2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO FLUORIDES, HYDROGEN FLUORIDE, AND FLUORINE IN THE UNITED STATES

Fluorine is the most electronegative and reactive of all elements; fluoride is the ionic form of fluorine. Fluorine and anhydrous hydrogen fluoride are naturally occurring gases that have a variety of industrial uses including the production of fluorine-containing chemicals, pharmaceuticals, high octane gasoline, and fluorescent light bulbs; aqueous hydrofluoric acid is a liquid used for stainless steel pickling, glass etching, and metal coatings. The general population is typically exposed to very low levels of gaseous fluoride (primarily as hydrogen fluoride); in the United States and Canada, the levels ranged from 0.01 to 1.65 μg/m^3. Populations living near industrial sources of hydrogen fluoride, including coal burning facilities, may be exposed to higher levels of hydrogen fluoride in the air. Additionally, vegetables and fruits grown near these sources may contain higher levels of fluoride, particularly from fluoride-containing dust settling on the plants.

Fluoride salts, generically referred to as fluorides, are naturally occurring components of rocks and soil. One of the more commonly used fluoride salt is sodium fluoride; its principal use is for the prevention of dental caries. Sodium fluoride and other fluoride compounds, such as fluorosilicic acid and sodium hexafluorisilicate, are used in the fluoridation of public water. Sodium monofluorophosphate and stanneous fluoride are commonly used in dentifrices such as toothpaste. The general population can be exposed to fluoride through the consumption of fluoridated drinking water, food, and dentifrices. The average dietary intake (including water) of fluoride ranges between 1.4 and 3.4 mg/day (0.02–0.048 mg/kg/day) for adults living in areas with 1.0 mg/L fluoride in the water. In areas with <0.3 mg/L fluoride in water, the adult dietary intakes ranged from 0.3 to 1.0 mg/day (0.004–0.014 mg/kg/day). In children, the dietary intakes ranged from 0.03 to 0.06 mg/kg/day in areas with fluoridated water and from 0.01 to 0.04 mg/kg/day in areas without fluoridated water. The Food and Nutrition Board of the Institute of Medicine has developed adequate intakes (AIs) for fluoride. The AI is the "estimated fluoride intake that has been shown to reduce the occurrence of dental caries maximally in a population without causing unwanted side effects including moderate dental fluorosis." The AIs for each age group are presented in Table 2-1.

Table 2-1. Adequate Intake Levels for Fluoride[a]

Age range	Adequate intake level (mg/day)	Adequate intake level (mg/kg/day)[b]
0–6 months	0.01	0.0014
6–12 months	0.5	0.056
1–3 years	0.7	0.054
4–8 years	1	0.045
9–13 years (males and females)	2	0.05
14–18 years (males)	3	0.046
14–18 years (females)	3	0.053
>18 years (males)	4	0.052
>18 years (females)	3	0.049

[a]Source: IOM 1997
[b]mg/kg/day doses were calculated by using reference body weights reported by IOM (1997)

2.2 SUMMARY OF HEALTH EFFECTS

Fluoride. The main health concern regarding fluoride is likely to be from excessive chronic oral exposure in drinking water. Due to the deposition of significant amounts of fluoride in bone, the primary target system for intermediate and chronic exposures of both humans and several laboratory animal species is the skeletal system (including teeth). Both beneficial and detrimental dental and skeletal effects have been observed in humans. Fluoride has been shown to decrease the prevalence of dental caries and, under certain conditions, has been used for the treatment of osteoporosis. However, excess fluoride can also result in dental fluorosis and can result in an increased prevalence of bone fractures in the elderly or skeletal fluorosis. Both the beneficial and detrimental effects of fluoride appear to be related to fluoride-induced alterations in tooth and bone mineralization.

Direct contact with fluoride can result in tissue damage. At high concentrations, fluoride can cause irritation and damage to the respiratory tract, stomach, and skin following inhalation, oral, and dermal exposure, respectively. At very high fluoride doses, fluoride can bind with serum calcium resulting in hypocalcemia and possibly hyperkalcemia; the severe cardiac effects (e.g., tetany, decreased myocardial contractility, cardiovascular collapse, ventricular fibrillation) observed at or near lethal doses are probably due to this electrolyte imbalance.

