Development Support Document
Final, October 8, 2009
Accessible 2013
Revised Odor Value: September 14, 2015

# Hydrogen Fluoride

# and

# Other Soluble Inorganic Fluorides

## CAS Registry Number: 7664-39-3

## (Other CAS Numbers:

## 32057-09-3, 326604-75-5, 37249-79-9)

Prepared by

Jong-Song Lee, Ph.D.

Toxicology Division

Chief Engineer's Office

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

# Revision History

Original Development Support Document (DSD) posted as final on October 8, 2009.

Revised DSD September 14, 2015: an odor-based value was added because hydrogen fluoride has a pungent, disagreeable odor (TCEQ 2015).

# TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

# Chapter 1 Summary Table

Table 1 provides a summary of health- and welfare-based values from an evaluation of acute and chronic exposures to hydrogen fluoride (HF) and other soluble inorganic fluorides (F). For air permit reviews, modeling data for soluble inorganic F [e.g., sodium fluoride (NaF), potassium fluoride (KF), carbonyl fluoride ($COF_2$)] are provided as fluoride equivalents (F). There are only minor differences between HF and F health- and welfare-based values. Table 2 provides summary information on the physical/chemical data for HF and NaF, one of the most commonly used soluble inorganic F.

**Table 1 Health- and Welfare-Based Values**

| Short-Term Values | Concentration | Notes |
|---|---|---|
| $^{acute}ESL$ [1 h] (HQ = 0.3) | 18 µg HF/$m^3$ (22 ppb) or 17 µg F/$m^3$ **Short-Term ESL for Air Permit Reviews** | **Critical Effect(s):** upper respiratory tract and eye irritation; and respiratory tract inflammation in human volunteers |
| acute ReV (HQ = 1) | 60 µg HF/m3 (73 ppb) or 57 µg F/m3 | Same as above |
| $^{acute}ESL_{odor}$ | 34 µg/$m^3$ (42 ppb) (for HF only) **Odor** | Pungent and irritating odor |
| $^{acute}ESL_{veg}$ [24 h] | 3.0 µg HF/$m^3$ (3.7 ppb) or 2.8 µg F/$m^3$ **Short-Term ESL for Air Permit Reviews in agricultural areas** | Threshold level for a trace of foliar injury/leaf necrosis in Conifers |
| Long-Term Values | Concentration | Notes |
| $^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3) | 8.7 µg HF/$m^3$ (11 ppb) or 8.1 µg F/$m^3$ **Long-Term ESL for Air Permit Reviews** | **Critical Effect(s):** increased bone density and skeletal fluorosis in workers |
| chronic ReV (HQ = 1) | 29 µg HF/$m^3$ (35 ppb) or 27 µg F/$m^3$ | Same as above |
| $^{chronic}ESL_{linear(c)}$ | --- | Data are inadequate for an assessment of human carcinogenic potential |
| $^{chronic}ESL_{cattle}$ [30 days] | 0.75 µg HF/$m^3$ (0.91 ppb) or 0.71 µg F/$m^3$ **Long-Term ESL for Air Permit Reviews in agricultural areas** | **Critical Effect(s):** fluoride poisoning (fluorosis), dental lesions, osseous lesions, lameness and stiffness in cattle and other livestock |
| $^{chronic}ESL_{veg}$ | 0.60 µg HF/$m^3$ (0.73 ppb) or 0.57 µg F/$m^3$ **Long-Term ESL for Air Permit Reviews in agricultural areas** | Threshold level for decrease in yield of bean, decrease in number of fruit per pot, dry weight of stems & leaves, and stem length on soybean |

Abbreviations: **HQ**, hazard quotient; **ppb**, parts per billion; ***µg/m*$^3$**, micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Levels; **ReV**, Reference Value; $^{acute}$**ESL**, acute health-based ESL; $^{acute}$**ESL$_{odor}$**, acute odor-based ESL; $^{acute}$**ESL$_{veg}$**, acute vegetation-based ESL; $^{chronic}$**ESL $_{linear(c)}$**, chronic health-based ESL for linear dose-response cancer effect; $^{chronic}$**ESL $_{nonlinear(c)}$**, chronic health-based ESL for nonlinear dose-response cancer effect; $^{chronic}$**ESL$_{nonlinear(nc)}$**, chronic health-based ESL for nonlinear dose-response noncancer effects; $^{chronic}$**ESL$_{linear(nc)}$**,

chronic health-based ESL for linear dose-response noncancer effects; $^{chronic}\mathbf{ESL}_{\mathbf{veg}}$, chronic vegetation-based ESL; and $^{chronic}\mathbf{ESL}_{\mathbf{cattle}}$, chronic cattle fluorosis-based ESL

**Table 2 Chemical and Physical Data**

| Parameter | Value | Value | Reference |
|---|---|---|---|
| Name of Chemical | Hydrogen Fluoride | Sodium Fluoride | ACGIH 2005 |
| Molecular Formula | HF | NaF | ACGIH 2005 |
| Chemical Structure | H-F | Na-F | ACGIH 2005 |
| Molecular Weight | 20.01 | 32.01 | ACGIH 2005 |
| Physical State | Colorless gas @ temperatures > boiling point or fuming liquid @ low temperatures | Crystal or powder | ACGIH 2005 |
| Color | Colorless | Clear or white | ACGIH 2005 |
| Odor | Irritating and pungent | Odorless | ACGIH 2005 |
| CAS Registry Number | 7664-39-3 | 7681-49-4 | ACGIH 2005 |
| Synonyms | Hydrofluoric acid, fluoric acid, fluorohydric acid, hydrofluoride, Antisal 2B, etching acid | Flura, Fluoridine, Fluoral, Flucare | ACGIH 2005 |
| Solubility in water | Very soluble | Soluble | ACGIH 2005 |
| Log $K_{ow}$ | No data | No data | ACGIH 2005 |
| Vapor Pressure | 760 mm Hg @20°C;<br>917 mm Hg @25°C | No data | ACGIH 2005 |
| Relative Vapor Density (air = 1) | 0.7 | No data | ACGIH 2005 |
| Melting Point °C | -83°C | 988 | ACGIH 2005 |
| Density (water = 1) | 0.988 at 14°C | 2.558 | ACGIH 2005 |
| Boiling Point °C | 19.5 | 1695 | ACGIH 2005 |
| Conversion Factors | 1 $\mu g/m^3$ = 1.22 ppb @25°C<br>1 ppb = 0.82 $\mu g/m^3$ | Not applicable | ACGIH 2005 |

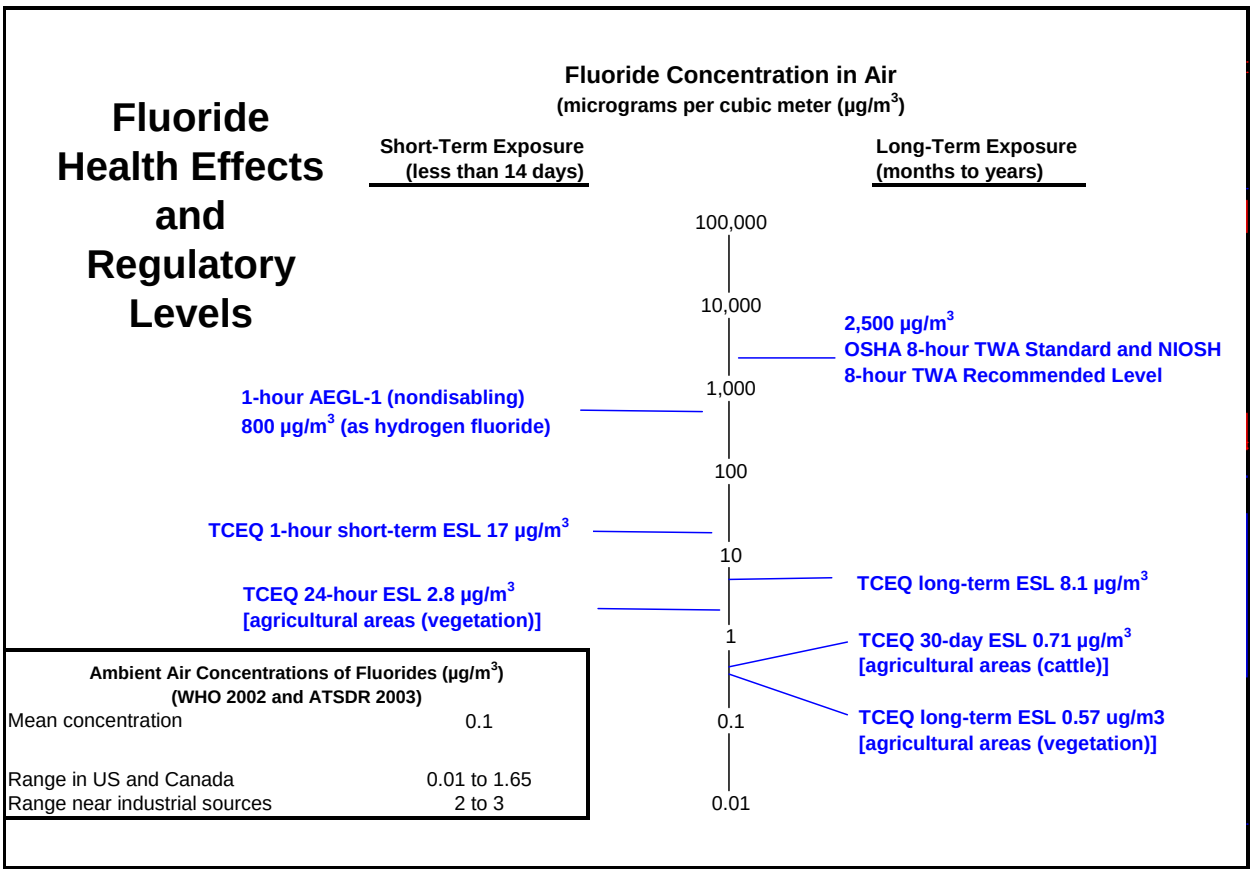


**Figure 1 Fluoride Health Effects and Regulatory Levels**

Figure 1 compares fluoride's acute toxicity values (health-based, short term ESL and 24-hour vegetation-based ESL) and chronic toxicity values (health-based long-term ESL, and long-term ESLs used in agricultural areas only (i.e., for vegetation and cattle) found in Table 1 to other values. Means and ranges of ambient concentrations were obtained from WHO (2002) and ATSDR (2003).

Abbreviations used: **TCEQ**, Texas Commission on Environmental Quality; **TWA**, time-weighted average; **ESL**, Effects Screening Level; **OSHA**, Occupational Safety and Health Administration; **NIOSH**, National Institute of Occupational Safety and Health; **AEGL-1,** Level-1 Acute Exposure Guideline Levels (nondisabling).

# Chapter 2 Major Uses or Sources

The term inorganic fluorides refer to numerous natural F-containing minerals as well as synthesized F compounds that are derived from hydrofluoric acid. F compounds exist in the atmosphere as both gas and particulates and are used in the production of aluminum, steel, phosphate fertilizers, phosphoric acid, glass, ceramic, and brick products (Lund et al. 1997). HF is widely used in industry. The most important use of HF is in the production of fluorocarbon chemicals. Anhydrous HF is used as a catalyst in the production of most fluorine-containing chemicals; as a fluorinating agent in the production of fluorine and aluminum fluoride; and in refining uranium. It is used in the production of refrigerants, herbicides, pharmaceuticals, high-octane gasoline, aluminum, plastics, electrical components, and fluorescent light bulbs. Aqueous hydrofluoric acid is used in stainless steel pickling, glass etching, metal coatings, exotic metal extraction, and quartz purification (ACGIH 2005 and ATSDR 2003).

An example of a soluble F is NaF which is one of the more commonly used F salts. It is mainly used as a wood preservative, pesticide, insecticide, fungicide, rodenticide, dentifrice, and additive to drinking water. NaF is also used in the manufacture of vitreous enamels, casein glues, and coated papers. Calcium fluoride is the compound in the common minerals fluorite and fluorspar. Fluorspar is the principal F-containing mineral from which HF is produced. It is also used in the production of glass and enamel and in the steel industry.

Naturally-occurring F including HF can be released into the air through volcanic activity, dust from soils, and sea-water droplets, carried into the atmosphere by winds. However, most of the airborne F is generated through the burning of F-containing fuels and from industrial sources. Major sources of industrial HF and F emissions are aluminum production and phosphate fertilizer plants. HF is released from other industries such as chemical production, steel, magnesium, and brick and clay tile products plants (ATSDR 2003, WHO 2004).

The mean concentrations of F (primarily HF) in ambient air in areas not in the direct vicinity of F emission source are generally less than 0.1 $\mu g/m^3$. However, the levels of airborne F usually do not exceed 2-3 $\mu g/m^3$ even in air near industrial sources (WHO 2002). The general population is typically exposed to very low levels of gaseous F. The levels ranged from 0.01 to 1.65 $\mu g/m^3$ in the United States and Canada (ATSDR 2003) (Figure 1).

