

NATIONAL AMBIENT AIR QUALITY OBJECTIVES FOR HYDROGEN FLUORIDE (HF)

SCIENCE ASSESSMENT DOCUMENT

**A Report by the CEPA/FPAC Working Group on
Air Quality Objectives and Guidelines**

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PREFACE

The Canadian Environmental Protection Act (CEPA), passed into law in 1988, replaces and builds upon the Clean Air Act and the Environmental Contaminants Act. The opening statement of the Act declares that "the protection of the environment is essential to the well-being of Canada." CEPA allows the federal government to assess substances and control their impact through national environmental quality objectives, guidelines, codes of practice, and/or regulations.

Provincial governments have the primary responsibility in many areas of air pollution control, with federal actions integrated with those of the provinces. The CEPA Federal/Provincial Working Group on Air Quality Objectives and Guidelines, consisting of representatives of federal, provincial and territorial departments of environment and health, reviews and recommends ambient air quality objectives.

Canada's National Ambient Air Quality Objectives prescribe targets for air quality, measured at the relevant receptor (persons, plants, animals, materials). Development of objectives follows a process which integrates the review of physical and chemical properties and sources; environmental, animal and human health effects; environmental and human exposure assessment within a framework of risk assessment. These targets may incorporate some element of cost-benefit-risk, reflecting a philosophy of environmental health protection and long-term risk reduction while recognizing technological and economic limits. The broad range of potential

responses by the population, the ecosystems, and organisms in the environments are considered. However, given the range of these sensitivities, the resulting objectives may not protect everyone. A document outlining the process followed in reviewing and interpreting scientific information leading to the recommendation of objectives is published separately.¹

The levels recommended as a result of this process accommodate two tiers, defined as follows:

- The *Reference Level* is a level above which there are demonstrated effects on human health and/or the environment. It provides a scientific basis for establishing goals for air quality management.
- The *Air Quality Objective* represents the air quality management goal for the protection of the general public and the environment in Canada. It is a level based upon consideration of scientific, social, economic and technological factors.

The process of establishing air quality objectives is a dynamic and continuous one. This document recommends Reference Level(s) for hydrogen fluoride.

The air quality objectives are established to provide the current state of knowledge about an air-quality parameter, a uniform scale for assessing the quality of air in all parts of Canada, and guidance to governments for making risk-management decisions such as planning control strategies and setting local standards.

¹ CEPA/FPAC, Working Group on Air Quality Objectives and Guidelines (1996) Protocol for the Development of National Ambient Air Quality Objectives
Science Assessment Document for HF

It is recognized that not all locations in Canada will meet these air quality objectives immediately, or at all times, and that priority given to meet these values may be based on factors such as available control technology, costs, benefits, and the degree to which the recommended levels are

exceeded. The expectation is that strategies be put into place to reduce ambient air concentrations to below these targets as soon as practicable. The principles of continuous improvement and non-degradation of environmental quality are advocated.

1 INTRODUCTION

This document reviews the scientific literature regarding the effects of gaseous fluorides on vegetation, animals and humans. The available data have been compiled, and studies that provide information which can be used to derive a reference level for gaseous HF have been extracted and evaluated. This evaluation provides the basis for the proposal of a reference level for each of four time periods. Each reference level represents an ambient-air HF concentration above which an effect is likely to occur. Information on gaseous HF effects on humans and animals is also provided in this document to assist in assessing the impact of HF in situations of extreme exposure.

While sufficient data is available to support the derivation of a reference level for each of the four periods, the number of species tested under conditions expected to occur in Canada is limited. Additionally, there is an indication that some plants of economic (grapevine, peach) or natural (wild grape) importance in Canada may be affected at the proposed levels; however, direct evidence is lacking. Further research will determine if these levels require revision. It is recommended that monitoring of ambient HF levels be conducted in those areas in which potentially sensitive species grow or are cultivated (e.g., vineyards, peach orchards), and which are located near sources of airborne fluorides. Derivation of an Air Quality Objective for HF should await the completion of these additional studies and monitoring efforts.

Fluorides have two different environmental effects. Fluorides accumulate and cause damage in vegetation; this is the primary environmental effect. The period during

which plants are exposed to HF, the concentration of HF in the air, and intervals between HF exposures, affect the extent of accumulation and damage. For the protection of vegetation from HF damage, reference levels for each of 1-, 7-, 30- and 90-day periods are proposed in this document.

The second environmental effect is the effect of fluorides accumulated in vegetation on herbivores (livestock and wildlife). Fluorides of all forms, both within the leaf and adhering to the exterior plant surface, contribute to fluoride toxicity. Additionally, some plants may accumulate levels of fluoride which are harmful to herbivores, but which are not toxic to the plants. Therefore, there is no means by which the proposed HF reference levels can be used to estimate fluoride levels in forage plants, or that can be considered adequate for the protection of herbivores. Consequently, for the protection of wildlife and livestock, a reference level for total fluoride content in plants is presented.

Although not used in the derivation of the reference levels, data regarding the effects of fluorides on animal and human health are included in this document. This material provides information on multi-pathway exposure routes as well as information about acute HF exposures.

This document represents an expert synthesis of the available scientific literature. A listing of comprehensive scientific reviews that provide additional details in support of this synthesis is given in References.

Unless explicitly stated otherwise, all units in this document are given as micrograms of hydrogen fluoride per cubic metre ($\mu\text{g HF m}^{-3}$)

for ambient concentration levels, or as micrograms of fluoride per gram dry weight ($\mu\text{g F g}^{-1} \text{ DW}$) for fluoride accumulation in forage.

2 RECOMMENDED REFERENCE LEVELS FOR HYDROGEN FLUORIDE

The recommended reference levels for hydrogen fluoride (HF) in ambient air are presented in table 1. Also presented is the recommended reference level for maximum fluoride accumulation in forage. These concentrations represent the concentrations

of HF in ambient air, and fluoride accumulation in forage, above which an effect on vegetation, and on animals which feed on this vegetation, may be expected from airborne fluorides.

Table 1 Reference levels for HF in ambient air, and maximum level of accumulated fluoride in vegetation					
	Averaging time				
Level	24 hours	7 days	30 days	90 days	Receptor
Reference level ($\mu\text{g HF m}^{-3}$)	1.1	0.5	0.4	0.4	Vegetation
Vegetation fluoride level ($\mu\text{g F}^{-1} \text{g}^{-1} \text{DW}$)	30				Livestock and wildlife

Hydrogen fluoride is the most prevalent gaseous fluoride. There is no phytotoxic information available for the covalently bonded gaseous fluorides, SF_6 or CF_4 . These covalently bonded gases do not dissociate to form the fluoride ion (as does HF) and subsequent phytotoxic impacts are expected to be negligible.

The gaseous HF concentration in ambient air varies from 0.01 to 1.65 $\mu\text{g m}^{-3}$ in Canada and the U.S.A. Levels are higher adjacent to facilities which emit HF. Ambient levels range from 100 to 10,000 times less than the estimated effect level derived from human studies. Children, people with impaired kidney function, industrially exposed workers, and persons living in the vicinity of a point source of fluoride emissions may be at somewhat greater risk than the general population, though all such groups are

expected to be exposed to HF well below the effects level. Human studies revealed a NOAEL (No Observable Adverse Effect Level) of 0.9 mg m^{-3} HF for skin and eye irritation and a NOAEL of 2.1 mg m^{-3} for irritation of the respiratory tract. The odour threshold ranged from 0.02 to 0.22 mg m^{-3} .

HF gas is a potent acute toxicant when animals are exposed to large quantities acutely via the respiratory route. The chemical properties of the compound account for its pharmacodynamic properties: it dissociates when mixed with water to form a strong acid resulting in burns, and it binds to calcium resulting in sequestration of calcium and alteration of bone calcium (chronic exposure). From the weak chronic study data, it appears as though a continual exposure to mammals should not exceed 7 mg m^{-3} .

2.1 RATIONALE FOR THE REFERENCE LEVELS FOR GASEOUS HYDROGEN FLUORIDE (HF)

Based on the literature review presented in the remainder of this document, it is concluded that vegetation is more sensitive than human health to the toxic effects of fluorides. Therefore, the reference levels are based on the results from investigations into the effects of HF on plants. Experimental data from 13 investigations into the effects of HF on plants, representing 32 separate effects results, have been judged acceptable for use (see appendix). This data set includes 18 points from studies using plants of horticultural importance, 10 from studies using agricultural species, and 4 from studies of effects on forest (conifer) species. There is insufficient data within each of these classes to derive separate reference levels for each class.

