standard for human consumption is 4 mg F/L; the secondary standard, apparently based upon cosmetic dental effects, is 2 mg F/L.

Our search of the literature pertaining to fluorosis in animals yielded similar results. We were not able to find *any* reports of toxic effects in livestock or wildlife that occurred at lower F⁻ dosages than cause osteo-dental fluorosis. Thus, as a practical matter, maximum tolerable concentrations of F⁻ in water for livestock and wildlife should be based upon dental and osteal effects.

The effects of F in feedstuffs and water are additive; what really counts is the *total* dose of biologically available F⁻ ingested by the animal. Most of the reports we reviewed, when reduced to mg F⁻/kg BW, indicate the threshold dose for chronic osteo-dental fluorosis in cattle is approximately 1 mg F⁻/kg BW. This is in agreement with the NRC,¹⁴⁷ which indicates 30-40 ppm dietary F⁻ (which translates to 0.75-1.0 mg F⁻/kg BW) is the tolerance level for the more sensitive (i.e. during dental development) classes of cattle.

Numerous studies have demonstrated the susceptibility of wild ungulates (deer, elk, etc.) to fluorosis; however, there has been only one controlled experiment²¹¹ from which dose-response can be extrapolated. A few other epidemiologic studies provide sufficient data to form rough estimates of the amount of F⁻ required to produce signs of fluorosis in cervids. Taken together, these indicate wild cervids are approximately as sensitive to the toxic effects of F⁻ as cattle. Sheep seem to be slightly less sensitive than cattle although one Australian report indicated long-term exposure to as little as 10 mg F⁻/L drinking water in Queensland decreased wool production.²⁰² Given temperatures in that region, water consumption probably resulted in 1-2 mg F⁻/kg BW for much of the year. The sole report that included any data on horses suggested horses are two-fold more tolerant than cattle, but it goes on to describe situations in which ruminants and horses, sharing a pasture and water supply, were similarly affected.

Assuming Wyoming forages normally contain less than 10 ppm F⁻²¹³, a water concentration of 3.75 mg F⁻/L would be required to achieve the 1 mg F⁻/kg BW necessary to cause fluorosis in cattle, and water containing less should not cause measurable production problems.

We recommend water for cattle contain less than 2.0 mg/L F⁻. By extension, these waters should also be safe for sheep, cervids, and probably horses.