# Chapter 3 Acute Evaluation

## *3.1 Health-Based Acute ReV and $^{acute}$ESL*

An acute Reference Value (ReV) and $^{acute}$ESL were developed for HF because the toxicity data for HF is adequate. There are limited data on the inhaled toxicity of other soluble inorganic F such as NaF (Section 3.2.2.2.3 Chen et al. (1999) and Yamamoto et al. (2001)). The Toxicology Division (TD) made a scientific policy decision to apply one set of acute toxicity factors for HF to all forms of soluble inorganic F, as F equivalents, noting this approach is likely health

protective. Effects on the respiratory system with respiratory inflammatory reactions were observed after exposure to both HF and NaF. In addition, Refsnes et al. (1999) demonstrated that F, in the forms of NaF and HF, induces a strong release of interlukin-6 (IL-6) and interlukin-8 (IL-8) from a human lung epithelial cell line (A549) and that F is at least partially responsible for the inflammatory response in humans after HF exposure. In addition, the toxicity of inorganic F compounds depends on the solubility; highly soluble compounds are more toxic than sparingly-soluble or insoluble ones. This lends support to applying the toxicity values based on HF to NaF and other soluble salts. In air permitting, emissions of soluble fluoride salts are provided as fluoride equivalents (F). The toxicity values for water-insoluble fluoride compounds will be derived separately.

## 3.1.1 Physical/Chemical Properties

HF is a colorless, pungent, acrid gas at temperatures above its boiling point of 19.5$^{o}$ C (close to room temperature) and a fuming liquid (hydrofluoric acid) at lower temperature. It is very soluble in many organic solvents and water, where it forms hydrofluoric acid. NaF is a white solid and is generally soluble in water. The main chemical and physical properties of HF and NaF are summarized in Table 2.

## 3.1.2 Key Studies

The upper respiratory tract is the most sensitive target of acute toxicity of F and HF exposure. HF gas is corrosive to the eyes and mucous membranes of the respiratory tract. Acute inhalation exposure to F or HF in humans has resulted in eye, nose and respiratory irritation, and inflammation of the airways. Exposure to high concentrations of HF can cause severe irritation, pulmonary edema, pulmonary hemorrhagic edema, tracheobronchitis, or death (ATSDR 2003). The results of acute human and animal studies show that humans might be more sensitive than rats to the irritation effects of HF or F, approximately by an order of magnitude.

Acute upper respiratory tract irritation and inflammation and lower respiratory tract inflammation have been observed in several human HF inhalation studies by Lund et al. (1997, 1999, 2002 and 2005). The lowest F concentration judged to cause irritation in the upper respiratory passages is 0.7-2.4 mg HF/m³ (Lund et al. 1997). At this exposure level there is also an increase in the number of CD3-positive cells in the bronchial part of broncholavage fluid (BAL), and at 2.5-5.2 mg HF/m³ there are indications of an inflammatory reaction (Lund et al. 1999). Indications of an inflammatory reaction were also seen in nasal lavage fluid 24 h after a 1-h exposure to 3.3-3.9 mg HF/m³, and 7 of 10 subjects reported upper airway discomfort (Lund et al. 2002). However, no early inflammatory response in the lungs was observed 2 h after a 1-h exposure to 3.3-3.9 mg HF/m³ (Lund et al. 2005). The Lund et al. (1999 and 2002) studies were selected as the key studies for the evaluation of acute HF toxicity, although the Lund et al. (1997) study is presented in the supporting study section since it was used by the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) and Agency for Toxic Substances and Disease Registry (ATSDR) to develop their

acute toxicity values.

### *3.1.2.1 Lund et al. (1999)*

Lund et al. (1999) examined the effects of HF exposure on biochemical and cellular indices in BAL samples. Nineteen healthy, nonsmoking men, aged 21-44 years were exposed to 0.2-0.6 (low, n=6), 0.7-2.4 (intermediate, n=7), or 2.5-5.2 mg/m³ (high, n=6) HF (analytical concentrations) for 1 hour (h). BAL was performed 3 weeks prior to exposure and 24 h after exposure. Data from the cell differential counts showed a significant increase in the percentage of lymphocytes and neutrophils in the bronchial portion and in the bronchoalveolar portion of the "intermediate" exposure group. However, no dose-response effect was found in the scatter plots, and no significant difference was found between the exposure groups by the Kruscal Walis test. Significant increases in the percentage of CD3-positive cells (a marker of T-lymphocytes) were found in the bronchial portion of BAL fluid individually before and 24 h after exposure to HF in the "intermediate" and "high" exposure groups (p=0.03), and in the bronchoalveolar portion in the "high" exposure group (p=0.04). A significant correlation between the individual changes in the percentage of CD3-positive cells and the changes in the percentage of lymphocytes from the bronchoalveolar portion was observed (r=0.68, p=0.008), while there was no significant correlation in the bronchial portion (r=0.25). Significant correlations were observed between the differences in the percentage of CD3-positive cells (r=0.68, p=0.008), between changes in the percentage of lymphocytes (r=0.53, p=0.04) in the bronchial and bronchoalveolar portions, individual changes in the percentage of CD3-positive cells, and in the percentage of lymphocytes from the bronchoalveolar portion.

The number of neutrophil did not increase, although significant increases in myeloperoxidase (MPO), a marker of neutrophil activation, and interleukin-6 (IL-6) concentrations were found in the bronchial portion, but not in the bronchoalveolar portion, in the "high" exposure group. There was a significant increase in MPO (p=0.005) for all the 19 subjects as a single exposure group (0.2-5.2 mg/m³). There was a significant correlation between the individual changes in MPO and the differences in neutrophils in the bronchial and the bronchoalveolar portions. The E-selection and total protein, a marker of injury to the epithelial-endothelial cell barrier, however, were decreased. The data indicate that inflammatory response seems to be prominent in the more proximal airways due to the high water solubility of HF leading to a higher absorption rate with a concomitant cellular response.

The Lund et al. (1999) study showed that exposure of healthy subjects to HF in the" intermediate" (0.7-2.4 mg/m³) and the "high" (2.5-5.2 mg/m³) exposure groups can induce an inflammatory reaction in the airways 24 h after the exposure. The authors concluded that the exposure of healthy subjects to HF concentrations above 0.6 mg/m³ may induce an inflammatory response in the airways, although no dose-response effect was found in the scatter plots and no significant difference was found between the exposure groups by the Kruscal Walis test. Thus, a lowest-observed-adverse-effect level (LOAEL) of 0.7 mg HF/m³, identified from the low end of the range of concentrations from the "intermediate" exposure group, and a no-observed-adverse-

effect level (NOAEL) of 0.6 mg/m³, identified from the highest concentration not producing airway inflammation from the "low' exposure group, were identified from this study. The lowest range of 0.2-0.6 mg/m³ was also considered a NOAEL by the Swedish National Institute for Working Life (NIWL 2005) while the American Governmental Industrial Hygienists Association (ACGIH 2005) considered 0.6 mg/m³ a NOAEL for airway inflammation. Thus, a NOAEL of 0.6 mg HF/m³, the highest concentration not producing airway inflammation, was used as the point of departure (POD) (TCEQ 2006).

### *3.1.2.2 Lund et al. (2002)*

Lund et al. (2002) further examined the immediate nasal response in humans who have experienced short-term and frequent HF exposures. Nasal lavage was performed on 10 healthy and nonsmoking male subjects, aged 22-41 years. Subjects were exposed to HF (3.3-3.9 mg/m³) for 1 h and samples were taken before, immediately after and 1.5 h after the end of exposure. The results show that 7 of 10 subjects reported increased upper airway symptoms and immediate increases in total cells, neutrophil, tumor necrosis factor-α (which induces the secretion of cytokines), and total protein in nasal lavage within 1.5 h after exposure. The increase in neutrophil numbers correlated significantly with the reported airway symptoms. The authors concluded that exposure to HF induced immediate nasal inflammatory responses in healthy human volunteers. These findings are supported by an *in vitro* study (Refsnes et al. 1999) that F, in the forms of NaF and HF, induce a strong release of IL-6 and IL-8 from a human lung epithelial cell line (A549) and that F are at least partially responsible for the inflammatory response in humans after HF exposure. The results of this study supported the investigators' earlier work which showed symptom increases and sub-clinical effects, i.e., BAL fluid changes, in the "intermediate" exposure group (0.7 to 2.4 mg/m³), and in upper airway symptoms in the "high" exposure group (2.5-5.2 mg/m³) (Lund et al. 1997 and 1999). Thus, a LOAEL of 3.3 mg HF/m³, the low end of the range of concentrations (3.3-3.9 mg/m³) for nasal airway inflammation was identified from this study and was also used as a POD.

## 3.1.3 Supporting Studies

### *3.1.3.1 Human Supporting Studies*

#### 3.1.3.1.1 Lund et al. (1997)

In this human study, 23 healthy, nonsmoking male volunteers (21–44 years of age) were exposed in an inhalation chamber to constant HF gas concentrations ranging from 0.2 to 5.2 mg/m³ for 1 h. For the purpose of analysis, the subjects were divided, according to their exposure to HF (analytical concentrations), into exposure groups of 0.2-0.6 (low, n=9), 0.7-2.4 (intermediate, n=7), or 2.5-5.2 mg/m³ (high, n=7). Symptoms from the eye, upper and lower airways (graded on a scale from 1 to 5 with a standardized questionnaire), lung function [forced expiratory volume in one second ($FEV_1$), and forced vital capacity (FVC)] were investigated before, during, and after exposure. Results after exposure were compared to results obtained before exposure began.

Symptoms, especially upper airways and eyes irritation, were significantly increased after exposure for all 23 subjects as a single exposure group (0.2-5.2 mg HF/m³) ($p < 0.001$ for upper airway and $p < 0.02$ for eye irritation), but these increases did not appear to be dose-dependent (ACGIH 2005, NIWL 2005). The upper airway symptom score was significantly increased for the" high" exposure group ($p=0.02$) and the same trend was found among the subjects in the "low" exposure group ($p=0.06$), but not in the "intermediate" exposure group ($p=0.10$). The eye irritation and lower airways score were not significantly increased for the "low', 'intermediate" and "high" exposure group. The total symptom scores were significantly increased in the "low" exposure group ($p=0.04$) and the "high" group ($p=0.02$), but not in the "intermediate" exposure group ($p=0.67$). There was no clear dose-response relationship for symptoms involving eyes and lower respiratory passages. Almost all symptoms had disappeared 4 h after the end of exposure. Because the increases of clinical symptoms score were not dose-dependent, a NOAEL or LOAEL for upper and lower airways, eye irritation, or total symptom score was not identified from this study.

No significant change was detected in $FEV_1$ following exposure at any HF concentration. However, a statistically significant post-exposure decrease in FVC was found in all 23 subjects as a single exposure group ($p<0.05$) and in the low-dose exposure group ($p<0.01$), but no changes in the "intermediate" and "high" exposure groups. Since significant reduction of FVC was seen in the low-exposure group, but not observed in the other groups it can not be interpreted as an effect of the exposure. The pulmonary function decrements observed in the Lund et al. (1997) study did not show evident dose-response relationship (ACGIH 2005, NIWL 2005). Furthermore, the $FEV_1$ did not change and no lower airway symptom score were significantly increased during exposure at any concentration. Therefore, a NOAEL or LOAEL for changes in lung function was not identified from this study.

NIWL indicated that since there were few subjects in the Lund et al. (1997) study, and they were not given a null exposure to allow them to become accustomed to the exposure chamber, it is difficult to assess the effect of the lowest exposure. NIWL further indicated that the most probable LOAEL was estimated to be 0.7-2.4 HF/m³ and the 0.2-0.6 HF/m³ was a NOAEL (NIWL 2005). The estimated LOAEL for upper respiratory symptoms and/or lung function supported the LOAEL for airways inflammation identified from the Lund et al. (1999) study (see Section 3.1.2.1).

The TD concurs with ACGIH and NIWL that the results of the Lund et al. (1997) study for symptom scores from the eyes and upper and lower airways, total symptom scores, and for pulmonary function decrements failed to identify a reliable NOAEL or LOAEL. Thus, the results of this study were not used to derive an acute ReV and ESL.

### 3.1.3.1.2 Lund et al. (2005)

In another study similar to Lund et al. (2002) (Section 3.1.2.1.1), Lund et al. (2005) examined early pulmonary responses to HF exposure. Bronchoscopy with BAL was performed on 10

healthy and nonsmoking male subjects, aged 22-41 years, 2 h after the end of a 1 h exposure to HF (3.3-3.9 mg/m³). Significant reductions in the total cell number, the numbers of neutrophil and lymphocytes, and the concentrations of soluble pro-inflammatory mediators, such as IL-6, and total protein in bronchoalveolar portion were observed. The study did not result in an acute inflammation in the lungs 2 h after the end of the exposure period.

The results of this study were different from a previous study (Lund et al. 1999) which demonstrated airway inflammation in healthy volunteers 24 h after exposure to HF. The unexpected findings of this study indicate that the development of inflammation following HF exposure follows different time courses in the nose (Lund et al. 2002) compared to that found in the lungs (Lund et al. 1999, 2005). The authors suggested that because HF is very hydrophilic and will effectively be absorbed in the nasal epithelium and upper airways, the higher deposition of HF in the nasal region may account for some of the difference in mucosal response.