The available data on the potential of fluoride to induce reproductive and/or developmental effects is inconclusive. A study of birth records found a significant association between high levels of fluoride in municipal drinking water (3 ppm and greater) and decreases in fertility rates; another study found decreases in serum testosterone levels in men with skeletal fluorosis (fluoride concentration in water was 3.9 ppm). However, design limitations of these studies, particularly the use of poorly matched controls, limits the usefulness of these studies. Some animal studies have found alterations in reproductive hormone levels, histology of the testes, spermatogenesis, and fertility following exposure to relatively high oral doses of sodium fluoride, roughly equivalent to a human exposure level of >150 ppm in drinking water. However, other animal studies, including two-generation studies, have not found alterations in serum hormone levels in male rats, testicular histopathology, sperm morphology, or fertility. None of the available laboratory animal studies examined reproductive toxicity at low fluoride doses. The inadequate human studies and conflicting animal studies do not allow for an assessment of the potential of fluoride to induce reproductive effects in humans. Available human studies provide suggestive evidence that exposure to elevated levels of fluoride in drinking water may decrease IQ in

children; however, neither study controlled for other confounding variables. Animal studies have not found increases in the incidences of birth defects in the absence of maternal toxicity; at doses that caused maternal toxicity (decreases in body weight gain and food consumption), increases in abnormalities were found.

Numerous community-based studies have examined the possible association between fluoridated water and cancer. Most of these studies did not find significant associations between water fluoridation and cancer mortality or site-specific cancer incidence. Some studies have found associations between water fluoridation and cancer mortality/incidence or site-specific cancer incidence (osteosarcoma or bone cancer). The lack of control for potential confounding variables (i.e., age, race) limits the interpretation of the total cancer study results. The weight of the evidence indicates that fluoridation of water does not increase the risk of developing cancer. A 2-year study in rats found a weak, equivocal fluoride-related increase in the occurrence of osteosarcomas in male rats, and no evidence of carcinogenicity in female rats or male or female mice. IARC has determined that the carcinogenicity of fluoride to humans is not classifiable.

Hydrogen Fluoride. Hydrogen fluoride is highly corrosive, the primary effects are tissue damage resulting from direct contact. Acute inhalation exposure can result in irritation, inflammation, bronchiolar ulceration, pulmonary hemorrhage and edema, and death. Gastrointestinal irritation has also been observed in humans exposed to low levels of hydrogen fluoride. Direct contact of hydrogen fluoride/hydrofluoric acid with the eyes or skin can produce skin burns, “burning sensation”, and lacrimation. In addition to these direct contact effects, exposure to hydrogen fluoride can result in skeletal and cardiac effects. Some evidence of early skeletal fluorosis has been observed in workers exposed to hydrogen fluoride and fluoride dusts. These studies did not adequately characterize fluoride exposure levels and, in most of the studies, there is some uncertainty regarding the diagnosis of skeletal fibrosis. Exposure to very high levels of hydrogen fluoride/hydrofluoric acid can result in severe cardiovascular effects, which are attributed to a combination of hypocalcemia and hyperkalemia; cardiac arrhythmias have been seen in humans following hydrofluoric acid splashes in the face region, and myocardial necrosis and congestion were observed in rabbits. Hepatic (fatty degeneration and necrosis) and renal effects (tubular degeneration and necrosis) have also been observed in animal studies.

Although elevated cancer rates have been reported in some occupational groups exposed to hydrogen fluoride and fluoride dusts, these studies were not controlled for the multiple substance exposures to which industrial workers are generally exposed. Because of these multiple exposures and the problems

inherent in all occupational studies in identifying appropriate reference populations, only limited evidence from such studies is specifically relevant to the investigation of possible carcinogenic effects of long-term dermal exposure to hydrofluoric acid and inhalation exposure to hydrogen fluoride and/or fluoride dusts in human beings. As noted previously, IARC has determined that the carcinogenicity of fluoride to humans is not classifiable.