Coulter et al. (1985) found that injury in *Gladiolus* had a closer relationship to the HF dose than to HF concentration, duration of exposure, or frequency of exposure. For this reason, each selected HF treatment was converted to a dose (concentration multiplied by the duration of exposure), which has the units $\mu\text{g days m}^{-3}$. This normalization assists in the comparison of studies.

Since the data were selected on the basis of expert judgement, and because many of the studies did not present a measure of variability or analysis of normality associated with the data, the data set of 32 points does not satisfy many assumptions required for analysis by most statistical methods. Curve-fitting techniques may be useful in making sense of the data; however, choice of the

type of curve (quadratic, polynomial) is not obvious, and in fact, none of the curves (up to a third-order polynomial) adequately described the data, and none gave an equation from which reference levels considered protective could be calculated.

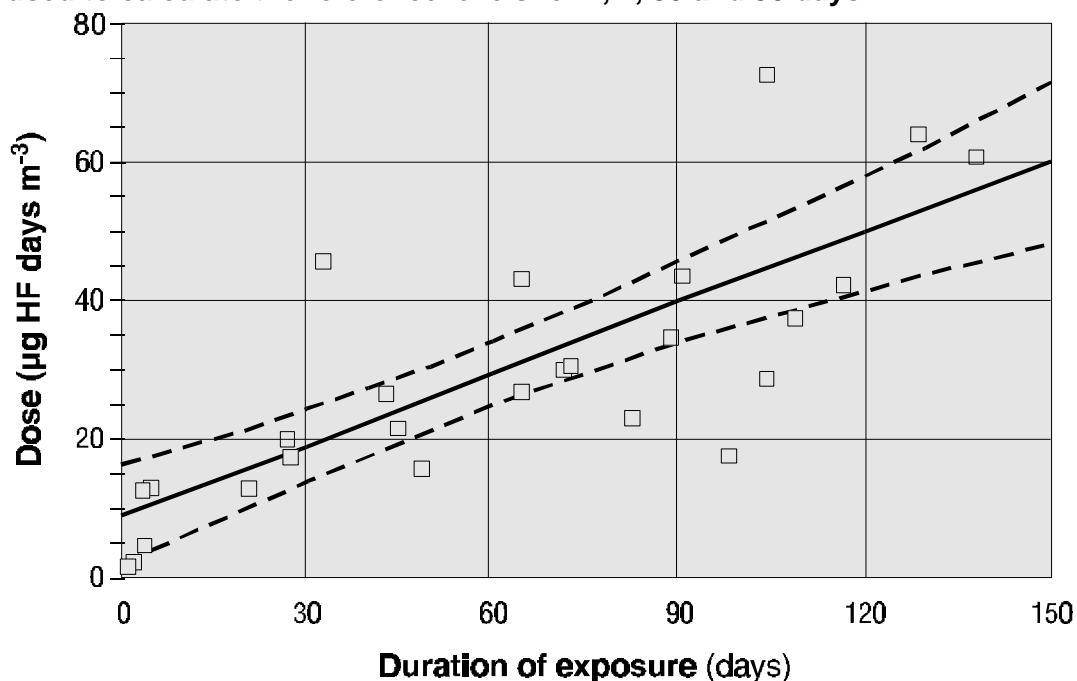
Although the data set likely does not meet the requirements for statistical treatment (random, normal distribution), statistical methods may be used as tools to help derive the reference levels. The results of such analyses must be evaluated in the context of what is known about the effects of HF on plants, and the reference levels calculated using such methods should be examined very carefully to determine if they represent an acceptable level of protection expected from the reference levels. The question to be answered is: Do the reference levels calculated using mathematical or statistical methods adequately describe a relationship between the duration of HF exposure and the dose (or concentration) above which an effect of HF on plants may be expected?

Regression analysis, including a calculation of confidence intervals, was chosen as the best tool to assist in the derivation of the reference levels. The results of this analysis are presented in fig. 1; it is based on data selected from the scientific literature shown in the appendix. It is important to note that some of the data points presented in fig. 1 should carry greater weight than others, based on experimental and statistical rigour included in the study. However, since variability associated with each of the points is not given, it is not possible to give greater weight to some of the points. Given this deficiency, the lines and the reference levels derived from them must be evaluated carefully.

The reference levels were calculated from the lower confidence level for 1-, 7-, 30- and 90-day periods using equations presented by

Steel and Torrie (1980) for calculating confidence intervals. The levels are presented in table 1.

Fig. 1 Regression analysis of HF-exposure data selected from the scientific literature shown in the appendix. The upper and lower 95% confidence levels are indicated by hatched lines. The lower 95% confidence level was used to calculate the reference levels for 1, 7, 30 and 90 days.



Evaluation of these levels must include an examination of the points which fall below the lower limit, since they represent instances where plants may be damaged by HF at doses and concentrations below the recommended reference levels. Seven data points lie below this line (fig. 1); these points were extracted from six studies. An assessment of each of these studies is required to determine if the reference levels derived from this line are protective.

Leaf injury in *Gladiolus* following HF exposure represents two of the seven points. Adams et al. (1956) reported that a small amount of leaf injury (0.7% of the leaf length was necrotic) was observed at $0.85 \mu\text{g m}^{-3}$ when treated in small fumigation

greenhouses for 24 hours. Treatment with $2.10 \mu\text{g m}^{-3}$ for 1 day per week for 7 weeks caused burning on *Gladiolus* leaf tips (McCune et al., 1966). While *Gladiolus* is generally believed to be the most sensitive species in terms of response to HF exposure, several of the data points well above the 95% confidence level were extracted from *Gladiolus* studies. The small amount of leaf damage observed in these studies is judged to be insufficient cause to modify the reference levels calculated from the line representing the 95% confidence interval.

The third point below the 95% confidence levels was extracted from MacLean et al. (1982). Leaf necrosis was observed

following treatment of Jerusalem cherry with $0.90 \mu\text{g m}^{-3}$ for 24 hours in the dark, followed by a light period without HF. Damage only occurred following transfer to the light. Dark exposure for a duration approximating a Canadian summer night (ca. 6 to 8 hours) was not investigated. This type of exposure is artificial, and while it does add to the understanding of HF responses in plants, it is not appropriate to lower the calculated reference levels based on this study.

First injury on grape leaves was observed at $0.17 \mu\text{g m}^{-3}$ after 99 continuous days of fumigation, and at 83 days following continuous treatment with $0.27 \mu\text{g m}^{-3}$ (Murray, 1984). This is the time to first observable injury on the leaves, and fruit yield and quality were not affected. These effects are not sufficient to modify the interpretation of the data represented by the 95% line.

Peach tree growth was reduced by about 25%, with a minor amount of leaf necrosis, at $0.34 \mu\text{g m}^{-3}$ for 110 days; this point falls just below the 95% confidence level (Hill and Pack, 1983). This is a substantial effect, and since peaches are grown in Canada, it must be seriously considered. However, the point is very close to the 95% line; adjusting the line downward to include this study would cause the reference levels to be lowered by a very small amount. The effect represented by this point (Hill and Pack, 1983), and its proximity to the line used to derive the reference level, makes it apparent that further work on the effects of HF on peach trees is required.

Peanut yield was reduced when treated with $0.26 \mu\text{g m}^{-3}$ HF for 105 days in the field in open-top chambers (Murray and Wilson, 1990). This study used levels of HF which are likely to occur in the environment, and

was conducted under as close to natural conditions as are technically possible at this time. While peanut does not represent a crop of importance in Canada, yield reductions in this species under these conditions raise the possibility that other cultivated crops, particularly related legumes, may be similarly affected.

Solberg et al. (1955) reported that a concentration of $0.51 \mu\text{g m}^{-3}$ for 24 hours injured one in five ponderosa pine trees (see appendix). While this study may indicate a level of HF below the proposed reference levels that could cause damage, Solberg et al. (1955) reported only nominal HF concentrations; actual treatment concentrations were not measured or reported. Without this information, the validity of the data cannot be evaluated, and this study was not used in the derivation of the reference level as presented in fig. 1.

Thus, while the regression analysis presented in this section does not satisfy statistical requirements, the analysis was used as a tool to assist in the evaluation of currently available scientific data. Based on this evaluation, the recommended reference levels are judged to represent an acceptable level of protection.