#### 3.1.3.1.3 Largent (1961)

In an inhalation study by Largent (1961), five human volunteers, one at a time, were exposed to HF at average concentrations of 1.42-4.74 ppm (1.16-3.89 mg/m³) for 6 h/day for 10-50 days. No noticeable effects were observed in one individual exposed at an average concentration of 1.42 ppm for 15 days. However, serious irritation and considerable discomfort in the nose were observed in the same subject when exposed at 3.39 ppm for 10 days. Slight irritation of the face, nose and eyes was noticed in four other subjects at concentrations averaging from 2.59 to 4.74 ppm (2.12-3.89 mg/m³). A NOAEL of 1.42 ppm (1.16 mg HF/m³) for nose/eye irritation was identified from this study.

### *3.1.3.2 Animal Supporting Studies*

As mentioned previously, the results of animal studies show that humans might be more sensitive than rats to the irritation effects of HF or F by approximately an order of magnitude.

#### 3.1.3.2.1 Dalbey et al. (1998a, 1998b)

Dalbey et al. (1998a, 1998b) conducted a series of acute inhalation exposures with airborne HF concentrations ranging from 135-8,621 ppm (111-7,069 mg HF/m³) for 2 or 10 minutes (min) to study a number of respiratory tract effects in rats. Mouth-breathing (MB) rats, with a tracheal cannula, exposed for 2 min manifested histological damage and BAL parameter alterations at 1,509 ppm and impaired lung function at 4,643 ppm. No adverse respiratory effects were observed at 563 ppm. In the MB rats exposed for 10 min, histopathological alterations (necrosis of the trachea only) and BAL parameters (polymorphonuclear leukocytes and myeloperoxidase levels only) were observed at 903 ppm; impaired respiratory function was observed at 1,676 ppm. No adverse effects were observed at 257 ppm. Observed respiratory effects were concentration related and appeared more pronounced in major airways near the point of entry, i.e., trachea. In other experiments, MB rats were exposed to HF for 60 min. No adverse respiratory effects were observed at 20 or 48 ppm.

In the nose-breathing (NB) rats, almost none of the BAL parameters, lung function tests, or other endpoints measured in the MB rats were affected. Respiratory effects observed in NB rats were limited primarily to the nose. Necrosis and acute inflammation of the ventral meatus, nasal septum, and nasoturbinates were observed in rats exposed to 6,072 ppm for 2 min and 1,586 ppm for 10 min. A dramatic decrease in breathing frequency was also observed in the NB rats at both exposure concentrations. The decrease in breathing frequency, which is a component of reflex apnea, is a response to sensory irritation. A 60-min NOAEL of 48 ppm (39 mg/m³) for respiratory tract effects exposure was identified from this study based on MB rats.

#### 3.1.3.2.2 Rosenholtz et al. (1963)

In a study by Rosenholtz et al. (1963 in OEHHA 1999; NAS 2004), rats were exposed to HF at 103, 126, 291, and 489 ppm (85, 103, 239, and 401 mg/m³) for 60 min. Mild and occasional signs of eye, nose, or respiratory irritation were observed in rats at 103 ppm. The signs resolved shortly after removal of the animals from the exposure. General discomfort, pawing at the nose, and tearing from the eyes were observed in rats at 126 ppm. The signs lasted for a few hours after exposure. A 60-min LOAEL of 103 ppm (85 mg HF/m³) for irritation was identified from this study.

#### 3.1.3.2.3 Chen et al. (1999) and Yamamoto et al. (2001)

In a study conducted by Chen et al. (1999) as cited in ATSDR (2003), significant increases in relative lung weight were observed in mice exposed to 13.3 mg F/$m^3$ as NaF 4 h/day for 10, 20, or 30 days. In another study of mice by Yamamoto et al. (2001) as cited in ATSDR (2003), lung damage, as evidenced by significant decreases in total cells and alveolar macrophages and increases in polymorphocytic neutrophils (PMNs) and lymphocytes in the BAL fluid, was found in mice exposed to 10 mg F/$m^3$ as NaF 4 h/day for 14 days. An increase in PMNs was also observed at 5 mg/$m^3$.

### 3.1.4 Reproductive/Developmental Effects Studies

No studies were available for developmental effects in animals after acute inhalation exposure to HF or F. Degenerative testicular changes and ulceration of the scrotum were observed for all 4 dogs exposed to 18 ppm (14.8 mg/m³) HF gas for 6 h/day, 6 days/week for 5 weeks (Stokinger 1948, cited in ATSDR 2003). However, reproductive effects were not observed at 8.2 ppm (6.7 mg/m³). The No Effects Level of 8.2 ppm was relatively high compared to studies with respiratory effects, thus no ReV for reproductive effects was developed.

### 3.1.5 Mode-of-Action (MOA) Analysis and Dose Metric

The MOA for upper respiratory tract irritation and airway inflammation for HF may be related to the aqueous solubility, reactivity, and acidic properties of HF. HF can cause dehydration and corrosion of tissues mediated by hydrogen ion. HF is very soluble in water and is readily absorbed in the upper respiratory tract. When inhaled in the absence of physical activity, HF is expected to deposit in the human nasal passageways. Like many water-soluble reactive gases,

HF tends to be scavenged effectively by the upper respiratory mucosa, causing upper respiratory irritation and injury (Bennion and Franzblau 1997). HF penetration in the lower respiratory tract may depend on concentration-exposure durations, because lower doses are effectively deposited only in the nasal passages (NAS 2004). At higher levels of HF exposure, the dissociated F ion, $F^-$, may penetrate into the lungs to cause severe pulmonary inflammation or injury. Since exposure concentration of HF is the most appropriate dose metric based on its MOA, exposure concentration of HF will be used as the dose metric.

For F, the toxicity of inorganic F compounds depends on the solubility (see Section 3.1). There is limited information on the respiratory effects of F. The MOA for respiratory tract irritation and airway inflammation is presumably similar to that for HF. Thus, exposure concentration of the F (mg F/$m^3$) will be used as the dose metric.

## 3.1.6 Critical Effect and Dosimetric Adjustments

A NOAEL of 0.6 mg HF/$m^3$ (0.73 ppm) for airway inflammation identified from the Lund et al. (1999) study and a LOAEL of 3.3 mg HF/$m^3$ (4 ppm) for nasal inflammatory and antioxidant responses from Lund et al. (2002) were used as PODs. The Lund et al. (1999) study was chosen because it was a well-conducted acute inhalation study with an adequate number of healthy human subjects at 1 h exposure duration and demonstrated dose-related responses. The Lund et al. (2002) study was also chosen because the critical effects such as immediate inflammatory responses in nasal tissues "contributed most significantly" to the assessment of the human health risk of exposure to HF. Since the exposure duration of both key studies is 1 h, no exposure duration adjustment was conducted.

## 3.1.7 Adjustments of the POD

### *3.1.7.1 POD (Lund et al. 1999)*

An acute Reference Value (ReV) of 60 $\mu$g HF/$m^3$ was derived by applying a total UF of 10 to the POD of 600 $\mu$g HF/$m^3$:

- an uncertainty factor (UF) of 10 to account for human variability; and
- a UF of 1 for database uncertainty because the overall quality of the studies is high with adequate human and animal studies.

### *3.1.7.2 POD (Lund et al. 2002)*

An acute ReV of 52 $\mu$g HF/$m^3$ was derived by applying a total UF of 63 to the POD of 3,300 $\mu$g HF/$m^3$:

- a $UF_H$ of 10 for human variability;
- a $UF_L$ of 6.3 for extrapolation from a mild LOAEL to a NOAEL. A $UF_L$ of 6.3 rather than 10 was used for extrapolation from a LOAEL to NOAEL because the acute nasal

inflammatory responses were mild (TCEQ 2006); and

- a $UF_D$ of 1 for database uncertainty. A UF of 1 was used for database uncertainty because the overall quality of the studies is high with adequate human and animal studies.

### *3.1.7.3 Comparison*

Table 3 shows a comparison of the derivations of the ReVs from the different PODs. The derived ReV of 52 $\mu$g HF/m$^3$ based on the LOAEL from the Lund et al. (2002) study is similar to the ReV of 60 $\mu$g HF/m$^3$ derived from the NOAEL from the Lund et al. (1999) study.

**Table 3 Comparison of ReVs from the Key Studies**

| Study and Critical Effects | POD | Exposure Duration | Total UFs | ReV |
|---|---|---|---|---|
| Increases in airway inflammation (Lund et al. 1999) | 600 $\mu$g/m$^3$ NOAEL | 1 h | 10 | 60 $\mu$g HF/m$^3$ * |
| Nasal inflammatory responses and upper airway symptoms (Lund et al. 2002) | 3,300 $\mu$g/m$^3$ LOAEL | 1 h | 63 | 52 $\mu$g HF/m$^3$ |

* preferred ReV because it is based on a NOAEL

## 3.1.8 Health-Based Acute ReV and $^{acute}$ESL

While the acute ReV from the Lund et al. (2002) study is slightly lower than the ReV derived from the Lund et al. (1999) study, the final ReV for HF and other soluble inorganic fluorides will be 60 $\mu$g HF/m$^3$ based on the NOAEL rather than the LOAEL. When calculating, no numbers were rounded between equations until the ReV was calculated. Once the ReV was calculated, it was rounded to two significant figures. The rounded ReV was then used to calculate the ESL, and the ESL subsequently rounded. The $^{acute}$ESL of 18 $\mu$g HF/m$^3$ (22 ppb) was calculated according to ESL guidelines (TCEQ 2006) based on the acute ReV of 60 $\mu$g/m$^3$ (73 ppb) multiplied by a hazard quotient (HQ) of 0.3. Table 4 provides a summary of the acute ReV and $^{acute}$ESL based on the Lund et al. (1999) study.

**Table 4 Derivation of the Acute ReV and $^{acute}$ESL**

| **Parameter** | **Summary** |
|---|---|
| Study | Lund et al. (1999) |
| Study population | 19-23 healthy nonsmoking male volunteers |
| Key Study Confidence Level | High |
| Exposure Method | Inhalation of 0.2-0.6 (low), 0.7-2.4 (intermediate), and 2.5-5.2 mg/m$^3$ (high) HF exposure groups |
| Critical Effects | Increases in airway inflammation |
| LOAEL | 0.7 mg/m$^3$ HF concentration |
| POD | 0.6 mg/m$^3$ HF concentration (NOAEL) |
| Exposure Duration | 1 h |
| Extrapolated 1 hr concentration | 0.6 mg/m$^3$ HF concentration |
| Total uncertainty factors (UFs) | 10 |
| *Interspecies UF* | N/A |
| *Intraspecies UF* | 10 |
| *LOAEL UF* | N/A |
| *Incomplete Database UF* | 1 |
| *Database Quality* | High |
| **Acute ReV (HQ = 1)** | **60 $\mu$g HF/m$^3$ (73 ppb)** |
| **$^{acute}$ESL (HQ = 0.3)** | **18 $\mu$g HF /m$^3$ (22 ppb)** |

## 3.1.9 Comparison of Various Acute Toxicity Values

Table 5 is a comparison of HF toxicity values derived by other federal and state agencies. The following sections discuss the differences between the PODs and toxicity value derived by different agencies.

**Table 5 Comparison of HF Acute Toxicity Values**

| | Acute Toxicity Value | POD | Key Study |
|---|---|---|---|
| ReV | 60 $\mu g/m^3$ (73 ppb) | 0.6 mg/m³ (NOAEL) [a] | Lund et al. (1999) |
| REL (OEHHA 1999) | 240 $\mu g/m^3$ (300 ppb) | 2.4 mg/m³ (NOAEL) [b] | Lund et al. (1997) |
| MRL (ATSDR 2003) | 16 $\mu g/m^3$ (20 ppb) | 0.4 mg/m³ (LOAEL) [c] | Lund et al. (1997) |
| TLV-TWA (ACGIH 2005) | 410 $\mu g/m^3$ (500 ppb, measured as F) | 0.6 mg/m³ (NOAEL) [a] | Lund et al. (1999) |

[a] The TD and ACGIH identified the intermediate exposure group as the LOAEL, and the high end of the range of concentrations from the low exposure group (0.2-0.6 mg HF/m³) of the Lund et al. (1999) studies as a NOAEL

[b] OEHHA identified the high end of the range of concentrations from the intermediate exposure groups (0.7-2.4 mg HF/m³ HF) of the Lund et al. (1997) study as a NOAEL

[c] ATSDR identified the midpoint of the range of concentrations from the low exposure group (0.2-0.6 mg HF/m³) of the Lund et al. (1997) studies as a LOAEL

### *3.1.9.1 OEHHA (1999)*

OEHHA (1999) derived an acute reference exposure level (REL) in March 1999 based on the Lund et al. (1997) study (see Section 3.1.3.1.1). In the Lund et al. (1997) study, self-reported upper airway and eye irritation occurred after 1 h of exposure to HF at 0.2-0.6 mg HF/$m^3$ with 4/9 subjects reporting low symptom scores. However, the scored symptoms were not statistically significantly different comparing before-exposure reported symptoms to after-exposure reported symptoms until concentrations exceeded 2.5 mg/$m^3$. OEHHA considered the 0.7-2.4 mg HF/m³ range a NOAEL and the range of 2.5-5.2 mg HF/m³ was deemed a LOAEL for upper airway irritation. The high end of the NOAEL (2.4 mg HF/m³) was then divided by an UF of 10 to account for human variability to calculate the acute REL of 240 $\mu$g HF/$m^3$ (300 ppb). However, as discussed in Section 3.1.3.1.1 above, the upper airway symptom scores were significantly increased in the "low" and "high" exposure group, but not in the "intermediate" exposure group, the TD believes that the Lund et al. (1997) study failed to establish a clear dose-response relationship.