Fluorine. Limited data exist on the toxicity of fluorine; the two possible routes of exposure to fluorine are inhalation or dermal contact with the gas. Fluorine gas is extremely irritating; human and animal data suggest that the primary health effects of acute fluorine inhalation are nasal and eye irritation (at low levels), and death due to pulmonary edema (at high levels). In animals, renal and hepatic damage have also been observed.

A greater detailed discussion of fluoride-induced skeletal effects and portal of entry effects following exposure to fluorides, hydrogen fluoride, hydrofluoric acid, or fluorine follows. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on other health effects.

Dental and Skeletal Effects. Human and animal data clearly indicate that fluoride accumulates in the teeth and bone resulting in beneficial and detrimental alterations in the structure. There is strong evidence that oral exposure to fluoride can reduce the risk of dental caries. However, elevated fluoride levels during enamel maturation can also result in dental fluorosis, which is characterized by hypo-mineralization of subsurface layers of enamel. In the mildest forms of dental fluorosis, the tooth is fully functional but has cosmetic alterations, almost invisible opaque white spots. In more severely fluorosed teeth, the enamel is pitted and discolored and is prone to fracture and wear. Several studies have found significant increases in the number of decayed, missing, or filled tooth surfaces in children with severe dental fluorosis. The prevalence and severity of dental fluorosis is strongly associated with fluoride exposure levels. Dose-response relationships cannot be established from most of these studies because all sources of fluoride were not considered and most studies used fluoride levels in drinking water as the dosimetric. A recent meta-analysis estimated that 48% of children living in communities with 1 ppm fluoride in the water would have evidence of dental fluorosis, most of it considered very mild. The predicted incidence of dental fluorosis of aesthetic concern was 12.5%. Although the exact mechanism of dental fluorosis is not known, it is generally believed to result in a fluoride-induced delay in the hydrolysis of the enamel matrix protein amelogenin during the early enamel maturation phase of tooth development.

In bone, fluoride replaces the hydroxyl ion in hydroxyapatite to form fluorapatite, thus changing the physicochemical properties of the bone. Ingestion (and inhalation) of large doses of fluoride for an extended period of time can result in thickened bones and exostoses (skeletal fluorosis). Signs of skeletal fluorosis range from increased bone density to severe deformity, known as crippling skeletal fluorosis. In the more severe cases of crippling fluorosis, complete rigidity of the spine can occur. Reported cases are found almost exclusively in developing countries, particularly India and China, and are often associated with malnutrition. It is generally stated that a dose of 10–20 mg/day (equivalent to 5–10 ppm in the water, for a person who ingests 2 L/day) for at least 10 years is necessary for the development of crippling skeletal fluorosis, but individual variation, variation in nutritional status, and the difficulty of determining water fluoride levels in such situations make it difficult to determine the critical dose.

At lower doses, fluoride can cause an increase in bone density and fragility. A large number of epidemiology studies have attempted to examine the relationship between fluoride in drinking water and the risk of bone fracture. The results of these predominantly ecological studies are inconsistent. Studies have found increases and decreases in hip fracture rates among older women living in areas with fluoride in the drinking water (typically about 1 ppm), as compared to women living in areas with very low levels of fluoride in the drinking water (<0.3 ppm). Other studies have not found an effect of fluoride on fracture risk. A relationship between exposure to 1 ppm fluoride in drinking water and the risk of bone fractures cannot be established from these studies. Studies involving exposure to higher doses of fluoride have consistently found significant increases in the risk of nonvertebral fractures, particularly hip fractures. A study involving lifetime exposure to 4.3–8 ppm fluoride in drinking water found an elevated risk of hip fractures among elderly men and women; this elevated risk of hip fracture was also observed in a community with very low fluoride (0.25–0.34 ppm) in the water. Studies of individuals using sodium fluoride for the treatment of osteoporosis also found significant increases in bone mineral density. Studies in laboratory animals have found defects in bone growth, fracture healing, and bone strength.