2.2 SUMMARY OF ANIMAL EFFECTS, AND THE RATIONALE FOR LIMITING FLUORIDE ACCUMULATION IN FORAGE

Minimal data is available from which to assess the effects of gaseous HF on livestock, wildlife or experimental animals (Rousseaux, 1995). Due to scarcity of data collected for a few exposure periods, some

of which are gleaned from older studies of varying analytical precision or accuracy, it is not appropriate to recommend exposure guidelines to protect animal health. HF is a potent, acute toxicant when animals are exposed to large quantities acutely via the respiratory route. Since HF rapidly becomes a fluoride salt, the majority of the toxicity issues can be considered under the evaluation of the toxicity of fluorides. Generally, HF toxicity can be attributed to the corrosive action of hydrofluoric acid, sequestering of free calcium to form calcium fluoride, and the alteration of the hydroxyapatite crystal in osseous materials. The recommended reference levels for HF are approximately two orders of magnitude less than those observed to have adverse effects on animals.

Fluoride uptake by livestock and wildlife via the accumulation of fluoride in forage may be of concern near sources of fluoride emissions. The accumulation of fluoride by vegetation is dependent upon the amount of ambient fluoride (gaseous or particulate), the pattern of exposure, the plant species and the environment before, during and following exposure. It is not possible to calculate previous ambient-air HF levels from vegetation fluoride content, although vegetation fluoride monitoring can be used to assist in the diagnosis of animal injury and in the identification of fluoride sources. Concentrations of 20 to 40 $\mu\text{g F}^- \text{g}^{-1}$ dry weight forage have been observed to cause adverse effects in livestock (Suttie, 1969; Joseph-Enriquez et al., 1990). Various experiments demonstrated that different types of forage could accumulate up to 40 $\mu\text{g g}^{-1}$ dry weight fluoride when they were exposed to 0.33 to 1.3 $\mu\text{g m}^{-3}$ fluorides for 30 days (National Research Council, 1971). The reference level recommended in table 1

(0.4 $\mu\text{g m}^{-3}$ for 30 days) is at the low end of this range. A study by Davison and Blakemore (1976) on forage exposed to 0.54 $\mu\text{g m}^{-3}$ fluorides for 30 days resulted in a fluoride concentration of 33 $\mu\text{g g}^{-1}$ dry weight in washed forage. The recommended air quality objectives for HF will not likely result in the accumulation of fluorides in forage from HF in amounts which would induce fluorosis in livestock and wildlife. It is important to note that the measurement of forage fluoride content should be performed on unwashed forage samples to ensure that the contribution of particulate forms of fluoride, as well as any other fluoride adhering to the exterior surfaces of the plant, are included in the analysis, since they are metabolically active and can contribute to fluorosis in animals.

A reference level of 30 $\mu\text{g F}^- \text{g}^{-1}$ dry weight forage is recommended for the protection of wildlife and livestock from fluorosis originating from fluoride accumulation in forage (table 1).

2.3 SUMMARY OF HUMAN HEALTH EFFECTS

Inhaled fluorides are rapidly absorbed in the upper respiratory tract; close to 100% of inhaled HF is absorbed. The fate or effects of absorbed fluorides are essentially independent of the fluoride source or the route of exposure. About 50% of absorbed fluoride is retained in the body.

Approximately 99% of the fluoride in the body is found in the skeleton, the remainder is distributed in soft tissue.

Studies in humans revealed a NOAEL (No Observable Adverse Effect Level) of 0.9 mg m^{-3} airborne HF for skin and eye irritation and a NOAEL of 2.1 mg m^{-3} for

irritation of respiratory tract. The odour threshold ranged from 0.02 to 0.22 mg m⁻³. Clinical studies and most epidemiological studies on the inhalation of fluorides were not adequately designed to derive a NOAEL for systemic effects, or to identify clear effect level. Often the individual exposure of fluorides by the ambient air is not monitored. In workplace studies, people are exposed to many other potentially toxic compounds in addition to gaseous and particulate fluorides in the ambient air. Cross-sectional studies were too small in number. Only a few chronic epidemiological studies provide some quantitative information on the exposure level indicative for toxic effects on skeleton (fluorosis and osteosclerosis) and the respiratory tract. However, a distinct NOAEL for airborne fluoride including HF could not be established. From the indicative estimates it can be concluded that levels below 1.78 to 2.5 mg m⁻³ airborne HF for an exposure time of 8 hours are generally considered not to cause skeletal alterations. Pulmonary effects are reported to appear in children above 200 µg F m⁻³ for gaseous fluoride (and 300 µg F m⁻³ for particulate fluoride). For

workers being exposed to multiple air pollutants, it is impossible to establish a NOAEL for gaseous fluorides. In humans, no effects of chronic exposure to airborne HF on kidneys, brain, thyroid, haematopoietic system, or sensitivity were convincingly established at exposure levels to be realistically feasible in ambient air or causing skeletal alterations or effects on the respiratory tract. No specific epidemiologic data on carcinogenic effects of airborne fluoride were available.

The ambient air concentration of gaseous fluoride varies from 0.01 to 1.65 µg m⁻³ in Canada and the U.S.A.. The exposure levels in most parts of Canada are below 5 µg m⁻³. Ambient exposures range from 100 to 10,000 less than the estimated effect level derived from human studies. Children, people with impaired kidney function, industrially exposed workers, and persons living in the vicinity of a point source of fluoride emissions may be at somewhat greater risk than the general population, though all such groups are expected to be well below the effects level.

3 BACKGROUND

Fluorine (F_2) is a halogen that exists as a gas under standard conditions. It is a light yellow-green, pungent, acrid gas. Fluorine is too reactive to be found in the environment in its elemental state and exists as inorganic fluoride (F^- , free ionic, matrix-bound, and ionically and covalently bonded in inorganic compounds) or organic fluoride (covalently bound in organic compounds). Fluorides exist in the atmosphere as gases and particulates. Gaseous fluorides at ambient temperatures and pressures are hydrogen fluoride (HF), sulphur hexafluoride (SF_6) and carbon tetrafluoride (CF_4). Polymeric fluorides are H_3F_3 , H_4F_4 , silicon fluoride (SiF_4), and hydrofluorosilic acid (H_2SiF_6). Common particulate fluorides are aluminum fluoride (AlF_3), cryolite (Na_3AlF_6), fluorapatite ($CaF_2 \cdot 3Ca_3P_2O_8$), calcium fluoride (CaF_2) and sodium fluoride (NaF).

Atmospheric fluorides affect the growth, development and productivity of vegetation. The effects of gaseous fluorides are more phytotoxic than those of particulate fluorides because they are more readily absorbed by vegetation.

3.1 PHYSICAL AND CHEMICAL CHARACTERISTICS OF HYDROGEN FLUORIDE

HF is the most reactive form in which fluorine exists in the environment. It is a colourless, pungent, acrid gas at room temperature. It is highly soluble in many organic solvents and water, where it forms hydrofluoric acid.

Approximately 75% of the atmospheric gaseous fluoride exists as HF. Combined with water, HF vapour forms an aerosol or

fog of aqueous hydrofluoric acid. Wet deposition is the primary removal mechanism of HF from the atmosphere.

3.2 SOURCES

The major natural source of gaseous fluoride (primarily as HF) emissions are volcanoes. Other sources of inorganic fluorides to the environment are mineral weathering and from marine aerosols. Global releases of HF from volcanic sources are estimated to be 6 to 6,000 ktonnes, 10% of which are injected into the stratosphere. Much of the volcanic HF is removed by precipitation. The primary anthropogenic emission sources in Canada are aluminum smelting operations (~75%), coal-burning facilities (~10%), and chemical production (~6%). Table 2 summarizes estimated HF emissions in Canada.

Canadian consumption of HF is ~70 ktonnes. HF is manufactured from calcium fluoride and used in the production of synthetic cryolite, aluminum trifluoride, motor gasoline alkylates, chlorofluorocarbons, uranium tetrafluoride and uranium hexafluoride. Canadian aluminum production utilizes the synthetic cryolite produced in Canada.

There are 11 primary aluminum producers in Canada: one in Kitimat, British Columbia, and 10 in Quebec (table 3). All of the aluminum in Canada is produced by the Hall-Heroult process (Environment Canada, 1976, 1994): the electrolytic dissociation of alumina (Al_2O_3) dissolved in a molten cryolite (Na_3AlF_6) bath. Electrolysis occurs in a carbon crucible (acting as the cathode) within a steel shell. Carbon anodes are suspended above the cell and the aluminum metal forms at the cathode in the bottom of

the crucible. Oxygen gas is released at the anode, burning the carbon anode. The electrolysis cell operates continuously, and fresh alumina and cryolite are added to the cell as required. Hoods over the cell collect the volatilized fluoride, hydrofluoric acid

vapours and particulate silicon fluoride. These gases are scrubbed prior to discharge into the atmosphere. The control efficiency for volatile fluoride emissions varies from 75% to 99%.