### *3.1.9.2 ATSDR (2003)*

ATSDR (2003) calculated an acute inhalation minimal risk level (MRL) of 0.02 ppm for HF based on the Lund et al. (1997) study and a supporting study by Lund et al. (1999). ATSDR

identified the midpoint of the range of concentrations from the low exposure group (0.2-0.6 mg HF/m³) of the Lund et al. (1997) study as a LOAEL (0.4 mg HF/m³) while OEHHA (1999) identified the high end of the range of concentrations from the intermediate exposure group (0.7-2.4 mg HF/m³) of the Lund et al. (1997) study as NOAEL (see Section 3.1.7.1 above). ATSDR indicated that the results of Lund et al. (1997) study showed a trend ($p = 0.06$) toward increased upper respiratory tract symptom score and a significant increase in the total symptom score ($p = 0.04$) which were observed at the lowest exposure concentrations (0.2-0.6 mg HF/$m^3$). A cumulative UF of 30 (3 for use of a minimal LOAEL and 10 for human variability) was applied to the 0.4 mg HF/m³ (0.5 ppm) LOAEL to derive the acute MRL of 16 µg HF/$m^3$ (20 ppb). However, as discussed in Section 3.1.8.1 above, ATSDR did not consider that the results of Lund et al. (1997) not shown a clear dose-response relationship. The TD believes that a NOAEL of 0.6 mg HF/m³ for increases in airway inflammation identified from Lund et al. (1999) (see Section 3.1.2.1) was more appropriate for use as a POD.

### *3.1.9.3 ACGIH (2005)*

ACGIH indicated that the results of the Lund et al. (1997) study for symptom scores from the eyes and upper and lower airways and total symptom score and for pulmonary function decrements failed to show a dose-response relationship. Based on the results of Lund et al. (1997 and 1999) studies which showed symptom increases and BAL fluid changes in the "intermediate" exposure group (0.7 to 2.4 mg/m³), ACGIH recommended a time-weighted average threshold limit value (TLV-TWA) of 0.5 ppm (0.4 mg/m³), as F. The TLV is consistent with the NOAEL of 0.6 mg/m³ which was used by the TD as a POD.

## *3.2 Welfare-Based Acute ESLs*

### 3.2.1 Odor Perception

HF has an irritating and pungent odor regardless of its physical state (ACGIH 2005). An odor threshold of 33 $\mu$g/$m^3$ (42 ppb) was reported by Sadilova (1968, cited in AIHA 1989 and USEPA 1992). An odor threshold of 42 ppb (34 µg/$m^3$) was reported by Amoore and Hautala (1983) and was a historical odor value used by the TCEQ. Based on an evidence integration approach and historical information (TCEQ 2015), the $^{acute}ESL_{odor}$ for HF is 42 ppb (34 µg/$m^3$). Since the perception of odor is a concentration-dependent effect, the same $^{acute}ESL_{odor}$ is assigned to all averaging times.

### 3.2.2 Vegetation Effects

F are potent phytotoxic air pollutant. The effects of F on plants have been well documented. HF and F produce a wide range of effects on plants such as reduction of plant growth, induction of leaf chlorosis (killing of leaf cells), and effects on photosynthesis, respiration, and enzyme activities. After exposure to F, plants progressively become necrotic (yellowing of the leaves due to chlorophyll reduction). F are accumulative toxicant, and injury is usually associated with long-term exposure (weeks or months) (McCune 1969a, Hill 1969).

Short-term exposure to F may cause necrosis in plants, predominately along the margins and tips of the leaves where the F have accumulated. Leaf chlorosis, however, usually is caused by chronic F exposure. The toxicity of F on vegetation depends on how readily it is absorbed into the plant tissue. Gaseous and soluble F have the most pronounced vegetation effects, and the insoluble F typically have very low phytotoxicity. HF, $H_2SiF_6$, $SiF_4$, and $F_2$ are the most phytotoxic gaseous forms. Particulate forms of F are generally much less toxic than the gaseous forms, and their toxicity is related to solubility and to the size of the hydrated ionic species (Weinstein 1977).

### *3.2.2.1 Relative Susceptibility of Plant Species*

Plant species and varieties differ greatly in susceptibility to airborne F, and extremely low concentrations can cause damage to sensitive species. For example, for gladiolus a concentration as low as 5 ppb of HF for about a week produces leaf scorch, and the leaves may become necrotic when gladiolus have accumulated as little as 20 ppm of F (20 $\mu$g of F per gram of dry weight) (Jacobson et al. 1966). In a study by Zimmerman and Hitchcock (1956), approximately 40 species of plants were exposed to HF gas at 50 ppb for 4-8 h to compare their susceptibility or resistance. The results show that highly susceptible species are Jerusalem cherry, gladiolus, tulip, maize, ixora, corn, apricot, and prune; and most resistant species are cotton, celery, tomato, alfalfa, eggplant, cucumber, and clover.

### *3.2.2.2 Key Studies*

The toxicity of F on vegetation commonly results from gradual accumulation of F in the plant tissue over a period of time. The degree of injury is related to the concentration of airborne F and cumulative exposure duration as well as to F accumulation (Weinstein 1977, Coulter et al. 1985). Exposure to HF for shorter averaging time, e.g., 1- to 8-h averages, may not adequately reflect the cumulative nature of F toxicity. Therefore, an $^{acute}ESL_{veg}$ set at longer averaging time, such as 24-h is more appropriate for the $^{acute}ESL_{veg}$. The TD used the 24-h average data from the McCune (1969a, 1969b) studies to set a 24-h $^{acute}ESL_{veg}$.

McCune (1969a, 1969b) summarized F dose-response relationships for foliar injury to different plant species from the available literature and presented a plot showing a series of curves describing threshold doses for foliar markings (as in tree fruits, conifers, or tomato) or effects on growth or yield (as in corn, sorghum, or gladiolus). McCune's data showed the 24-h mean HF threshold concentrations ranging from 3 to 12 $\mu g/m^3$ (3.7 to 14.6 ppb) for the following sensitive plants:

- Conifers – 3.0 $\mu g/m^3$ (3.7 ppb)
- Fruit trees – 4.5 $\mu g/m^3$ (5.5 ppb)
- Gladiolus – 6.0 $\mu g/m^3$ (7.3 ppb)
- Corn – 10.5 $\mu g/m^3$ (12.8 ppb)

- Tomato – 12 $\mu$g/m$^3$ (14.6 ppb)

The 24-h mean HF threshold concentration of 3 $\mu$g/m$^3$ (3.7 ppb) for effects on conifers was the lowest observed effect level (LOEL) for mild effects on foliar markings and growth or yield, and was used to set the 24-h vegetation-based ESL.

### *3.2.2.3 Supporting Studies*

McCune (1974) as cited in Heggestad and Bennett (1984) proposed general limiting values of 5-10 ppb for 2 to 4 h (peak concentrations), or 0.3-0.6 ppb for 30-60 days exposures to protect most vegetation. Bennett and Hill (1973) as cited in Heggestad and Bennett (1984) reported that HF exposure for several hours above 10 ppb can measurably depress $CO_2$ exchange-rates (photosynthesis rates) of alfalfa and barley canopies. Approximately 15-20 ppb HF for 2 h is sufficient to cause a trace of leaf necrosis in these two species. Slower recovery after termination of the treatments was observed in non-necrotic tissues. A 2-h LOEL of 15-20 ppb producing a trace of leaf necrosis in alfalfa and barley was identified from the Bennett and Hill (1973) study. As discussed in Section 3.2.2.2 above, F injury to plants commonly results from gradual accumulation of F in the plant tissue over a period of time, so a longer averaging time, such as 24-h is more appropriate for the HF $^{acute}ESL_{veg}$. Therefore, a 1-h $^{acute}ESL_{veg}$ was not developed.

### *3.2.2.4 MOA Analysis*

F interfere with the major physiological functions in vegetation, such as photosynthesis or respiration, or with metabolic pathways such as glycolysis or the pentose phosphate pathway (Jacobson et al. 1966). The portal of entry is the pores of the leaves. F then move into the cells, the plant water stream via the veins, and is finally deposited at the tip and edges of the leaf (Weinstein and McCune 1971). Airborne F can be absorbed by the surface of leaves and can accumulate at the tips of leaves of narrow-leaved plants and the margins of leaves of broad-leaved plants. The toxic effects of F are related to the movement of F after penetrating the leaf and the final distribution of F in relation to leaf structure. F injury to plants commonly results from gradual accumulation of F in the plant tissue over a period of time. Therefore, severity of injury is related to both concentration and duration of exposure (Weinstein 1977, Coulter et al. 1985). Jacobson et al. (1966) suggested that the variation in the susceptibility to injury and degree of F accumulation may be due to differences in the mean of accumulation, translocation, and distribution of F between plant species and varieties.

### *3.2.2.5 Derivation of the $^{acute}ESL_{veg}$*

According to the 2006 TCEQ guidelines, vegetation-based ESLs are set at the lowest threshold concentration for adverse effects that won't significantly affect species survival or plant yield (TCEQ 2006). Therefore, a 24-h $^{acute}ESL_{veg}$ for HF and soluble F was derived based on a 24-h mean HF LOEL of 3.0 $\mu$g/m$^3$ (3.7 ppb) for foliar injury on conifers reported by McCune (1969a, 1969b). Accordingly, the 24- h $^{acute}ESL_{veg}$ is 3.0 $\mu$g HF/m$^3$ (3.7 ppb) (see Section 3.2.2.2.).

### 3.2.3 Comparison of Various Vegetation-Based Acute Toxicity Values

Table 6 is a comparison of the vegetation toxicity values set by other agencies. The table shows that the 24-h $^{acute}ESL_{veg}$ is consistent with the secondary standards of some other states.

**Table 6 Comparison of HF Acute Vegetation Toxicity Values**

| Parameter | 12-h Toxicity Value | 24-h Toxicity Value | 7-day Toxicity Value |
|---|---|---|---|
| $^{acute}ESL_{veg}$ (TCEQ) | | 3.0 $\mu g/m^3$ | |
| Reference Level (CEPA 1996) | | 1.1 $\mu g/m^3$ | 0.5 $\mu g/m^3$ |
| Ambient Standard [a] (Washington) | 3.5 $\mu g/m^3$ | 2.7 $\mu g/m^3$ | 1.6 $\mu g/m^3$ |
| Ambient Standard [a] (Kentucky) | 3.7 $\mu g/m^3$ | 2.85 $\mu g/m^3$ | 1.65 $\mu g/m^3$ |
| Ambient Standard [a] (Wyoming) | 3.5 $\mu g/m^3$ | 2.7 $\mu g/m^3$ | 1.6 $\mu g/m^3$ |
| Ambient Standard [a] (Tennessee) | 3.7 $\mu g/m^3$ | 2.9 $\mu g/m^3$ | 1.6 $\mu g/m^3$ |

[a] Secondary standards for the protection of vegetation

## *3.3 Short-Term ReV and $^{acute}$ESLs*

This acute evaluation resulted in the derivation of the following acute values for

- acute ReV = 60 $\mu g/m^3$ (73 ppb)
- $^{acute}ESL$ = 18 $\mu g/m^3$ (22 ppb)
- $^{acute}ESL_{odor}$ = 34 $\mu g/m^3$ (42 ppb) (for HF only)
- $^{acute}ESL_{veg}$ [24 h] = 3.0 $\mu g/m^3$ (3.7 ppb)

The short-term ESL for air permit evaluations is the health-based $^{acute}$ESL of 18 µg HF/$m^3$ (22 ppb). However, the 24-h $^{acute}$ $ESL_{veg}$ of 3 µg HF/$m^3$ (3.7 ppb) is also used for facilities located in agricultural areas where the most sensitive plant, conifers, may be planted (Table 1). For other sensitive plants such as fruit trees, gladiolus, corn or tomato, higher 24-h $^{acute}$ $ESL_{veg}$ other than 3 µgHF/$m^3$ (3.7 ppb) may be used. Acute values for F equivalents based on HF are shown in Table 1.

# Chapter 4 Chronic Evaluation

## *4.1 Noncarcinogenic Potential*

The major noncarcinogenic effects from chronic inhalation exposure to F are skeletal fluorosis and respiratory effects. Numerous occupational exposure studies on respiratory tract and skeletal effects from exposures to HF or mixtures of HF gas and F dusts have been reported. However, these occupational exposure studies are somewhat limited by co-exposure to a number of other chemicals (e.g., sulfur dioxide ($SO_2$), polycyclic organic matter and other particulate matter) and limited exposure data (ATSDR 2003). Since there were difficulties in specifically separating potential risks posed by co-existing air contaminants for respiratory tract effects, the occupational exposure studies of the respiratory tract were not used to develop toxicity values for HF and/or F. However, the potential risks for skeletal fluorosis are not likely to be affected as much by co-existing air contaminants. Therefore, the TD used studies of skeletal fluorosis to develop F/HF toxicity values. No chronic studies of the respiratory tract and skeletal effects after chronic inhalation of HF or F in animals were reported. However, there are some subchronic inhalation studies of HF or F for respiratory effects in animals.