Respiratory, Gastrointestinal, Dermal, and Ocular Effects. Fluoride, hydrogen fluoride, hydrofluoric acid, and fluorine are extremely irritating chemicals and can cause tissue damage after direct contact. The respiratory tract is the primary target of toxicity following inhalation exposure to hydrogen fluoride or fluorine. Single exposures to relatively low concentrations of hydrogen fluoride (≥0.5 ppm) or fluorine (≥10 ppm) can result in upper respiratory tract irritation in humans. At higher concentrations pulmonary congestion, necrosis and/or edema have been observed in laboratory animals; pulmonary edema has also been observed in humans exposed to lethal concentrations of hydrogen fluoride.

Pulmonary and nasal irritations have also been reported following repeated exposures for about 30 days. Chronic exposure to hydrogen fluoride and cryolite dust has resulted in impaired lung function in workers. The observed respiratory effects are attributed to its highly corrosive properties. Human and animal data suggest that preexposure to lower levels can reduce the respiratory effects.

Acute and chronic oral exposure to high doses of sodium fluoride, typically >1 mg fluoride/kg, can result in nausea, vomiting, and gastric pain. Nausea, loss of appetite, and vomiting has also been reported by workers exposed to cryolite dust for >2 years. The effects occur shortly after ingestion and are likely due to the formation of hydrofluoric acid in the stomach. There is some evidence to suggest that these overt signs of gastric irritation may not be sensitive indicators of gastric mucosa damage. Petechiae and/or erosions were observed in most subjects exposed to sodium fluoride or a dental gel; however, nausea was only reported by 33% of the subjects. Similar findings were reported in animal studies; thickening of the glandular stomach mucosa and punctate hemorrhages were observed in rats ingesting high doses of sodium fluoride in drinking water for an intermediate duration. Gastrointestinal effects have been observed following inhalation and oral exposure to hydrogen fluoride. Populations living near a smelter emitting hydrogen fluoride or exposed during an accidental release of hydrogen fluoride have reported gastrointestinal effects, including nausea, gastrointestinal distress, and vomiting.

Fluorine and hydrogen fluoride are highly reactive chemicals; direct contact can result in severe damage to the skin or eyes. The severity of the damage is directly related to the concentration and duration of exposure. Humans exposed to hydrogen fluoride gas for an acute duration have reported symptoms of skin irritation (itching and burning sensation) and eye irritation. Most of these human data are inadequate for establishing concentration-response relationships; the data on ocular irritation do provide some information of the threshold of toxicity. Very mild eye irritation was observed in subjects exposed to 0.5–4.5 ppm hydrogen fluoride for 1 hour, mild eye irritation was reported during a 15–50-day, 6-hour/day exposure to 3 ppm. Aqueous hydrofluoric acid applied directly to the skin can cause extensive damage; it is quickly absorbed through the epidermis causing necrosis in underlying tissues (Chela et al. 1989). In rabbits, a 1-minute exposure to 2% hydrofluoric acid did not produce skin lesions; however, necrotic lesions were observed after a 1–4-hour exposure to this concentration.

There are limited data on the dermal and ocular toxicity of fluorine. A human study reported slight eye irritation following a repeated exposure to 10 ppm fluorine (no irritation was reported a during 15-minute exposure to this concentration), mild eye irritation during a 3-minute exposure to 30–50 ppm, and marked irritation during a <1-minute exposure to 100 ppm.

2.3 MINIMAL RISK LEVELS

Fluorides

Inhalation MRLs

No inhalation MRLs were derived for fluoride. Several occupational exposure studies examined fluoride toxicity in aluminum potroom workers (Carnow and Conibear 1981; Chan-Yeung et al. 1983b; Czerwinski et al. 1988; Dinman et al. 1976c; Kaltreider et al. 1972). Interpretation of these studies is limited by co-exposure to hydrogen fluoride and other chemicals including aluminum. There are limited data on the inhaled toxicity of fluoride. Significant increases in lung weight and pulmonary edema have been observed in mice exposed to 10 mg fluoride/m^3 as sodium fluoride 4 hours/day, for 10–14 days (Chen et al. 1999; Yamamoto et al. 2001). Impaired pulmonary bactericidal activity has also been observed in mice exposed to 5 mg fluoride/m^3 as sodium fluoride (Yamamoto et al. 2001). These studies cannot be used for MRL derivation because none of the studies examined the skeletal system, which has been shown to be a sensitive target following oral exposure.