Table 2 Estimates of HF air emissions		
Source sector	Air releases (tonnes year⁻¹)	Relative Contributions
Biogenic		
Volcanic emissions	0.06–6 × 10 ⁶	100
Anthropogenic		
Primary aluminum producers	4,063.4	75
Coal-burning utilities	543.1	10
Chemical producers	305.3	6
Steel producers	238.9	4
Phosphate fertilizer producers	107.6	2
Magnesium producers	100	2
Other	51.3	1
Total	5,409.6	100
Source: Environment Canada, 1994		

HF is also emitted from coal-burning utilities (table 4). The primary coal types used in Canada are bituminous and sub-bituminous. A small amount of lignite coal is also burned. The HF emission factors for bituminous and lignite coals are 0.12 kg HF Mg⁻¹ coal and 0.01 kg HF Mg⁻¹ coal, respectively (Emmel et al., 1989).

a local source on surrounding areas or to provide information on a specific area of concern as identified by total ambient fluoride

3.3 MONITORING METHODOLOGIES

HF is not monitored by Environment Canada or the provinces on a continuous basis. Measurements are made on a site specific basis, typically to characterize the impact of

monitoring. The two most prevalent methods used in Canada for monitoring total ambient fluorides are the passive and the dual-tape sampler methods.

Passive techniques do not differentiate between gaseous and particulate forms of ambient fluorides, but provide information on overall fluoridation rates. This cannot be directly related to vegetation impact or to the accumulation of fluoride in forage. Passive methods provide an inexact quantification of HF since fluoride collection depends upon local meteorological conditions, which control the flux of fluoride to and from the collecting surface, and retention of HF on the sampler surface. Error rates of up to 50% have been reported (Ontario Ministry of the Environment, 1979). Passive techniques are inexpensive and robust, and do serve to provide a long-

term record of total ambient fluoride levels. Currently, passive techniques are used to assess general dispersion conditions around a source, and to locate a potential area of concern which may then be examined using an HF-specific methodology.

Producers	Plants	Capacity (tonnes)
Alcan Smelters and Chemicals Ltd.	Kitimat, B.C.	272,000
	Isle-Malign, Alma, Que.	73,000
	Beauharnois, Que.	48,000
	Grande-Baie, Que.	180,000
	Arvida, Jonquière, Que.	232,000
	Laterrière, Que.	204,000
	Shawinigan, Que.	84,000
Aluminerie de Bécancour Inc.	Bécancour, Que.	360,000
Canadian Reynolds Metals Company Ltd.	Baie-Comeau, Que.	400,000
Aluminerie Luralco Inc.	Deschambault, Que.	215,000
Aluminerie Alouette Inc.	Sept-Îles, Que.	215,000
Total		2,283,000
Source: Natural Resources Canada, 1995		

In order to determine whether or not a region may be exceeding the recommended air quality reference levels for HF or ambient HF objectives, one of the HF-specific methodologies must be used (discussed at the end of this section).

The passive "fluoride plate" or "fluoride candle" methods for monitoring ambient fluorides have been used as a qualitative index of gaseous fluoride levels (Korruri, 1984). These methods use a circular or cylindrical filter paper impregnated with an alkaline solution (Ontario Ministry of the

Environment, 1979; Bumbaco and Shelton, 1978, 1982). The "plates" or "candles" are exposed to the atmosphere for a given time period (of the order of a month) sheltered by a petri dish or louvered case. Analysis involves solution extraction of the filter paper followed by analysis for total fluorides using a fluoride ion-specific electrode. Resultant fluoride concentrations are expressed as fluoridation rates in units of $\mu\text{g F}^- \text{cm}^{-2}$ per 30 days. Identification and quantification of the fluoride on the filter paper may also be made using a mass spectrometer.

Name	Lat. (N)	Long. (W)	Name	Lat. (N)	Long. (W)
Glance Bay, N.S.	46.2	59.95	Richard L. Hearn, Ont.	43.7	79.33
Lingan, N.S.	46.2	60.03	Thunder Bay, Ont.	48.4	89.22
Maccan, N.S.	45.7	64.25	Brandon, Man.	49.8	99.88
Point Tupper, N.S.	45.6	61.37	Selkirk, Man.	50.2	96.87
Trenton, N.S.	45.6	63.63	Amy Street, Winnipeg, Man.	49.9	97.15
Chatham, N.B.	47.0	65.47	Boundary Dam, Sask.	49.1	102.98
Dalhousie #2, N.B.	48.1	66.40	Estevan, Sask.	49.1	102.98
Grand Lake #2, N.B.	46.1	66.02	Poplar River, Sask.	49.1	105.52
Atikokan, Ont.	48.8	91.62	Battle River, Alta.	52.6	112.07
J. Clarke Keith, Ont.	42.3	83.10	H. R. Milner, Alta.	53.9	118.50
Lakeview, Ont.	43.6	79.55	Sheerness, Alta.	51.5	111.67
Lambton, Ont.	42.8	82.43	Keephills, Alta.	53.5	114.55
Nanticoke, Ont.	43.6	79.55	Sundance, Alta.	53.5	114.55
			Wabamun, Alta.	53.6	114.48

Source: Statistics Canada, 1990

Adams (1961) was able to derive an equation which related data obtained from limed papers to atmospheric HF levels. In this work, HF was added to air entering a growth chamber and, therefore, the only fluoride present was HF. In addition to limed

papers, direct measurements of gaseous HF were made (continuous air withdrawal, fluoride adsorption onto a glass substrate, followed by titration to measure fluoride) which allowed the development of a correlation between atmospheric HF and

fluorides trapped on the papers. This is a very simple situation compared with field measurement of ambient fluoride levels in air. It was concluded that direct conversion from limed paper data to atmospheric HF concentrations in the field is not possible (Adams, 1961), and that the limed papers are only useful to delineate areas of fluoride contamination, to determine relative intensities of fluoride pollution among sites, and to monitor changes in pollution intensity due to reductions in emissions or addition of new emission sources to an area. Sidhu (1979) monitored atmospheric fluoride levels in the vicinity of a phosphorous reduction plant using both sodium formate papers (which are also effective fluoride traps) and sequential samplers. The use of these different techniques at the same site allowed the derivation of an equation that could be used to calculate total atmospheric fluoride concentrations ($\mu\text{g F}^- \text{m}^{-3}$) from limed-paper data ($\mu\text{g F}^- \text{dm}^{-2} \text{week}^{-1}$). However, since the proportion of HF in the total atmospheric fluoride load was not known, Sidhu (1979) did not determine the amount HF in the atmosphere at the monitoring sites. Adams (1961) also acknowledged this shortcoming, and pointed out that limed-paper monitoring is susceptible to variation due to changes in the environment, particularly to temperature and wind velocity, both of which will affect the amount of fluoride trapped by the papers. Error rates of up to 50% have been reported (Ontario Ministry of the Environment, 1979; ASTM, 1991) since the flux of fluoride to and from the collecting surface (and its retention of it) depends greatly upon local meteorological conditions. However, passive methods are useful in defining a potential area of environmental impact from HF.

Double paper-tape samplers (dual-tape samplers) have been developed for monitoring ambient gaseous and particulate fluorides (ASTM, 1991). Individual air samples may be collected automatically over time periods of minutes to three hours.

The paper tapes are removed from the sampler and treated so as to dissolve the fluoride, and the solubilized fluoride is analyzed by potentiometric or photometric methods. This monitoring method provides the means of automatically separating and collecting atmospheric particulate and acidic gaseous-fluoride samples. Interferents with the methodology are particulate-metal salts and acid aerosols or gases which may neutralize or acidify the alkali-treated tapes. Contamination of the acidic gaseous-fluoride fraction by small particulate fluorides ($<1 \mu\text{m}$) is usual. For a one-hour sample, the precision expressed as the relative standard deviation is 5% in the range of 1 to 3 $\mu\text{g F}^- \text{m}^{-3}$. Fluoride recovery is usually 95% for known amounts of fluoride in the range of 2 to 20 $\mu\text{g F}^- \text{m}^{-3}$.