### 4.1.1 Physical/Chemical Properties and Key Studies

Physical/chemical properties for HF and soluble F salts are discussed in Section 3.1.1. The key study for skeletal fluorosis is Derryberry et al. (1963).

### 4.1.2. Key Study for Skeletal Fluorosis (Derryberry et al. 1963)

Exposure to high levels of HF and/or F may lead to toxic effects and disease, such as fluorosis. Fluorosis is characterized by stiffness and immobility of the spine and rheumatic pains in the back and extremities. Changes in bone density in association with F exposure have been observed in several studies, and appear to be the most sensitive health effects after chronic exposure (OEHHA 2003). The degree of skeletal fluorosis (osteosclerosis) increases with the concentration and duration of exposure (Massmann 1981 in CEPA 1996).

In an occupational study by Derryberry et al. (1963), exposure to F levels, urinary F analysis, and the health effects of F on 74 male workers in a fertilizer manufacturing plant were evaluated. The length of employment for these 74 workers ranged from 4.5-25.9 years (average 14.1 years) with 76% of workers having over 10 years of employment. An 8-h time weighted average (TWA) airborne F exposure was calculated for the period of employment of each worker. The overall average 8-h TWA exposure to total F was 2.81 mg F/$m^3$ (range: 0.5-8.32 mg F/$m^3$) for the total exposed group. The results show no significant differences in gastrointestinal, cardiovascular, or hematologic systems between 74 exposed and 67 unexposed individuals. A positive ($p < 0.05$) increase in the incidence of acute respiratory disease as determined from past medical histories physical findings were found in the exposed group.

A minimal or questionable degree of increased bone density (grade 1 fluorosis) was found in 17

of 74 exposed workers. However, none of the radiographs showed sufficient increased bone density to be recognized in routine radiological practice. The average F exposure for those 17 workers with increased bone density was 3.38 mg F/$m^3$ (range: 1.78-7.73 mg F/$m^3$). The remaining 57 workers were exposed to an average concentration of 2.64-3.38 mg F/$m^3$. In addition, the average urinary F excretion levels were 4.67, 5.18 and 4.53 mg/L, respectively, for the total exposed group, and the subgroup with and without increased bone density group. The results demonstrate an association between increased F levels in the urine and an increase in suspected cases of osteosclerosis.

The data from the Derryberry et al. (1963) study were further analyzed by OEHHA (2003). The calculated TWA F exposure levels for those 74 potroom workers were divided into 5 exposure groups. All 14 workers (Group 1) exposed to an average 8-h TWA concentration of 1.07 mg F/$m^3$ did not exhibit bone density changes. A binomial distribution analysis was used for the comparison of group mean bone density responses. The results showed that the probabilities of obtaining increased bone density observations in the 1.89, 2.34, 3.22, and 5.41 mg F/$m^3$ group (Groups 2-5, 15 workers per group) when compared with Group 1 were all $p < 0.05$. The 1.89 mg F/$m^3$ group (Group 2) and the 1.07 mg F/$m^3$ group (Group 1) were therefore considered a LOAEL and NOAEL, respectively, for chronic skeletal fluorosis. Benchmark dose modeling was conducted using this dataset (*Section 4.1.5 PODs for Key Studies*).

## 4.1.3 Human Supporting Studies

### *4.1.3.1 Skeletal Fluorosis*

#### 4.1.3.1.1 Kaltreider et al. (1972)

In a health survey of aluminum workers by Kaltreider et al. (1972), roentgenographic examinations and urinary F analyses were conducted on workers in two aluminum smelter plants. Examination of 107 potroom workers [mean age 51.9 years (range: 27-65 years); mean length of employment 19.1 years (range: 2-40 years)] in one plant showed that limited motion of the dorsolumbar spine were found in 22 potroom workers and in none of the 108 controls. Seventy-six of 79 workers x-rayed revealed increased bone density at one plant. The estimated 8-h TWA exposure to total F ranged from 2.4 to 6.4 mg/$m^3$. The average post-shift urinary F concentrations were about 9 mg/L. The average urinary F excretion for the controls was 0.7 mg/L. The authors concluded that the majority of potroom workers will develop some degree of skeletal fluorosis after 10 years of exposure to relatively high concentrations of F. Those with more than 15 years of such exposure may develop moderate to severe osteosclerosis with limitation of movement of the dorsolumbar spine.

#### 4.1.3.1.2 Chan-Yeung et al. (1983b)

In another health study by Chan-Yeung et al. (1983b), 2,066 workers in an aluminum smelter in Kitima, British Columbia were examined for effects on the musculoskeletal systems,

hemopoietic tissue, liver, and renal function. Urinary F measurements and personal sampling for airborne F were also conducted at the time of the health study. The average measured levels of total F for potroom workers were 0.48 ± 0.35 mg/$m^3$ and 0.053 ± 0.12 mg/$m^3$ for those of the control group. Historical F levels for the potroom workers were believed to be below the TLV of 2.5 mg/$m^3$. None of the potroom workers had a pre-shift urinary F level that exceeded 4 mg/L or a post-shift urinary F level that was greater than 9 mg/L. The results of this study showed that no definite cases of skeletal fluorosis were found in potroom workers exposed to total F levels below 2.5 mg/$m^3$.

#### 4.1.3.1.3 Yang et al. (1987)

In a health survey of metallurgical plant workers in China by Yang et al. (1987), 9,624 workers from 63 F-emitting plants, aged 18-70 years (average 34 years) with the majority of length of employment ranging from 10-20 years, and 400 non-F workers were studied for industrial fluorosis. The measured F levels at 63 plants frequently exceeded the criteria levels of 1 mg HF/$m^3$ and/or 2.5 mg F/$m^3$ in the workplace.

The study results showed that clinical manifestations such as restricted joint movement and chronic nasopharyngitis were significantly different between the exposed and control groups. Increased frequency of these clinical manifestations was associated with prolonged F exposure. The mean urinary F levels in exposed workers (0.3-7.5 mg/L) were higher than those in non-exposed controls (0.25-1.8 mg/L). The correlation between the F level in workplaces and urinary F content in workers was significantly positive for 2,373 workers from 19 plants ($r = 0.69$, $p < 0.01$). Additionally, significant differences in x-ray skeletal changes mainly osteosclerosis, were found between two groups. The incidence of fluorosis among workers was 3.2%. The incidence of industrial fluorosis and degree of fluorosis were found to be related to the employment period and airborne F levels in workplaces.

#### 4.1.3.1.4 Czerwinski et al. (1988)

Czerwinski et al. (1988) conducted a clinical and radiological investigation on 2,258 workers [average age 51.9 years (range: 18-79 years); average length of employment 17.6 years (range: 1-32 years)] in an aluminum plant near Cracow, Poland. The airborne F concentrations in three working zones of the plant were ≥ 1.5-2.0 mg/$m^3$ in zone I, ≥ 1.0-1.5 mg/$m^3$ in zone II, and ≤ 1.0 mg/$m^3$ in zone III. A semi-quantitative assessment of early fluorosis was applied in this study. The results found 20.2 % of cases had possible or definite fluorosis, but only 5.12% had stage OI (initial fluorosis), 1.0% had stage 1 (definite fluorosis), and most of cases (14%) had stage O (possible fluorosis). The result also showed a close positive correlation between the occurrence of fluorosis and the length of employment and magnitudes of F exposure.

### *4.1.3.2 Respiratory Effects*

Numerous occupational exposure studies on respiratory tract effects from exposure to HF or mixtures of HF gas and F dust have been reported. However, because there were difficulties in

specifically separating potential risks posed by co-existing air contaminants, the occupational exposure studies for respiratory tract effects were not used to develop toxicity values for HF and/or F (see Section 4.1). Some of the occupational exposure studies of the respiratory tract were briefly discussed below.

#### 4.1.3.2.1 Golusinski et al. (1973)

Golusinski et al. (1973) examined the nasal mucosa in 130 Polish workers who were exposed to concentrations of HF which often considerably exceed 0.5 $mg/m^3$ (Polish's occupational exposure standard) at an aluminum plant. The results show that chronic inflammatory changes, either hypertrophic or atrophic rhinitis, were observed in 30% of these workers. Changes characteristic of rhinitis occurs several months after HF exposure and that prolonged exposure to HF can cause transitional hypertrophic changes in nasal mucosa. After 1 or 2 years of work, the nasal mucosa became atrophic. The percentage of atrophic lesions increased gradually until after 10 years of work, 70% of the examined workers were affected. No exposure data for airborne HF and other co-air contaminants were available for this study.

#### 4.1.3.2.2 Chan-Yeung et al. (1983a)

In an epidemiologic health study by Chan-Yeung et al. (1983a), prevalence of respiratory symptoms surveys and lung function tests were conducted in 797 male potroom workers in an aluminum smelter in British Columbia and 713 unexposed workers (control). The results show that workers who spent > 50% of their working time in the potroom had a significantly increased frequency of coughing and wheezing and a significantly lower mean forced expiratory volume in one second ($FEV_1$) and maximal mid-expiratory flow rate ($MEF_{25-75\%}$) than did control workers. There are a number of airborne contaminants, e.g., gaseous and particulate F, $SO_2$, polycyclic organic matters and other particulate matters coexisting in potrooms which may all be responsible for causing respiratory tract effects in potroom workers. No previous levels of exposure for these air contaminants were available for this study.

#### 4.1.3.2.3 Larsson et al. (1989)

In a study by Larsson et al. (1989), lung function and bronchial reactivity were measured in 38 nonsmoking male aluminum potroom workers [mean age 39 (range 21-63) years] who had been working for an average of 13.6 (range: 1-32) years and 20 unexposed nonsmoking office workers [mean age 48 (range: 24-65) years]. The levels of exposure to airborne dust (primarily alumina) and F were determined from samples taken in the breathing zone of the workers during 8 h of work. The mean exposure concentrations were 1.77 (range: 0.49-4.5) $mg/m^3$ for total dust and 0.31 (range: 0.1-0.5) $mg/m^3$ for total (gaseous and particulate) F. The results of this study show that minor obstructive lung function impairment with a significant decrease in expiratory flow and an increase in residual volume were found in aluminum potroom workers. No difference in bronchial reactivity was found between the exposed and control groups. Due to lack of correlation between lung function and the magnitude of exposure, no dose-response relation was established from this study.

### 4.1.3.2.4 Tatsumi et al. (1991)

In an epidemiological study by Tatsumi et al. (1991), the respiratory symptoms and ventilatory lung functions of 99 production-line workers at an aluminum plant in China were compared with 44 age-matched office workers. F levels in the work environment were at or below the ACGIH TLV of 2.5 mg/m$^3$. The results of this study showed that the potroom workers had a higher prevalence of respiratory symptoms than controls and their complaints of phlegm were significantly increased in the older subjects. The means of expiratory flow rate at 25% of the vital capacity/height ($V_{25}$/HT) for the exposed group were decreased which indicated the small airway obstruction resulting from F-exposure. No exposure data for airborne HF and other co-air contaminants were available for this study. Similar results were reported by other epidemiological studies (Saric et al. 1979, Wergeland et al. 1987, and Ernst et al. 1986 in Tatsumi et al. 1991).

### 4.1.3.2.5 Soyseth and Kongerud (1992)

In a cross-sectional study by Soyseth and Kongerud (1992), prevalence of respiratory disorders among 370 aluminum potroom workers [39 women and 331 men, median age 32.8 (range 18.5-66.5) years] in western Norway were studied. Increased prevalence of respiratory symptoms, work related asthmatic symptoms, and abnormal lung function were found in subjects exposed to total F above 0.5 mg/m$^3$ when compared with workers exposed to total fluoride at concentrations of < 0.5 mg/m$^3$. No significant association between bronchial responsiveness and exposure to F was found. Other air contaminants such as $SO_2$ and dust were also emitted into the workplace air. These contaminants, especially $SO_2$ as well as smoking status, were possible confounding factors for this study.

### 4.1.3.2.6 Romundstad et al. (2000)

Romundstad et al. (2000) investigated the association between exposure to F and nonmalignant mortality among 10,857 male workers employed for more than 3 years from 1962 to 1996 in six Norwegian aluminum plants. The results showed that there was an increased mortality from chronic obstructive lung disease (asthma, emphysema, and chronic bronchitis) among F-exposed workers [standard mortality ratio (SMR) 1.2 (95% confidence interval (CI) 1.0-1.5)]. Dose-response relations were found by internal comparisons using Poisson regression and by stratified analyses for SMR. Mortality from these respiratory diseases was associated with cumulative exposure to F. The mg/m$^3$-year mean F exposure ranges and corresponding rate ratios were as follows:

- 0.1-7.4 mg/m$^3$-year: 1.3 (95% CI 0.7-2.4)
- 7.5-19.9 mg/m$^3$-year: 1.9 (95% CI 1.1-3.4)
- $\geq$ 20 mg/m$^3$-year: 2.5 (95% CI 1.5-4.3)

A subanalysis which controlled for smoking in three plants where smoking data was available produced the following rate ratios:

- 0.1-7.4 mg/$m^3$-year: 1.3 (95% CI 0.6-2.8)
- 7.5-19.9 mg/$m^3$-year: 1.8 (95% CI 0.8-3.8)
- $\geq$ 20 mg/$m^3$-year: 2.6 (95% CI 1.2-5.7)

This data was not used to develop toxicity factors because there were difficulties in specifically separating potential risks posed by $SO_2$, total particulate, and F, as there was a strong correlation between exposure estimates from these compounds.