Oral MRLs

A limited number of end points have been examined in humans and animals following acute oral exposure to fluorides. Most of the available data involved exposure to lethal doses of fluoride; other examined potential targets of toxicity include the gastrointestinal tract, bone, sperm morphology, and the developing organism. Symptoms of gastric irritation, such as nausea, vomiting, and gastric pain, have been observed shortly after exposure to fluoride in drinking water (Hoffman et al. 1980; Spak et al. 1989, 1990; Spoerke et al. 1980). Spak et al. (1989) reported macroscopic and microscopic signs of gastric irritation in subjects ingesting 20 mg fluoride (1,000 ppm) as sodium fluoride; other studies have not reliably identified exposure concentrations. A decrease in modulus of elasticity was observed in the bones of weanling rats exposed to 9.5 mg fluoride/kg/day as sodium fluoride in drinking water for 2 weeks (Guggenheim et al. 1976). No alterations in sperm morphology were observed in mice exposed to 32 mg fluoride/kg/day as sodium fluoride (Li et al. 1987a). In the absence of maternal toxicity, no adverse effects in rat or rabbit offsprings were observed (Heindel et al. 1996); skeletal and visceral alterations were observed in the offspring of rat dams with decreases in body weight and feed consumption (Guna Sherlin and Verma 2001). From the available data, it appears that the stomach is a

sensitive target of fluoride toxicity following consumption of a bolus dose of fluoride. However, the observed effect (gastric irritation) is likely due to the fluoride concentration rather than a daily dose (expressed as mg/kg/day). It is not known whether the gastric mucosa would adapt to repeated exposure to this concentration of fluoride. An acute-duration oral MRL for fluorides was not derived due to the previously mentioned uncertainties in basing the MRL on a study that administered a single bolus dose of sodium fluoride and because the resultant MRL would be lower than the chronic-duration oral MRL.

Several studies have examined the toxicity of sodium fluoride following intermediate-duration exposure in laboratory animals. These studies have identified a number of potentially sensitive targets of fluoride toxicity. The lowest identified lowest-observed-adverse-effect levels (LOAELs) are 0.5 mg fluoride/kg/day for thyroid effects in rats exposed to sodium fluoride in drinking water for 2 months (Bobek et al. 1976) and 0.80 mg fluoride/kg/day for increased bone formation in mice exposed to sodium fluoride in drinking water for 4 weeks (Marie and Hott 1986). Neither study identified a no-observed-adverse-effect level (NOAEL). Derivation of an intermediate-duration MRL from either study would result in an MRL that is lower than the chronic-duration oral MRL.

- A chronic-duration oral MRL of 0.05 mg fluoride/kg/day was derived for fluoride.

A number of studies have examined the possible association between exposure to fluoridated water and the risk of increased bone fractures, particularly hip fractures. In general, the studies involved comparing the incidence of hip fractures among residents aged 55 years and older living in a community with fluoridated water (around 1 ppm) with the incidence in a comparable community with lower levels of fluoride in the water. Inconsistent results have been found, with studies finding decreases (Lehmann et al. 1998; Phipps et al. 2000; Simonen and Laittinen 1985), increases (Cooper et al. 1990, 1991; Danielson et al. 1992; Jacobsen et al. 1990, 1992; Kurttio et al. 1999), or no effect (Arnala et al. 1986; Cauley et al. 1995; Goggin et al. 1965; Jacobsen et al. 1993; Karagas et al. 1996; Kröger et al 1994; Suarez-Almazor et al. 1993) on hip fracture risk. Studies by Li et al. (2001) and Sowers et al. (1986) have examined communities with higher levels of naturally occurring fluoride in the water. Both studies found increases in the incidence of hip fractures in residents exposed to 4 ppm fluoride and higher (Li et al. 2001; Sowers et al. 1986, 1991); the hip fracture incidence in the highly exposed community was compared to the rates in communities with approximately 1 ppm fluoride in the water. Significant increases in the occurrence of nonvertebral fractures were also observed in postmenopausal women ingesting sodium fluoride (34 mg fluoride/day; 0.56 mg fluoride/kg/day) for the treatment of osteoporosis (Riggs et al. 1990, 1994). This result was not found in another study of postmenopausal women with spinal osteoporosis treated with 34 mg fluoride/day as sodium fluoride (Kleerekoper et al. 1991). A meta-analysis of these data, as well