One review of double-tape sampling methods has estimated detection limits of 0.07 $\mu\text{g HF m}^{-3}$ for a 2-hour sample (Zankel et al. 1987). However, operationally, large variations in the measured ambient HF concentrations monitored by dual-tape samplers may occur due to variations in air-sample flow rates (Bisson et al., 1995). Thus, the accuracy of the method is questionable. The precision of measurement of the trapped HF is high; Bisson et al. (1995) have stated that sample repeatability is satisfactory and the percentage error small, with detection limits of 0.3 $\mu\text{g F}^- \text{m}^{-3}$ on the filter, and quantification limits of 1.1 $\mu\text{g F}^- \text{m}^{-3}$. Nevertheless, until the sampling airflow problems are solved, precise analytical

measurement of trapped fluoride is not useful.

Commercial instruments, which use a liquid scrubber and fluoride ion specific electrodes, are available for continuous monitoring. The measurement principle is to continuously sample ambient air, removing solid particles in a cyclone separator, and scrubbing the air sample in an aerosol gas scrubber, followed by analysis of the condensed aerosol gas with the ion-selective electrode. Operational detection limits are approximately 0.1 to 0.2 $\mu\text{g F m}^{-3}$. There are no known interferences with the methodology.

Real-time analysis of HF may also be performed with an atmospheric pressure chemical ionization tandem mass spectrometer (De Brou et al., 1991). The ion chemistry is dominated by dissociative attachment reactions:



where R refers to OH, SO₂ or CO₃ and X refers to F⁻ or Cl⁻. The X⁻ ion may arise from a variety of F⁻ or Cl⁻ containing species, therefore this method is only a good identifier of HF in the absence of other fluorinated species. Established spectra are used to identify HF in a complex matrix which includes other fluorinated species. The standard monitoring period is 30 minutes, with instantaneous measurements acquired every five seconds. Real-time detection limits are in the range of 0.2 to 0.5 $\mu\text{g m}^{-3}$.

3.4 ENVIRONMENTAL LEVELS IN CANADA

Mean atmospheric levels in Canada range from 0.01 to 1.0 $\mu\text{g F}^- \text{m}^{-3}$ (Environment Canada, 1994). Current areas of concern in Canada are in the provinces of British Columbia, Ontario and Quebec. However, future industrial installations with HF

emissions may warrant a study of ambient HF levels elsewhere in Canada. No information is available on indoor concentrations.

The data in table 5 illustrate the variation in HF concentration ranges across Canada. More intensive and continuous monitoring has been performed by the B.C. Ministry of Environment, Lands and Parks in association with Alcan in Kitimat, B.C., using a continuous methodology, and by the Ontario Ministry of Environment and Energy in southern Ontario using fluoride candles. Fig. 2 shows the variation in the monthly HF concentration averages from January 1992 to July 1994 at each of four sites near Kitimat. During that period, the average monthly concentration exceeded the recommended 30-day reference level of 0.4 $\mu\text{g m}^{-3}$ twice at the Minnette site in 1992; for five consecutive months (Jan. to May 1993) at the Alcan Dock and once at the Workshop site (July 1993).

HF monitoring by the Ontario Ministry of Environment and Energy is performed to establish relative amounts of gaseous fluorides present over an extended period of time, primarily to assess vegetation effects (Ontario Ministry of Environment and Energy, 1991, 1992). This passive monitoring technique provides data in units of μg per 100 cm^2 per 30 days. This information cannot accurately be translated to $\mu\text{g m}^{-3}$ (as discussed in previous section), therefore the data presented in fig. 3 should be viewed from the perspective of providing information on relative changes in ambient HF concentrations. There is no obvious seasonal pattern over the two years. In 1991 and 1992, the highest annual arithmetic means and monthly values were recorded

in Hamilton. This station is immediately adjacent to a brick manufacturer.

3.5 AMBIENT AIR OBJECTIVES AND STANDARDS IN OTHER JURISDICTIONS

Various agencies around the world have air quality objectives and guidelines for gaseous fluorides (table 6). The United States has not set a federal standard for gaseous fluorides (as HF); however, the U.S., as required by the U.S. Clean Air Act 1990, identified

potential hazards to public health and the environment from HF considering a range of events that included worst-case accidental releases (Environmental Protection Agency, 1993). Analysis of public exposure to routine emissions were not included due to the focus on worst-case releases.

Additionally, other jurisdictions have established a limit on vegetation fluoride accumulation. These limits are also summarized in table 6. Since they are based on the same information as reviewed in this document, it is not surprising that the limits are essentially the same.

Source and location	Year(s)	Dist. (km)	Statistic	Concentration range ($\mu\text{g m}^{-3}$)	Reference
1. Lead and zinc mining and phosphate fertilizer operation, Trail, B.C.	1990–91	<5	mean levels	0.43–0.59	EC†, 1993
2. Lead and zinc smelter and fertilizer operation, Trail, B.C.	1984–85	0.6–10.5	range	0.13–0.60	White et al., 1986
3. Hydrofluoric acid plant, Amherstburg, Ont.	1987–90	near	growing season	0.076–2.36	Gizyn, 1991
4. Steel plant, Hamilton, Ont.	1991	near	mean	0.17–0.24	EC, 1993
5. Residential area, Toronto, Ont.	1981		mean	0.03	McGrath, 1983
6. Brick manufacturing plant, Brampton, Ont.	1980–81	0.8	mean	0.07–0.73	McGrath, 1983
7. New York Aluminum smelter, Cornwall Island, Ont.	1987–91	1.6–4	mean	0.43–0.85	EC, 1994
8. Aluminum smelters, Quebec		8	mean	0.1–0.71	EC, 1993
9. Lead smelter, Belledune, N.B.	1988–90	near	yearly avg.	0.027–0.06	Murphy, 1991
10. Phosphorous reduction plant, Long Harbour, Nfld.	1980	1.4 8 18.7	average	2.45 0.4 0.06	EC, 1994
11. Background, Alert, N.W.T.		remote	mean	0.00568	Barrie and Hoff, 1985

Source: Environment Canada, 1994
† EC = Environment Canada

Fig. 2 Average monthly ambient HF concentration from January 1992 through July 1994 at four sites near Kitimat, B.C..