#### 4.1.3.2.7 Taiwo et al. (2006)

Taiwo et al. (2006) assessed the incidence of asthma among aluminum workers by analyzing seven years of health claim records (1996-2002) and workplace exposure data from 13 aluminum production facilities in the U.S.A. After adjusting for smoking status, the asthma incidence rate between potroom and nonpotroom workers was 1.40. The mean total F level for exposed workers was 1.25 mg/$m^3$ (1.02 mg/$m^3$ was particulate F and 0.22 mg/$m^3$ was gaseous F). The mean levels for total dust and $SO_2$ were 7.0 and 0.45 mg/$m^3$, respectively. Multivariate analysis showed a significant relationship between mean gaseous F exposure and the incidence of asthma. However, the effects in mean total F, particulate F, $SO_2$, and total dust were not statistically significant.

### 4.1.4 MOA Analysis and Dose Metric

The MOA of particulate and/or gaseous F for skeletal fluorosis may be related to the deposition of significant amounts of F in bone in which the $F^-$ replace the hydroxyl ion in hydroxyapatite to form fluorapatite and in the action of F on the bone cells, and in the enzymes and hormones regulating bone metabolism, thus changing the physicochemical properties of bone. Absorbed F are incorporated into hard tissues primarily by an exchange process and by incorporation into the apatite during bone mineralization (Czerwinski et al. 1981, Thiessen 1988 in CEPA 1996). The dose metric for fluorosis could be blood concentration of F or some other dose metric, but since only the concentration of the total F (particulate and/or gaseous F) was provided it will be used as the dose metric.

### 4.1.5 POD for Key Study on Skeletal Fluorosis

The TD performed benchmark dose modeling (BMD) using USEPA BMD software (version 2.0), for individual mean air exposure data and incidence data (Derryberry et al. 1963) provided by OEHHA (2003). Data from the highest exposure group (group 5) were not included because none of the models fit the range of exposure well enough for this group. BMD modeling results for the benchmark concentration at a benchmark response of 5 and 10 % ($BMC_{05}$ and $BMC_{10}$) and the 95% confidence limit on the $BMC_{05}$ and $BMC_{10}$ ($BMCL_{05}$ and $BMCL_{10}$) for individual data as well as for grouped data are available in Appendix A. The log probit model provided the best fit of the data with acceptable p values and lowest Akaike's Information Criterion (AIC) (data not shown). A summary of modeling results are shown in Table 7.

**Table 7 Log Probit Modeling Results from Derryberry et al. (1963)**

| Data | $BMC_{05}$ | $BMCL_{05}$ | $BMC_{10}$ | $BMCL_{10}$ | p-value for fit | Scaled Residual |
|---|---|---|---|---|---|---|
| Individual data | 1.26 mg F/$m^3$ | 0.370 mg F/$m^3$ | 1.617 mg F/$m^3$ | 0.749 mg F/$m^3$ | 0.641 | < \|2\| |
| Grouped data | 1.26 mg F/$m^3$ | 0.374 mg F/$m^3$ | 1.623 mg F/$m^3$ | 0.756 mg F/$m^3$ | 0.575 | -0.658 |

The $BMCL_{05}$ value obtained from the log probit model (unrestricted slope parameter) was identical to that (0.37 mg F/$m^3$) obtained by OEHHA (2003) using BMD Software version 1.3. As shown in Table 7, the TD gets an almost identical $BMCL_{05}$ (0.374 mg F/$m^3$) from the log probit model using the grouped mean exposure data and dropping the highest exposed group. In addition, the $BMCL_{05}$ and $BMCL_{10}$ obtained using grouped data are similar to those using individual data (Table 7).

Changes in bone density, investigated in the Derryberry et al. (1963) study are considered the most sensitive endpoint for chronic effects of F exposure and the quality of the Derryberry et al. (1963) study was superior to other key studies. While skeletal fluorosis is considered a severe health effect (TCEQ 2006), as indicated in Section 4.1.2, the maximum effect observed in the Derryberry et al. (1963) study was only grade 1 fluorosis (minimally increased bone density) with none of the radiographs showing sufficient increased bone density. In addition, according to Shupe et al. (1983, as cited in ACGIH 2005), grade 1 fluorosis does not result in medically recognized dysfunction. Therefore, the $BMCL_{10}$ value 0.756 mg F/$m^3$ (from grouped data) instead of the $BMCL_{05}$ was used as the occupational exposure POD ($POD_{OC}$) for skeletal fluorosis of F and HF.

## 4.1.6 Dosimetric Adjustments and Critical Effect (Skeletal Fluorosis)

A $BMCL_{10}$ of 0.756 mg F/$m^3$ for skeletal fluorosis based on the data of Derryberry et al. (1963) study was used as the $POD_{OC.}$ To convert from occupational exposure to continuous exposure relevant to the general population to calculate a human equivalent concentration POD ($POD_{HEC}$), the $POD_{OC}$ of 0.756 mg/$m^3$ for F was multiplied by a dosimetric adjustment factor for exposure continuity using default occupational and nonoccupational ventilation rates and exposure frequencies (TCEQ 2006):

$POD_{HEC} = POD_{OC}$ x ($VE_{ho}/VE_h$) x (days per $week_{oc}$/days per $week_{res}$)

where: $VE_{ho}$ = occupational ventilation rate for an 8-h day (10 $m^3$/day)
$VE_h$ = non-occupational ventilation rate for a 24-h day (20 $m^3$/day)
days per $week_{oc}$ = occupational weekly exposure frequency (study specific)
days per $week_{res}$ = residential weekly exposure frequency (7 days per week)

$POD_{HEC}$ = 0.756 mg F/$m^3$ x [10/20 $m^3$ day] x [5 d/7 d]) = 0.269 mg F/$m^3$

### 4.1.7 Adjustments of $POD_{HEC}$ to Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

The chronic ReV of 26.9 $\mu$g F/$m^3$ was calculated by applying a total UF of 10 to the $POD_{HEC}$ of 269 $\mu$g F/$m^3$:

- an intraspecies UF of 10 to account for human variability;
- a UF of 1 was used for database uncertainty because human studies investigating a wide range of health endpoints was available and the overall quality of the key studies is high; and
- it was not necessary to incorporate a UF to adjust for the use of a subchronic study since the average exposure duration of 14.1 years in the Derryberry et al. (1963) study is more than 10% of the life span in humans. Therefore, the study was considered a chronic study.

When calculating, numbers were rounded to three significant figures between equations until the ReV was calculated. Once the ReV was calculated, it was rounded to two significant figures. The rounded ReV was then used to calculate the ESL, and the ESL subsequently rounded. The $^{chronic}ESL_{nonlinear(nc)}$ of 8.1 $\mu$g F/$m^3$ was calculated according to the ESL guidance (TCEQ 2006) based on the chronic ReV of 27 $\mu$g F/$m^3$ multiplied by an HQ of 0.3 (Table 8).

**Table 8 Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$**

| **Parameter** | **Summary** |
|---|---|
| Study | Derryberry et al. (1963) |
| Study population | 74 male workers in a fertilizer manufacturing plant |
| Key Study Confidence Level | Medium to high |
| Exposure Method | Workplace inhalation |
| Critical Effects | Skeletal fluorosis: increased bone density |
| $POD_{OC}$ | 0.756 mg F/$m^3$ ($BMCL_{10}$) |
| Exposure Duration | 8 h/day, 5 days/week, for an average of 14.1 years (range: 4.5-25.9 years) |
| $POD_{HEC}$<br>Dosimetry adjustment from occupational to general population | 0.269 mg F/$m^3$ |
| Total UFs | 10 |
| *Interspecies UF* | N/A |
| *Intraspecies UF* | 10 |
| *LOAEL UF* | N/A |
| *Subchronic to chronic UF* | N/A |
| *Incomplete Database UF*<br>*Database Quality* | 1<br>High |
| **Chronic ReV (HQ = 1)** | **27 $\mu$g F/$m^3$ or 29 $\mu$g HF/$m^3$ (35 ppb)** |
| **$^{Chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)** | **8.1 $\mu$g F/$m^3$ or 8.7 $\mu$g HF/$m^3$ (11 ppb)** |

## *4.2 Carcinogenic Potential*

There is a significant database on the genotoxicity of fluoride compounds in several species and several cell types. However, the results have been controversial. Some studies have reported that F are mutagenic agents and cause chromosomal damage, but others have shown F do not produce genotoxic effects. In general, positive genotoxicity findings occurred at doses that are highly toxic to cells and to whole animals. Lower doses were generally negative for genotoxicity (WHO 1984, ATSDR 2003).

Bucher et al. (1991) reported the results and conclusions of the 1990 National Toxicology Program (NTP) rodent carcinogenicity studies. F344/N rats and $B6C3F_1$ mice were administered 0, 25, 100 and 175 ppm NaF (equivalent to 0, 11, 45 or 79 ppm F) in drinking water for 2 years. The results showed no increases in neoplasm in female rats or in male or female mice that were attributed to NaF administration. There were only 4 osteosarcomas of bone in treated male rats (1 in the 100 ppm and 3 in the 175 ppm dose group). The findings of the NTP studies showed weak support of an association between NaF administration and the occurrence of osteosarcomas, but were not conclusive.

No data on carcinogenicity were located for animals following inhalation exposure. No specific epidemiologic evidence on the potential carcinogenic effects to humans of airborne F or HF was available. Increased rates of respiratory tract cancer have been reported for cryolite, aluminum production, fluorspar mining, and stainless steel picking workers involving possible F exposure. However, the confounding exposure to other chemicals and smoking status, along with the lack of clear exposure levels, prevent these studies from clearly identifying F or HF as the cause of cancer (WHO 1984, CEPA 1996, ATSDR 2003). USEPA and the International Agency for Research on Cancer (IARC) have not yet evaluated F and HF for potential human carcinogenicity. Because the available data are inadequate to assess carcinogenicity in humans via the inhalation route, the $^{chronic}ESL_{linear(c)}$ was not developed.

## *4.3 Welfare-Based Chronic ESL*

### 4.3.1 Vegetation Effects

Atmospheric F and HF affect the growth, development, and productivity of vegetation. Chlorosis, necrosis, or growth suppression of leaves of sensitive plants may be induced by extended exposure to airborne F concentrations of 0.6 $\mu g/m^3$ (Hitchcock et al. 1962, as cited in Jacobson et al. 1966). Gaseous and soluble F compounds are more phytotoxic than those of insoluble particulate F compounds because they are more readily absorbed by vegetation. The degree of injury is related to the concentration of airborne F and duration of exposure as well as to F accumulation (Weinstein 1977). Plants exhibit a broad range of tolerances to foliar injury by accumulated F. Most sensitive plants, such as gladiolus, may develop leaf necrosis when the tissue concentration exceeds 20 ppm (20 $\mu$g F/g dry weight), while tolerant species, such as cotton, may survive at concentrations more than 4,000 ppm (Jacobson et al. 1966).

#### *4.3.1.1 Key Study*

In a study by MacLean et al. (1977), field plots of bean (Tendergreen) and tomato (Fireball 861 VR) plants were exposed to filtered ambient air or gaseous HF at a mean concentration of 0.6 $\mu$g $HF/m^3$ for 43 and 93 days, respectively. The results showed that chronic exposure of bean to HF did not affect growth or induce foliar injury, whereas the number and the fresh mass of marketable pods were reduced by about 20 and 25%, respectively. There was no effect of HF on growth or fruiting in tomato. The LOEL of 0.6 $\mu$g $F/m^3$ (0.73 ppb HF v/v) on yield of bean was

identified from this study and was used to set the chronic vegetation-based ESL. The LOEL is consistent with that of 0.64 $\mu$g HF/m$^3$ (0.78 ppb HF) for soybean identified from the Pack and Sulzbach (1976) study described below.

### *4.3.1.2 Supporting Study*

In a study by Pack and Sulzbach (1976), 10 plant species were exposed to HF gas in growth chambers 10-16 h/day for 7-183 days to evaluate the effects on fruiting. The measured response parameters, including numbers of fruit, fresh weight of fruit, dry weight of stems and leaves, seeds per fruit, weight per seed, and stem length were made at the end of exposures for the different species. The results showed that development of fewer seeds was the most common response of fruiting to HF. Soybean was the most sensitive to HF of the plant tested and produced almost no seeds under continuous exposure to HF at 0.64 $\mu$g/m$^3$, whereas cotton showed no apparent effects at 8.0 $\mu$g/m$^3$. The results of the LOEL values for the most sensitive endpoint for each plant species are summarized in Table 9. The lowest LOEL for the effects on the most sensitive plant species (soybean) was 0.64 $\mu$g HF/m$^3$ (0.78 ppb HF).