as other clinical studies, found a significant correlation between exposure to high levels of fluoride and an increased relative risk of nonvertebral fractures (Haguenauer et al. 2000). The Li et al. (2001) study was selected as the basis for the chronic-duration oral MRL. This study was selected because other potential sources of fluoride were considered (the Riggs et al. [1990] study did not provide information on the level of fluoride in the drinking water or other sources of fluoride) and calcium levels were similar among the different communities (the Sowers et al. [1986] study did not control for calcium intake). The Li et al. (2001) study identified a NOAEL of 2.62–3.56 ppm (0.15 mg fluoride/kg/day) and LOAEL of 4.32–7.97 ppm (0.25 mg fluoride/kg/day). An MRL of 0.05 mg fluoride/kg/day is calculated by dividing the NOAEL of 0.15 mg/kg/day by an uncertainty factor of 3 to account for human variability; a partial uncertainty factor was used because the most sensitive subpopulation, elderly men and women, was examined.

Hydrogen Fluoride/Hydrofluoric Acid

Inhalation MRLs

- An acute-duration inhalation MRL of 0.02 ppm fluoride was derived for hydrogen fluoride.

The respiratory tract appears to be the primary target of hydrogen fluoride toxicity. Upper respiratory tract irritation and inflammation and lower respiratory tract inflammation have been observed in several human studies. Nasal irritation was reported by one subject exposed to 3.22 ppm fluoride as hydrogen fluoride 6 hours/day for 10 days (Largent 1960). Very mild to moderate upper respiratory symptoms were reported by healthy men exposed to 0.5 ppm fluoride as hydrogen fluoride for 1 hour (Lund et al. 1997). At higher concentrations, 4.2–4.5 ppm fluoride as hydrogen fluoride for 1 hour, more severe symptoms of upper respiratory irritation were noted (Lund et al. 1997, 2002). In subjects exposed to 4.2 ppm for 1 hour, analysis of nasal lavage fluid provided suggestive evidence that hydrogen fluoride induces an inflammatory response in the nasal cavity (Lund et al. 2002). Similarly, bronchoalveolar lavage fluid analysis revealed suggestive evidence of bronchial inflammation in another study of subjects exposed to 1.9 ppm fluoride as hydrogen fluoride for 1 hour (Lund et al. 1999); no alterations were observed at 0.5 ppm. Respiratory effects have also been reported in rats acutely exposed to hydrogen fluoride. Mild nasal irritation was observed during a 60-minute exposure to 120 ppm fluoride (Rosenholtz et al. 1963), and respiratory distress was observed at 2,310, 1,339, 1,308, and 465 ppm fluoride for 5, 15, 30, or 60 minutes, respectively (Rosenholtz et al. 1963). Midtracheal necrosis was reported in rats exposed to 902 or 1,509 ppm fluoride as hydrogen fluoride for 2 or 10 minutes using a

mouth breathing model with a tracheal cannula (Dalbey et al. 1998a, 1998b). These effects were not observed when the tracheal cannula was not used.

The Lund et al. (1997, 1999) study was selected as the basis of the acute-duration inhalation MRL for hydrogen fluoride. As reported in the 1997 publication, a trend ($p=0.06$) toward increased upper respiratory tract symptom score, as compared to pre-exposure symptom scores, was observed at the lowest concentration tested (0.5 ppm). A significant increase in the total symptom score was also observed at this concentration. No significant alterations in symptom scores were observed at the mid concentration (1.9 ppm), and increases in upper respiratory and total symptom scores were observed at the high concentration (4.5 ppm). Suggestive evidence of bronchial inflammation was also observed at ≥1.9 ppm fluoride (Lund et al. 1999), although no alterations in lower respiratory tract symptoms (Lund et al. 1997) or lung function (Lund et al. 1997) were observed at any of the tested concentrations. The MRL is based on the minimal LOAEL of 0.5 ppm fluoride for upper respiratory tract irritation. Data on nasal irritation from the Largent (1960) report, the Lund et al. (2002) study, and the intermediate-duration study by Largent (1960) provide suggestive evidence that the severity of nasal irritation does not increase with increasing exposure duration. These three studies identified similar LOAEL values for different exposure durations: 3.22 ppm 6 hours/day for 10 days (Largent 1960), 3.8 ppm 1 hour/day for 1 day (Lund et al. 2002), and 2.98 ppm 6 hours/day, 6 days/week for 15–50 days (Largent 1960). Thus, time scaling was not used to derive the acute MRL. The MRL of 0.02 ppm was calculated by dividing the minimal LOAEL of 0.5 ppm by an uncertainty factor of 30 (3 for the use of a minimal LOAEL and 10 to account for human variability).