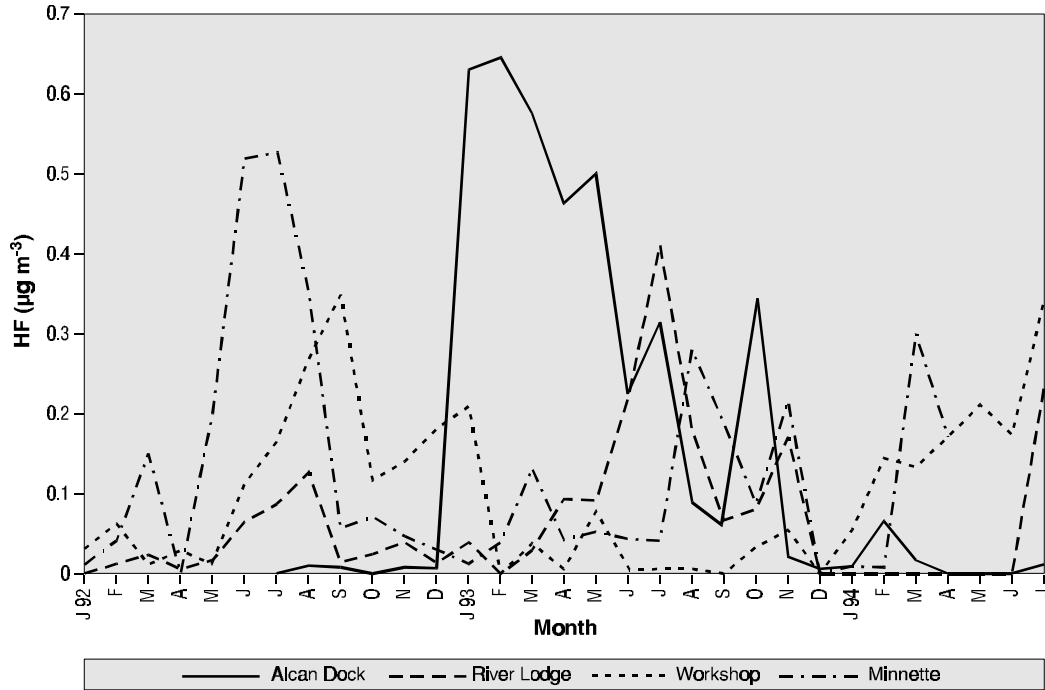
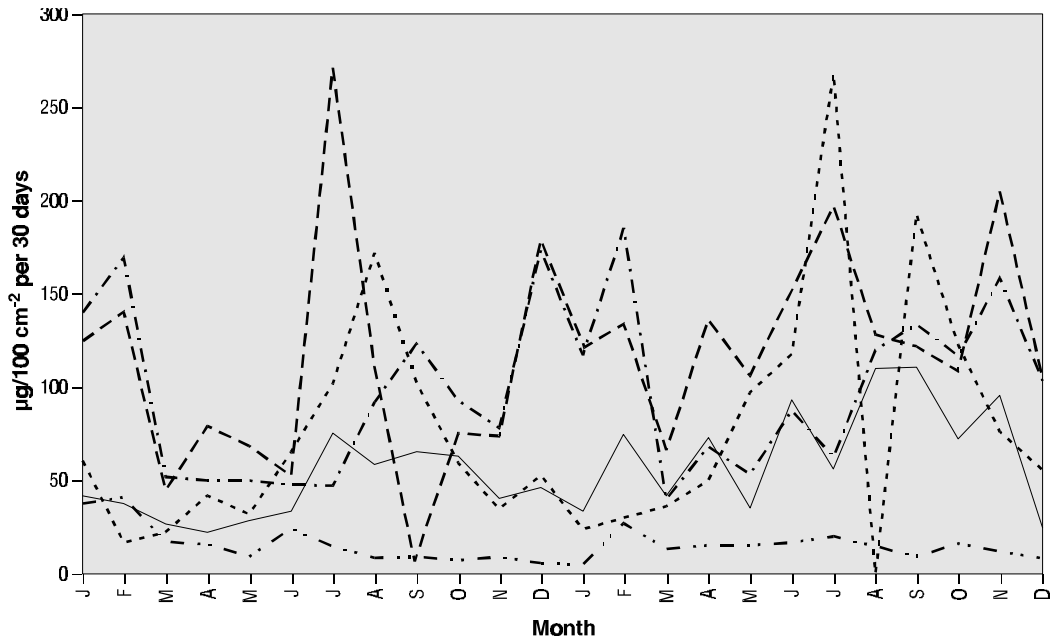
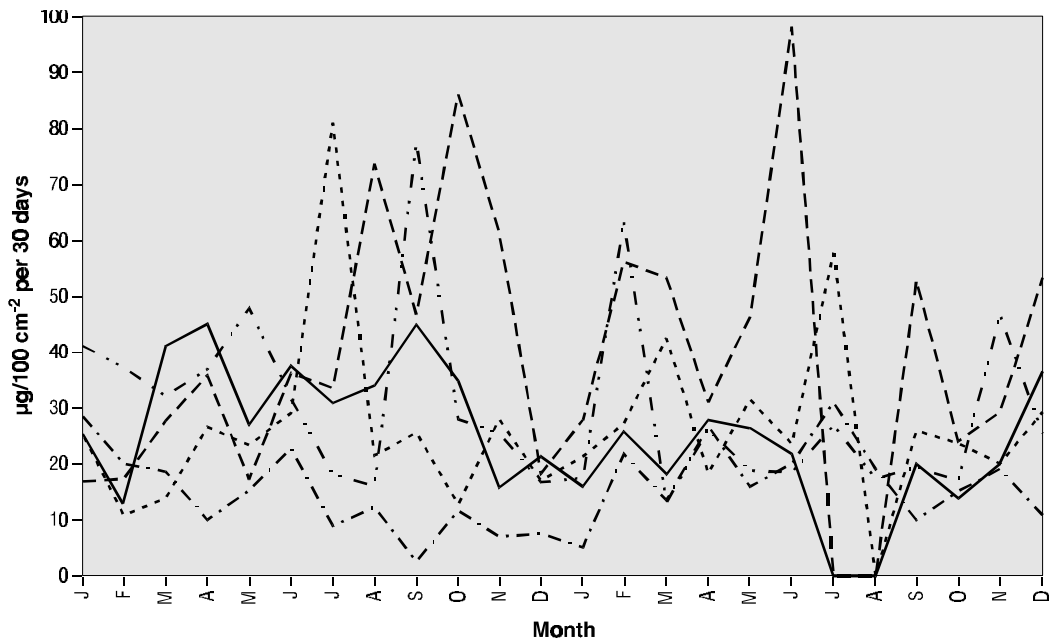


Fig. 3 HF fluoridation rate monthly averages for Ontario, 1991–92, for: (a) urban areas and (b) rural areas.



(a)

— Windsor - - - Burlington ····· Hamilton - · - · Mississauga - - - - Oakville - - - - Brampton



(b)

— Amherstburg - - - Ingersoll ····· Nanticoke - · - · Milton - - - - Port Hope

Table 6 Ambient air quality standards and objectives for gaseous fluorides ($\mu\text{g m}^{-3}$), and fluoride levels in vegetation ($\mu\text{g g}^{-1}$ DW), in other jurisdictions

Jurisdiction	90 days	30 days	7 days	24 hours	12 hours	Other	Vegetation content
Canada (proposed Reference Levels)	0.4	0.4	0.5	1.1	—	—	30
Manitoba	—	—	—	0.40 D† 0.85 A	—	—	—
Newfoundland	—	0.45	—	0.90	—	—	—
Ontario (Apr. 15 to Oct. 15)	—	0.34	—	0.86	—	—	—
British Columbia	—	0.35	0.55	0.85	—	—	—
Montreal Urban Community	—	0.34	—	0.86	—	1.85 (8 hours) 2.00 (1 hour)	—
Kentucky	—	0.82	1.64	2.86	3.68	—	gr. season - 40 2-mo. - 60 1-mo. - 80
Maryland	—	—	—	1.20	—	0.4 (72 hours)	—
New York	—	0.80	1.65	2.85	3.70	—	—
South Carolina	—	0.80	1.60	2.90	3.70	—	—
Tennessee	—	1.20	1.60	2.90	3.70	—	—
Washington	—	0.84	1.70	2.90	3.70	0.5 (Mar. to Oct.)	—
Australia							
New South Wales	—	0.84	1.7	2.9	3.7	—	—
Victoria	0.59	—	2.0	2.9	—	—	—
Japan	—	—	0.5	1.0	—	—	—
Netherlands	—	0.8	—	2.8	—	0.4 (growing season)	—
New Zealand	—	0.5	1.0	—	—	70 (1 hour)	—
Norway	—	0.4	—	1.0	—	—	—

Sources: (Streeton, 1990; International Union of Air Pollution Associations, 1992

† D = desirable; A = acceptable

4 EFFECTS ON VEGETATION

A considerable amount of research has been conducted on the effects of fluoride on higher plants, with a number of extensive review articles written. This section is based primarily on a review of the following references: Drury et al. (1980), Environment Canada (1994), Linzon (1971), McLaughlin (1991), Miller (1993), National Research Council (1971), Thomas and Alther (1966), Treshow and Pack (1970), Weinstein (1970, 1977) and Zwiazek (1994).

4.1 EFFECTS OF FLUORIDES ON VEGETATION

Injury to plants results from absorption of fluoride by the plant. Gaseous fluorides are readily absorbed, whereas particulate fluorides collect on external surfaces and cause little or no injury unless dissolved by precipitation or dew and absorbed. Absorption of atmospheric fluorides by plants can result in high concentrations of fluoride in leaves, but only slightly elevated amounts have been found in stems and roots. Injured portions of leaves usually contain more fluoride than uninjured portions. The lowest concentrations of fluoride are found in the fruit and seeds of plants. The length of plant exposure to atmospheric fluoride is important because the effect of fluoride is cumulative. However, inactivation of fluoride within the plant, growth dilution, physiological condition of the plant, plant nutrient status, fumigation dynamics, stomatal activity and loss from the plant make direct comparison between concentrations of fluoride in the air and plant impossible.

While a considerable amount of work has been carried out on non-visible or metabolic

fluoride injury, the exact mechanisms by which fluorides injure higher plants are not well known. Much of this work has involved the study of various enzymes, systems or organelles *in vitro* by exposing whole plants or plant parts to sodium fluoride solutions. Fluorides have been found to inhibit or stimulate enzymes involved in glycolysis, respiration, photosynthesis, metabolite transport across membranes and other processes. Depending on many factors, fluorides may inhibit or stimulate respiration, which is one of the earliest symptoms of fluoride toxicity. Respiration inhibition is possibly linked to the inhibition of respiratory enzymes, while stimulations may be linked to fluoride acting as an uncoupler of phosphorylation. *In vitro*, fluorides may affect membranes by inhibiting ATPase, disrupting the membrane pH gradient, and blocking chloride antiport movement. *In vivo* experiments involving HF fumigation of white pine seedlings show that changes in membrane permeability, greater electrolyte leakage, plasma membrane lipid composition and increased plasma membrane ATPase activity occur during the early stages of fluoride injury. No changes in mesophyll cell structure were observed before the appearance of visible injury.