**Table 9 Summary of LOEL for Most Sensitive Endpoint for Each Plant Species**

| Plant Species | Days Exposure | Endpoint | LOEL ($\mu$g HF/m$^3$) |
|---|---|---|---|
| Soybean | 98 | Fruit per pot, dry weight of stems & leaves, stem length | 0.64 |
| Bell Pepper | 112 | Number of fruit, fresh weight of fruit, dry weight of stems & leaves | 2.2 |
| Sorghum | 114 | Weight per seed | 2.2 |
| Sweet Corn | 77 | Seed production, stem length | 2.3 |
| Cucumber | 72 | Number of fruit, fresh weight of fruit, seediness | 2.3 |
| Pea | 56 | Seeds of fruit, weight per seed, stem length, dry weight of stems & leaves | 4.4 |
| Wheat | 130 | Seeds per head, weight per seed, dry weight of stems & leaves | 8.2 |
| Oat | 147 | Seeds per head | 9.1 |
| Cotton | 164 | No significant differences for all measured parameters | 8.0 |

### *4.3.1.3 MOA Analysis*

The MOA of chronic effects of F or HF on plants is similar to the MOA of acute effects (see Section 3.2.2.3). Plants absorb F slowly which results in accumulation of concentrations sufficient to cause injury or cell death. The characteristic damage is seen at the edges of the leaves and will progress inward with increasing amounts and duration of exposure (Weinstein and McCune 1971, WHO 1984).

### *4.3.1.4 Derivation of the $^{chronic}ESL_{veg}$*

Vegetation-based ESLs are set at the threshold concentration for adverse effects and are determined in accordance to ESL Guidelines (TCEQ 2006). Therefore, the $^{chronic}ESL_{veg}$ for HF and soluble F is derived based on the lowest LOEL of 0.6 $\mu$g HF/m$^3$ for bean identified from the MacLean et al. (1977) study. Accordingly, the $^{chronic}ESL_{veg}$ of 0.6 $\mu$g HF/m$^3$ (0.73 ppb HF) or 0.57 $\mu$g F/m$^3$ for long-term exposures was determined.

## 4.3.2 Fluorosis of Livestock

Chronic F intoxication (fluorosis) in domestic livestock has been shown to be caused by the consumption of pasture or cured forage contaminated with inorganic F from phosphate or aluminum industry sources (Suttie 1969, 1977; Shupe 1969; Shupe et al. 1972). Dairy cattle have been the species most often affected by F and the symptoms of toxicity include dental and skeletal lesions, lameness and stiffness, skeletal F accumulation, increase in F content of urine

and body tissues, appetite impairment and diminished milk production. The effects and dietary tolerance of animals to long-term exposure to levels of F were reviewed by the US National Academy of Sciences (NAS 1974 in WHO 1984), Suttie (1977), and US EPA (1980 in WHO 1984).

### *4.3.2.1 Key Studies*

Suttie (1969, 1977) reported that animals receiving F at levels > 50 ppm (mg/kg, dry weight basis) in the ration for 3-4 years exhibited exostotoic lesions, lameness, and severely affected incisors of poor wearing quality, decreased milk production, and had high concentrations of F in the urine and bones. Discernable dental mottling was observed in livestock fed with forage containing 20-30 ppm F during the formative period of the tooth. The author suggested that if the first exposure of cattle to elevated F occurs after the permanent teeth are formed; up to 50 ppm F can be ingested with no adverse effects. The author further recommended that F emissions should be regulated so that the yearly average (calculated from monthly samples) F content of the forage does not exceed 40 ppm (dry weight), and F content of the forage does not exceed 60 ppm F for more than two consecutive months or does not exceed 80 ppm F for more than one month. The recommended F contents in forage are consistent with a maximum allowable F content of 50 ppm reported by Hapke (1977, cited in van der Eerden, 1991) or 55 ppm reported by Gezondheidsraad (1981, cited in van der Eerden, 1991).

Available studies on the effects of F in the diet on livestock were critically assessed by NAS (1974 in WHO 1984). Symptoms or signs developed progressively in cattle at total F dietary concentrations exceeding 20-30 ppm. Tolerance level for F in the diet was defined for various classes of cattle and livestock. NAS set the dietary F tolerance level of 40 and 50 ppm respectively for breeding cows and bulls beef or dairy heifers and dairy cattle. The tolerance levels for other domestic animals such as beef breeding cows and finishing animals are much higher than 50 ppm.

### *4.3.2.2 Supporting Studies*

#### 4.3.2.2.1 Shupe (1969)

Shupe (1969) reported that there is no chronic fluorosis in dairy cattle when the F content of the total ration is < 30 ppm (mg/kg, dry weight basis). The range of 30-40 ppm, 40-60 ppm, and 60-109 ppm will result in borderline, moderate, and severe adverse effects, respectively. The author indicated that the levels of 30-60 ppm of the total ration for dairy, breeding, or lactating animals are within the lower part of the range 30-50 ppm considered safe by the Nation Research Council (NRC).

#### 4.3.2.2.2 Crissman et al. (1980)

Crissman et al. (1980) reported that 63 of 82 dairy cattle on a farm located approximately 1.3-2.8 km downwind from an aluminum plant were slaughtered because of chronic F poisoning.

Ambient air F levels measured 1.5 km from the aluminum plant showed that mean particulate F was 0.31 $\mu g/m^3$ with a 12-h maximum of 5.53 $\mu g/m^3$. The mean gaseous F was 0.36 $\mu g/m^3$ with a 12-h maximum of 6.41 $\mu g/m^3$. F contamination of forage (pasture grass, timothy, clover, alfalfa) ranged from 14.9 to 25.2 ppm on a dry weight basis. Clinical observations for the 19 cattle left on the farm found that dental fluorosis was absent in the 3 youngest calves, moderate dental fluorosis was observed in old heifers, and moderate to severe dental fluorosis was observed in the 4 young adult cattle. F concentrations in bone ash were 280 and 2,800 ppm in a stillborn calf and in the oldest cattle, respectively. The increase in ash F was significantly correlated to age. The authors concluded that the ambient air F level caused chronic fluorosis in cattle on this dairy farm via contamination of forage, and that the NAS tolerance levels for F ingestion in cattle do not protect dairy cattle health.

### *4.3.2.3 MOA Analysis*

Chronic fluorosis in livestock is caused by ingestion of F contaminated vegetation, pasture, or cured forage. Grass can absorb F and retain gaseous F from ambient air. The factors that affect the accumulation of F in vegetation and the correlation of ambient F concentrations with accumulation in vegetation have been described by Weinstein (1977). The relationship between airborne F and how much F is accumulated in forage is described in Section 4.3.2.3 below. The F then is absorbed by cattle eating the grass. Following absorption, F are distributed throughout the body, the concentration in most soft tissues is roughly equal to that in the plasma. The tissues where F are selectively accumulated are skeletal and dental (Shupe et al. 1972). The accumulation of F in cattle's teeth and bones can damage their health as well as milk production. The characteristic damage will progress with the ingestion of F-contaminated forage over an extended period (Bunce 1985).

### *4.3.2.4 Relationship between F in Air and in the Forage*

It is useful to know what concentration of ambient air F is required to produce critical levels of F in the forage. Various experimental data suggest that different types of forage could accumulate up to 40 ppm dry weight F when exposed to 0.33-1.3 $\mu g/m^3$ HF (NRC 1971). Davison and Blakemore (1976 in CEPA 1996) reported that forage exposed to 0.54 $\mu g/m^3$ F for 30 days resulted in an F concentration of 33 ppm dry weight in washed forage. Several researchers have described the relationship between the F content in grass and the atmospheric F concentration. However, the relationship does not appear to be consistent.

#### 4.3.2.4.1 Bunce (1985)

Bunce (1985) conducted a multiple regression analysis using available experimental data on F accumulation in grass in relation to concentration of F in air and duration of exposure (≥ 30 days). These data were collected from studies conducted by the Boyce Thompson Institute and others under laboratory or controlled field conditions, as well as field measurements in areas where F was emitted from aluminum smelters or fertilizer plants. A total of 40 sets of comparative data were analyzed and a regression equation expressing the relationship between F in air and in grass was developed:

$$\text{Log } Y = 1.742 + 0.928 \log X$$

Where: $X = \mu g\ F/m^3$ in the ambient air, and

$Y$ = ppm F in the grass.

The correlation coefficient $r = 0.83$, $r^2 = 0.68$, and the coefficient of variance was 20.2%.

#### 4.3.2.4.2 van der Erden (1991)

Van der Erden (1991) conducted field samplings around two aluminum smelters and one glass factory located in The Netherlands. All three facilities emitted F continuously. Pasture grass was sampled monthly at 8-12 sites in the vicinity of each of these facilities. The F concentrations in air ($F_A$) and accumulation in grasses ($F_G$) were measured. A relation between the $F_A$ (24-h average) and $F_G$ was modeled. The linear regression equation was:

$$F_G = -1.8 + 72.3\ F_A$$

where $F_A$ was the average over the 24- h sampling periods. The coefficient of variance was 39% (n=22). If, instead of the average, the highest $F_A$ was used (indicated by $F^*_A$), the regression equation was:

$$F_G = 3.8 + 31.0\ F^*_A$$

The coefficient of variance increased considerably to 68% indicating that a peak in $F_A$ is more important to $F_G$ than the average $F_G$.

### *4.3.2.5 Derivation of the Cattle Chronic ESL ($^{chronic}ESL_{cattle}$)*

Suttie (1969, 1977) recommended that F emissions should be regulated so that the yearly average (calculated from monthly samples) F content of the forage does not exceed 40 ppm (dry weight), and F content of the forage does not exceed 60 ppm F for more than two consecutive months, or does not exceed 80 ppm F for more than one month. The level of 40 ppm was also the lowest dietary F tolerance level set by the NAS for livestock (see Section 4.3.2.1). Although chronic fluorosis was observed by Crissman et al. (1980) in cattle ingesting forage contaminated with F at a level lower than the NAS tolerance level of 40 ppm F (see Section 4.3.2.2.2), there might be other sources such as high-F water or soils, or feed supplements rich in F which might also

contribute to the total F intake of cattle (Shupe 1969). Until the NAS revises its standards for allowable F contents, the NAS annual average tolerance level of 40 ppm F, instead of the maximum tolerance level of 80 ppm F (monthly average), in the forage for cattle will be used by the TD to derive the $^{chronic}ESL_{cattle}$.

The regression equation developed by Bunce (1985) (log Y = 1.742 + 0.928 log X) was used to derive the $^{chronic}ESL_{cattle}$ because the duration of exposure for the F concentrations in air (≥ 30 days) was more appropriate for chronic exposure (see Section 4.3.2.4.1). The regression equation developed by Van der Erden (1991) was not used to derive $^{chronic}ESL_{cattle}$ because the duration of exposure for the F concentrations in air was a 24-h average (see Section 4.3.2.4.2). Accordingly, for the tolerance level of 40 ppm F in the forage (Y), the concentration of F in air for duration of exposure ≥ 30 days (X) was estimated to be 0.71 $\mu$g F/m$^3$. The TD conservatively chose duration of exposure at 30 days for forage to accumulate up to 40 ppm dry weight F when exposed to 0.71 $\mu$g F/m$^3$. Therefore, a 30-day $^{chronic}ESL_{cattle}$ of 0.71 $\mu$g F/m$^3$ or 0.75 $\mu$g HF/m$^3$ (0.91 ppb) was derived to protect cattle F poisoning in agricultural areas.

## *4.4 Long-Term ReV and $^{chronic}$ESLs*

This chronic evaluation resulted in the derivation of the following chronic values for HF or F:

- chronic ReV = 29 $\mu$g HF/m$^3$ (35 ppb) or 27 $\mu$g F/m$^3$
- $^{chronic}ESL_{nonlinear(nc)}$ = 8.7 $\mu$g/m$^3$ (11 ppb) or 8.1 $\mu$g F/m$^3$
- $^{chronic}$ $ESL_{veg}$ = 0.6 $\mu$g/m$^3$ (0.73 ppb) or 0.57 $\mu$g F/m$^3$
- $^{chronic}$ $ESL_{cattle}$ [30-day] = 0.75 $\mu$g/m$^3$ ( 0.91 ppb) or 0.71 $\mu$g F/m$^3$

The long-term ESL for air permit evaluations is the $^{chronic}ESL_{nonlinear(nc)}$ for facilities located in non-agricultural areas, and is the $^{chronic}$ $ESL_{veg}$ for facilities located in agricultural areas where sensitive plants e.g., soybean, bell pepper, sorghum, sweet corn, or cucumber (see Table 9), may be planted (Table 1). A 30-day $^{chronic}ESL_{cattle}$ must also be evaluated for facilities located in agricultural areas where cattle may be raised. Chronic values for F equivalents are shown in Table 1.

# Chapter 5 References

## *5.1. References Cited in Development Support Document*

American Industrial Hygiene Association (AIHA). 1989. Odor Thresholds for Chemical with Established Occupational Health Standards. Akron, OH.

Agency for Toxic Substances and Disease Registry (ATSDR). 2003. Toxicological profile for fluorides, hydrogen fluoride and fluorine. U.S. Department of Health and Human Services Public Health Service. Atlanta, GA. Available from: http://www.atsdr.cdc.gov/toxprofiles.