There are limited data on the long-term toxicity of hydrogen fluoride. Slight nasal irritation was reported by volunteers exposed to an average concentration of 2.98 ppm fluoride, 6 hours/day for 15–50 days (Largent 1960). In rats, rabbits, and dogs, pulmonary hemorrhages were observed after exposure to 31 ppm fluoride for 6 hours/day, 6 days/week for 5 weeks (Stokinger 1949). An intermediate-duration inhalation MRL was not derived for hydrogen fluoride because an MRL based on the Largent (1960) study is higher than the acute-duration inhalation MRL derived from the Lund et al. (1997, 1999) study.

No chronic-duration studies were located for hydrogen fluoride; thus, a chronic-duration inhalation MRL was not derived.

Oral MRLs

No oral MRLs were derived for hydrogen fluoride/hydrofluoric acid. Only lethality studies were identified for hydrogen fluoride/hydrofluoric acid, precluding derivation of oral MRLs for this chemical.

Fluorine

Inhalation MRLs

- An acute-duration inhalation MRL of 0.01 ppm fluorine was derived for fluorine.

Irritation appears to be the primary effect following acute inhalation exposure to fluorine. The observed effects include eye, skin, and nasal irritation in humans intermittently exposed to ≥10 ppm for 0.5–15 minutes (Keplinger and Suissa 1968) and dyspnea and lung congestion in rats and mice exposed to 47–175 ppm fluorine for 5–60 minutes (Keplinger and Suissa 1968). The threshold for the respiratory effects appears to be duration-related. Necrosis was also observed in the liver parenchymal tissue and in the renal tubules of rodents acutely exposed to fluorine. In general, the liver and kidney effects occurred at higher concentrations than the respiratory effects.

The NOAEL and LOAEL values for nasal irritation identified in the human study by Keplinger and Suissa (1968) were selected as the basis of an acute-duration inhalation MRL for fluorine. Subjects did not report nasal or eye irritation following a 3-, 5-, or 15-minute exposure to 10 ppm. Eye irritation was observed at ≥23 ppm; nose irritation at ≥50 ppm, and skin irritation at ≥78 ppm. The severity of the irritation was concentration related. Exposure to 100 ppm was considered very irritating and the subjects did not inhale during the exposure period. The NOAEL of 10 ppm was adjusted for intermittent exposure (0.25 hour/24 hours) and divided by an uncertainty factor of 10 to account for human variability to derive an acute-duration inhalation MRL of 0.01 ppm fluorine.

Longer-duration exposure studies are limited to a multi-species intermediate-duration study (Stokinger 1949) and an occupational exposure study (Lyon 1962). As with acute-duration exposure, the primary effect of intermediate-duration exposure to fluorine was eye, nose, and mouth irritation, which was observed in rats and dogs (Stokinger 1949). Evidence of pulmonary damage (bronchitis, hemorrhage, and edema) was also observed in rats, rabbits, and dogs. The study author noted that there was some difficulty in measuring the exposure concentrations and considered the measurements of exposure concentrations to be questionable. The chronic-duration study of workers exposed to fluorine (Lyon 1962) was not considered for MRL derivation because it used a relatively insensitive measure of

respiratory effects (absences from work and visits to the medical department with respiratory complaints) and the workers and the controls were exposed to uranium hexafluoride and hydrogen fluoride.