The mechanisms by which some plants are more tolerant to fluoride than other plants are also not well understood. Tolerant plants may be able to deactivate fluoride better than sensitive plants. Possible mechanisms of fluoride deactivation in plants include shifts to fluoride insensitive metabolic pathways, removal from sites of enzyme inhibition via reactions with organic compounds, reaction with cationic sites,

sequestration in vacuoles, and translocation to the leaf surface. In addition to physiological effects, fluorides can cause mutagenic effects such as chromosomal aberrations, bridges, fragments and multipolar mitosis.

A number of factors influence the action of fluorides on vegetation and the uptake and accumulation of fluoride by plants. These factors include temperature, relative humidity, wind speed, soil moisture, plant nutrition, stage of growth and plant species. Injury symptoms similar to those caused by atmospheric fluorides may also be due to other agents, such as insects, disease, nutritional disorder, and adverse weather.

Gaseous fluorides enter the leaves of plants primarily through the stomata. Injury rarely occurs at the absorption site, as the fluorides dissolve within the aqueous phase of the substomal cavity and move as ions through the apoplastic space of the mesophyll cell walls with the transpirational stream to the leaf tips and margins, where fluoride accumulates. When the accumulated fluoride concentration exceeds a certain threshold level, which varies with plant species and with varieties of the same species, leaf injury occurs. Fluoride injury symptoms vary considerably, depending on whether the vegetation is narrow-leaved or broad-leaved, relative susceptibility to fluoride, the concentration in the air, and duration of exposure. The injury may take the form of chlorosis (yellowing of the leaves due to chlorophyll reduction) or necrosis (killing of leaf cells). In general, plants injured by chronic atmospheric fluoride usually display leaf chlorosis. Necrosis generally occurs at the leaf tips and margins, and these necrotic areas may be separated from healthy leaf

tissue by a darker zonate line. All forms of injury are not present in all injured plants.

Fluoride injury to plants may be acute or chronic. Acute fluoride injury is caused by short-term exposures to high concentrations of atmospheric fluorides. Inactivation and translocation of fluoride cannot keep pace with absorption, resulting in leaf lesions. The amount of accumulated fluoride could be less than that required to cause chronic injury because sudden absorption of high concentrations of fluoride disrupts plant metabolism quickly. Chronic fluoride injury is caused by variable exposure periods at different concentrations of atmospheric fluoride. Plants absorb fluoride slowly and the unidirectional distal movement of the fluoride eventually results in the accumulation of concentrations sufficient to cause injury or cell death. The concentration of fluoride in the leaf tips and margins or injured areas is higher than in the rest of the leaf. Lesions continue to enlarge as the plants are subjected to low concentrations of atmospheric fluorides. With continued exposure, the necrotic areas spread inward from the margins of leaves of dicotyledonous plants and downward from the leaf tips of conifers and monocotyledonous plants. The necrotic areas may extend across large veins and even cross the midrib in deciduous leaves. (This is a pattern seldom seen in sulphur dioxide-caused lesions.) Premature defoliation follows leaf injury on some plants, and while others retain their leaves, the leaves often have desiccated margins that break away. Exposure of coniferous tree foliage to atmospheric fluoride results in chlorotic needle tips followed by reddening (likely needle necrosis). Needle elongation is retarded and the needles may be shed prematurely. Corn leaves, if not actually injured with collapse of leaf areas, show a

general mottled appearance. In *Gladiolus*, tip burn gradually extends down the leaf and kills all tissue, including veins. As the fluoride concentration increases and duration decreases, marginal injury predominates, expanding across the leaf, occasionally leaving an isolated green tip. In rare instances, flower bracts might develop marginal burn in a severe fumigation, with the petals sometimes displaying injury. Some investigators have observed a black tip condition in cherries, while others have noted a soft spot along the suture line of peaches following HF exposure. Fruit drop and poor fruit set have been observed in orchards subjected to heavy fumigations.

4.2 FLUORIDE ACCUMULATION IN VEGETATION

In Ontario, maple foliage ranges from >0.5 to 10 µg F g⁻¹ DW. Plants exhibit a broad range in their sensitivity to injury from atmospheric fluorides. Sensitivity varies not only among species but among varieties of the same species. Sensitive plant species include varieties of apricot, barley, blueberry, sweet corn, Douglas fir, *Gladiolus*, grape, Manitoba maple (box elder), peach, pine, plum, St. John's wort, tulip, and western larch. Sensitive varieties of *Gladiolus* and strains of eastern white pine may display leaf injury with accumulations of less than 30 µg g⁻¹ DW in the injured leaves. Plants of intermediate resistance, such as apple and raspberry, may not display injury until they have accumulated 100 µg g⁻¹ DW. Plants strongly resistant to fluorides, such as wheat and alfalfa, may not display leaf injury until accumulated concentrations exceed 200 µg g⁻¹ DW. Bitternut hickory can accumulate up to 1,000 µg g⁻¹ DW and

display no foliar injury. The relative sensitivity of different plant species and varieties to fluoride is generally based on visible foliar injury symptoms and their relationship to fluoride dose, fluoride concentration in the leaf, or threshold dose for visible foliar injury. However, it has recently been shown (McLaughlin, 1991) that for nine tree species there was very little agreement between the fluoride sensitivity ratings based on foliar injury and sensitivity ratings based on the reduction of annual xylem growth during a 20-year period of high fluoride emissions around an aluminum smelter. Oak and maple, which were classed as tolerant based on foliar injury, were sensitive to intermediate based on xylem growth.

Accurate prediction of fluoride accumulation, and knowledge of plant responses to accumulated fluoride, would allow the establishment of guidelines which would limit fluoride uptake and minimize fluoride-induced damage. In its most simple form, uptake can be expressed as

$$F_v = kCt + b \quad [1]$$

where F_v is plant fluoride content (µg F g⁻¹ DW), k is the accumulation constant for the species, C is the ambient concentration of HF (µg m⁻³), t is the duration of exposure (days), and b is the y-intercept (theoretically, b is the amount of fluoride present in the tissue as a result of accumulation from natural sources). Gritsan (1992) developed predictive equations based on the format of equation [1] for field-grown wheat and barley, and for seedlings of wheat and barley grown in growth chambers. Accumulation constants for barley were two-fold greater than for wheat in both environments. Accumulation of fluoride has been examined in grapevine (Doley, 1982), where it was found that both b and k varied

with the total dose provided to the plants. MacLean and Schneider (1973) compared fluoride accumulations in continuously fumigated forage (a mixture of timothy grass and red clover) to fluoride accumulations in plants intermittently fumigated with HF. Plants exposed continuously to HF accumulated more fluoride than those exposed intermittently to the same total HF dose. Investigations of fluoride accumulation by orchard grass and alfalfa led McCune and Hitchcock (1971) to derive predictive equations based on the format of equation [1]. However, while these regressions were highly significant, they only accounted for 54% (orchard grass) and 70% (alfalfa) of the variability. Further investigation revealed that the time between the end of the exposure period and sampling was an important parameter in determining fluoride levels. In alfalfa, fluoride concentrations declined with an apparent half-life of about eight days. To account for this, the regression equation

$$F_v = 4.21C^{0.82} t^{0.70} e^{-0.032D} \quad [2]$$

was derived, where D is the number of days between the end of fumigation and the time that the samples were harvested for analysis, and e is the base of the natural logarithm. Similar analysis of the post-fumigation period length only slightly improved the regression fit for orchard grass, and this improvement was not statistically significant.

Some plants are able to reduce leaf internal fluoride levels by exporting fluoride to the exterior leaf surface. This ability varies by species, with cotton and tomato being relatively efficient at exuding fluorides (Jacobson et al., 1966). Davison (1982) reviewed the literature on the loss of fluoride from leaves, and noted that losses may be of the same magnitude as accumulation rates.

In a very simplistic sense, foliar fluoride may be considered to be compartmentalized into interior and exterior compartments. Fluoride which remains in the interior compartment may be physiologically active, while that on the exterior is not. Under natural conditions, rainfall may wash the leaves of exterior fluorides. De Temmerman (cited in van der Eerden, 1991) accounted for the effect of rainfall and the decline in fluorides as a function of time with the equation

$$F_v = 128F_3^{0.13} F_2^{0.59} F_1^{0.45} e^{-0.0043N} \quad [3]$$

where F_1 , F_2 and F_3 are the average ambient fluoride levels in the preceding 1st, 2nd and 3rd weeks prior to grass sampling, respectively, and N is the rainfall (mm) in the preceding two weeks. Variation in the amount of foliar fluoride with the season was observed by van der Eerden (1991), who incorporated a "seasons index" into his predictive model.