American Conference of Governmental Industrial Hygienists (ACGIH). 2005. Documentation of the threshold limit value for hydrogen fluoride. Cincinnati, OH.

Bennion, JR and A Franzblau 1997. Chemical pneumonitis following household exposure to hydrofluoric acid. *Am J Ind Med* 31:474-478.

Bucher JR, MR Hejtmancik, JD Toft 2nd et al. 1991. Results and conclusions of the National Toxicology Program's rodent carcinogenicity studies with sodium fluoride. *Int J Cancer* 48(5):733-737.

Bunce H.W.F. 1985. Fluoride in air, grass, and cattle. *J Dairy Sci* 68:1706-1711.

Canadian Environmental Protection Act (CEPA) Report. 1996. National Ambient Air Quality Objectives for Hydrogen Fluoride (HF). 1. Science Assessment Document for HF. Federal-Provincial Working Group on Air Quality Objectives and Guidelines. En42-17/6-1997E. Ottawa, Canada.

Crissman, JW, GA Maylin and L Krook. 1980. New York State and U.S. federal fluoride pollution standards do not protect cattle health. *Cornell Vet* 70:183-192.

Czerwinski E, W Pospulka, G Nowacki et al. 1981. Effects of fluoride after discontinuation of occupational exposure. *Fluoride* 14:61-68.

Czerwinski E, J Nowak, D Dabrowksa et al. 1988. Bone and joint pathology in fluoride-exposed workers. *Arch Environ Health* 43:340-343.

Chan-Yeuon, M, R Wong, F Tan et al. 1983a. Epidemiologic health study of workers in an aluminum smelter in British Columbia, Canada: Effects on the respiratory system. *Am Rev Respir Dis* 127:465-469.

Chan-Yeuon, M, R Wong, F Tan et al. 1983b. Epidemiologic health study of workers in an aluminum smelter in Kitimat, British Columbia, Canada: II. Effects on musculoskeletal

and other systems. *Arch Environ Health* 38:34-40.

Coulter CT, MR Pack, and CW Sulzbach. 1985. An evaluation of the dose-response relationship of fluoride injury to Gladiolus. *Atmosphere Environ* 19(6):1001-1007.

Dalbey W, B Dunn, R Bannister, et al. 1998a. Acute effects of 10-minute exposure to hydrogen fluoride in rats and derivation of a short-term exposure limit for humans. *Reg Toxicol Pharmacol* 27:207-216.

Dalbey W, B Dunn, R Bannister, et al. 1998b. Short-term exposures of rats to airborne hydrogen fluoride. *J Toxicol Environ Health* 55(4):241-275.

Golusinski, J, Z Szmeja and H Sowinski. 1973. Clinical and histochemical examinations of the nasal mucosa in aluminum workers. *Fluoride* 6:138-142.

Heggestad, HE and JH Bennet. 1984. Impact of Atmospheric Pollution on Agriculture. Pp. 357-395 in Air Pollution and Plant Life (Ed. M Treshow). John Wiley & Sons, New York.

Hill, AC. 1969. Air quality standard for fluoride vegetation effects. *J Air Pollu Control Assoc* 19(5): 331-336.

Jacobson, JS, LH Weinstein, DC McCune et al. 1966. The accumulation of fluorine by plants. *J Air Poll Control Assoc* 16(8): 412-417.

Largent, EJ. 1961. Fluorosis: The health aspects of fluorine compounds. Ohio State University Press. Columbus, Ohio.

Larsson. K, R Ekland, R Arns, et al. 1989. Lung function and bronchial reactivity in aluminum potroom workers. *Scand J Work Environ Health* 15:296-301.

Lund, K, J Ekstrand, J Poe, et al. 1997. Exposure to hydrogen fluoride: an experimental study in humans of concentrations of fluoride in plasma, symptoms, and lung function. *Occup Environ Med* 54:32-37.

Lund, K, M Refsnes, T Sandstrøm, et al. 1999. Increased CD3 positive cells in bronchoalveolar lavage fluid after hydrogen fluoride inhalation. *Scand J Work Environ Health* 25:326-334.

Lund, K, M Refsnes, I Ramis, et al. 2002. Human exposure to hydrogen fluoride induces acute neutrophilic, eisosanoid, and antioxidant changes in nasal fluid. *Inhalation Toxicology* 14:119-132.

Lund, K, C Dunster, I Ramis, et al. 2005. Inflammatory markers in bronchoalveolar lavage fluid

from human volunteers 2 hours after hydrogen fluoride exposure. *Human Experimental Toxicology* 24:101-108.

MacLean, DC, RE Schneider, and DC McCune. 1977. Effects of chronic exposure to gaseous fluoride on yield of field-grown bean and tomato plants. *J Amer Soc Hort Sci* 102(3):297-299.

McCune, DC. 1969a. Fluoride criteria for vegetation reflect the diversity of plant kingdom. A Symposium- The Technical Significance of Air. *Environ Sci & Technol* 3(8): 720, 727-735.

McCune, DC. 1969b. On the Establishment of Air Quality Criteria, with Reference to the Effects of Atmospheric Fluorine on Vegetation. Air Quality Monographs. Monograph #69-3. American Petroleum Institute. New York, NY.

National Academy of Sciences (NAS). 2004. Hydrogen Fluoride Acute Exposure Guideline Levels. Acute exposure guideline levels for selected airborne chemicals. Vol. 4. pp 123-197. The National Academies Press, Washington, DC. Available from: http://www.epa.gov/oppt/aegl/pubs/tsd53.pdf

National Institute for Working Life (NIWL). 2005. Consensus Report for Hydrogen Fluoride, Aluminum Trifluoride, Ammonium Fluoride, Calcium Fluoride, Potassium Fluoride, Sodium FluorideScientific Basis for Swedish Occupational Standards XXVI. NR 2005:17. Stockholm, Sweden. Available from: http://www.inchem.org/documents/kemi/kemi/ah2005_17.pdf

National Research Council (NRC). 1971. Fluorides. Natl Acad Sci., Washington, DC.

Office of Environmental Health Hazard Assessment (OEHHA). 1999. Acute Toxicity Summary. Hydrogen Fluoride. Determination of acute reference exposure levels for airborne toxicants. California Environmental Protection Agency, Berkeley, CA. Available from: http://www.oehha.ca.gov/air/acute_rels/pdf/7664393A.pdf

Office of Environmental Health Hazard Assessment (OEHHA). 2003. Chronic Toxicity Summary. Fluorides including Hydrogen Fluoride. Determination of chronic reference exposure levels for airborne toxicants. California Environmental Protection Agency, Berkeley, CA. Available from: http://www.oehha.ca.gov/air/chronic_rels/pdf/2ApnA_Fluoride_Final.pdf

Pack, MR and CW Sulzbach. 1976. Response of plant fruiting to hydrogen fluoride fumigation. *Atmospheric Environment* 10: 73-81.

Refsnes, M, R Becher, M Lag et al. 1999. Fluoride-induced interleukin-6 and interleukin-8

synthesis in human epithelial lung cells. *Human Exp Toxcol* 18:645-652.

Romundstad P, A Anderson, T Haldorsen et al. 2000. Nonmalignant mortality among workers in six Norwegian aluminum plants. *Scand J Work Environ Health* 26(6): 470-475.

Shupe, JL. 1969. Levels of toxicity to animals provide sound basis for fluoride standards. *Environ Sci & Technol* 3(8):721-726.

Shupe, JL, AE Olson and RP Sharma. 1971. Fluoride toxicity in domestic and wild animals. *Clin Toxicol* 5(2):195-213.

Soyseth, V and J Kongerud. 1992. Prevalence of respiratory disorders among aluminum potroom workers in relation to exposure to fluoride. *Brit J Ind Med* 49: 125-130.

Sutti, JW. 1969. Air quality standards for the protection of farm animals from fluoride. *J Air Poll Control Assoc* 19:239-242.

Sutti, JW. 1977. Effects of fluoride on livestock. *J Occup Med* 19(1):40-48.

Taiwo OA, KD Sircar, and MD Slade et al. 2006. Incidence of asthma among aluminum workers. *J Occup Environ Med* 48(3):275-82.

Tatsumi, M, C-J Mu, F Liang et al. 1991. Health survey of workers of an aluminum plant in China. III. Respiratory symptoms and ventilatory functions. *Fluorides* 24(3):90-94.

Texas Commission on Environmental Quality (TCEQ). 2006. Guidelines to develop effects screening levels, reference values, and unit risk factors. Chief Engineer's Office. RG-442.

Texas Commission on Environmental Quality (TCEQ). 2015. Approaches to derive odor-based values. Texas Commission on Environmental Quality. Office of the Executive Director, Austin, TX.

United States Environmental Protection Agency (USEPA). 1992. Reference Guide to Odor Thresholdsfor Hazardous Air Pollutants Listed in the Clean Air Act Amendments of 1990. EPA600/R-92/047. Office of Research and Development, Washington, DC.

Van der Eerden, LJ. 1991. Fluoride content in grass as related to atmospheric fluoride concentrations: a simplified predictive model. *Agric Ecosystems Environ* 37:257-273.

Weinstein, LH and DC McCune. 1971. Effects of fluoride on agriculture. J Air Poll Control Assoc 21(7): 410-413.

Weinstein, LH. 1977. Fluoride and plant life. *J Occup Med* 19: 49-78.

World Health Organization (WHO). 1984. Fluorine and Fluorides. Environmental Health Criteria 36. WHO, Geneva.

World Health Organization (WHO). 2002. Fluorides. Environmental Health Criteria 227. WHO, Geneva.

Yang, Z, Y Luo, L Zhang, et al. 1987. Industrial fluoride pollution in the metallurgical industry in China. *Fluoride* 20(3):118-125

Zimmerman, PM and AE Hitchcock. 1956. Susceptibility of plants to hydrofluoric acid and sulfur dixoide gases. Contributions from Boyce Thompson Institute. Vol. 18: 263-279. Boyce Thompson Institute for Plant Research, Inc.

## *5.2. Other References Reviewed by TD*

Alexeeff, GV, DC Lewis, and NL Roughly. 1993. Estimation of potential health effects from acute exposure to hydrogen fluoride using a benchmark dose approach. *Risk Anal* 13:63-69.

Carnow, BW, and SA Conibear. 1981. Industrial fluorosis. *Fluoride* 14:172-181.

Critsan, NP. 1992. Phytotoxic effects of gaseous fluorides on grain crops in the southeast Ukraine. *Fluoride* 25(3): 115-122.

Dayal HH, M Brokwick, R Morris, et al. 1992. A community-based epidemiologic study of health sequelae of exposure to hydrofluoric acid. Ann Epidemiol 2(3):213-230.

Fritschi L, MR Slim, A Forbes et al. 2003. Respiratory symptoms and lung-function changes with exposure to five substances in aluminum smelters. *Int Arch Occup Environ Health* 76(2):103-10.

Kongerud, J and SO Samuelsen. 1991. A longitudinal study of respiratory symptoms in aluminum potroom workers. *Am rev respire Dis* 144:10-16.

Kongerud, J, J Boe, V Soyseth, et al. 1994. Aluminum potroom asthma: the Norwegian experience. *Eur Respir* J 7:165-172.

Morris, JB and FA Smith. 1982. Regional deposition and absorption of inhaled hydrogen fluoride. *Toxicol Appl Pharmacol* 62: 81-89.

O'Donnell TV. 1995. Asthma and respiratory problems – a review. *Sci Total Environ* 163:137-145. Saric M, E Zuskin and M Gomzi. 1979. Bronchoconstriction in potroom workers. *Brit J Ind Med* 36:211-215.

Slameňova D, K Ruppova, A Gabelova, et al. 1996. Evaluation of mutagenic and cytotoxic effects of sodium fluoride on mammalian cells influenced by an acid environment. *Cell Biol Toxicol* 12:11-17.

Sjögren B. (2004). Fluoride exposure and respiratory symptoms in welders. *Int J Occup Environ Health* 10:310-2.

Soyseth, V, J Kongerud, J Ekstrand, et al. 1994. Relation between exposure to fluoride and bronchial responsiveness in aluminum potroom workers with work-related asthma-like symptoms. *Thorax* 49: 984-989.

Soyseth, V, J Kongerud, D Haarr et al. 1995. Relation of exposure to airway irritants in infancy to prevalence of bronchial hyper-responsiveness in school children. *The Lancet* 345: 217-220.

Walton, KC. 1988. Environmental fluoride and fluorosis in mammals. Mammal Rev 18(2): 7-90.

Wing JS, LM Sanderson, JD Brender, et al. 1991. Acute health effects in a community after a release of hydrofluoric acid. *Arch Environ Health* 46(3):155-160.

# Appendix A: Benchmark Dose Modeling Results

## *A-1 Results Using Individual Data*

In order to obtain benchmark dose modeling results using individual data, please send an email providing the name of the DSD and requesting the benchmark dose modeling results to the following email: tox@tceq.texas.gov.

## *A-2 Results Using Grouped Mean Exposure Data*

In order to obtain benchmark dose modeling results using grouped mean data, please send an email providing the name of the DSD and requesting the benchmark dose modeling results to the following email: tox@tceq.texas.gov.