As illustrated by these equations, the accumulation of fluoride by plants is dependent upon the amount of fluoride, the pattern of fluoride exposure, the plant species, and the environment before, during and following exposure. These models generate valid predictions only under the conditions from which the data originate (van der Eerden, 1991; MacLean et al., 1989). The reverse of this situation (i.e., the use of vegetation fluoride content as a quantitative measurement of ambient HF levels) is also invalid (MacLean et al., 1969), although vegetation fluoride monitoring can be used as a qualitative tool to assist in the diagnosis of injury and in the identification of fluoride sources. Chemical analysis is a valuable tool in diagnosing fluoride injury. Plants in polluted areas continually accumulate fluoride, and thus repeated analysis can indicate the relative intensity of injury. Also,

the fluoride emission source can usually be determined since the fluoride concentration in plants increases with proximity to the source.

When considering fluoride content of plants to be used as forage, all forms of fluoride must be taken into account since all fluorides are metabolically active (to differing degrees) within a herbivore. To account for both gaseous and particulate loadings onto forage (grass), Blakemore (cited in van der Eerden, 1991) derived the regression

$$F_v = -31.1 + 0.67F_{G1} + 281F_{Ag} + 223F_{Ap} \quad [4]$$

where F_{G1} is the fluoride content of the grass one week prior to sampling, and F_{Ag} and F_{Ap} are the average atmospheric gaseous and particulate fluoride concentrations during the preceding week, respectively. Consideration of both particulate and gaseous fluorides is necessary in areas close to facilities which emit fluorides, since both forms are likely to be present in and on the plant.

Analysis of washed tissues will provide an indication of the internal fluoride content of the tissue. The analysis of unwashed tissue samples will result in a determination of total fluoride content, which includes internal and external fluorides. When analyzing for fluoride levels in forage, determination of total fluoride is the only meaningful, practical analysis. For the protection of livestock and wildlife, limits on forage fluoride content have been proposed or established. A limit of $55 \mu\text{g F g}^{-1}$ DW has been suggested by van der Eerden (1991). Kentucky standards include limits of 80, 60 and $40 \mu\text{g F}^{-1} \text{g}^{-1}$ DW in forage for average 1-month, 2-month and growing season fluoride levels, respectively. These limits were proposed by Suttie (1969), and were accepted by Mitchell et al. (1981) and adopted by the State of

Kentucky (table 6). A maximum of 20 to $30 \mu\text{g F g}^{-1}$ DW is suggested for forage fluoride content in section 5 of this document. The ambient guidelines proposed for HF will probably not result in the accumulation of fluorides in amounts which would induce fluorosis. However, near sources of fluoride emission where plants are exposed to multiple forms of fluoride, monitoring of fluoride content in unwashed forage samples is necessary to ensure that animals are not exposed to harmful dietary fluoride levels.

Soil normally contains between 20 and 500 ppm fluoride. In Ontario, the typical range for fluoride in medium to fine textured soils is between 20 and 160 ppm. Atmospheric fluoride emissions that are not removed by other receptors eventually settle on soil and increase its fluoride content. The application of fertilizer can also increase soil fluoride content. In alkaline soils, most of the fluoride is immobilized on clay particles with little root uptake occurring in plants. More fluoride is soluble in acidic or saline soils, where sodium replaces calcium as the dominant cation, and greater root uptake takes place. The lesions on leaves caused by uptake of soluble fluorides from soils are quite similar to those caused by absorption of atmospheric fluorides, but in some species there tends to be a greater degree of injury to the interior than to the margins of leaves. Analyses show that plant roots can contain very high fluoride concentrations ($1,000$ to $6,000 \mu\text{g g}^{-1}$ DW) when fluoride enters from the soil, whereas the concentration is very low (about $10 \mu\text{g g}^{-1}$ DW) in roots when fluoride enters via the leaves.

There has been little research conducted on the effects of accumulated fluorides on insects. Jia-xi and Yong-mei (1988) found a

threshold level of about $30 \mu\text{g F}^- \text{g}^{-1}$ DW in mulberry leaves for an effect of fluoride on feeding silkworms (increased mortality, decreased weight gain in larvae). Insects (pollinators, predators, foliage feeders, and cambial region feeders) collected from an area near a fluoride emission source were found to have elevated fluoride levels relative to those collected from control areas at least 50 miles distant from the source (Dewey, 1973). Pollinating and foliage feeding insects accumulated the most fluoride. The effects of the accumulated fluoride on insect physiology, reproduction, and behaviour were not investigated.

4.3 CANADIAN CASE STUDIES

Common industrial sources of fluoride emissions in Canada include the production of super-phosphate fertilizers, uranium hexafluoride, hydrofluoric acid, chlorofluorocarbons, fibreglass, appliances, ceramic tiles, bricks, aluminum smelting and casting, steel manufacturing, and petrochemical refineries. Listed below are a number of examples documenting the impact of fluoride emissions on vegetation in the vicinity of some of these industrial sources.

The range of impact from a given source is usually estimated from observed fluoride ion concentrations in vegetation and surface materials such as leaf litter or snow. For the Long Harbour, Newfoundland, phosphorous reduction plant (no longer in operation) over a 20-week period, no vegetation damage was observed beyond 13 km from the source (Sidhu, 1979). Extrapolating from leaf litter, rain and snow water fluoride measurements, the range of impact did not extend beyond 30–35 km from the source (Sidhu, 1982a, 1982b). Comparison of snow fluoride

concentrations near two aluminum smelters within the Saguenay–Lac Saint-Jean region of Quebec before 1978 and after the 1984 completion of a depollution program showed that the area of influence (defined as total fluoride levels $>50 \mu\text{g L}^{-1}$ melted snow) was approximately $3,000 \text{ km}^2$ and 100 km^2 , respectively (Ouellet, 1987). It was further surmised that the greater portion of this reduction was attributable to reductions in particulate fluorides rather than to gaseous HF. It was estimated that in 1975, HF represented 50% of the volatilized fluoride emissions from the aluminum smelters, and approximately 80% in 1984. It is not expected that the impact from HF emissions would extend beyond approximately 30 km from a given major source.

4.3.1 Phosphorus Reduction Long Harbour, Newfoundland

A number of major studies on the various effects of fluoride emissions on vegetation have been conducted in the vicinity of a phosphorus reduction plant at Long Harbour, Newfoundland (Linzon, 1978a; Roberts and Thompson, 1980; Sidhu 1979, 1982a, 1982b; Sidhu and Staniforth, 1986; Staniforth and Sidhu, 1984; Thompson et al., 1979). The facility first became operational in 1968 and fluoride injury to trees was first observed in 1970. Fluoride emissions were both gaseous and particulate, with the impact of the particulate being restricted to the immediate vicinity of the plant. HF and SiF_4 are the main fluorides emitted. The investigation of the fluoride impact was conducted to a distance of 20 km downwind of the facility in 1973, 1974 and 1975 (Thompson et al., 1979). Injury to balsam fir, black spruce and white spruce ranged from complete defoliation to trace tip burn.

Marginal fluoride injury was observed on white birch and alder. Fluoride levels in conifer foliage ranged from 281 $\mu\text{g g}^{-1}$ DW in the severely injured zone to 44 $\mu\text{g g}^{-1}$ DW in the lightly injured zone to 7 $\mu\text{g g}^{-1}$ DW in controls. Soil fluoride concentrations ranged from 908 ppm to 58 ppm to 10 ppm in the respective zones. Fluoride deposition to the soil was five times greater from precipitation than from leaf litter (Sidhu, 1982a, 1982b). In black spruce needles, fluoride levels of 100 to 200 $\mu\text{g g}^{-1}$ DW covered 12 km^2 , 50 to 100 $\mu\text{g g}^{-1}$ DW covered 31 km^2 , 20 to 50 $\mu\text{g g}^{-1}$ DW covered 23 km^2 , and 10 to 20 $\mu\text{g g}^{-1}$ DW covered 88 km^2 . The extent of observed fluoride injury covered 80 km^2 ; no visible injury was observed with foliage levels up to 20 $\mu\text{g g}^{-1}$ DW.

In 1976, foliage of balsam fir, black spruce, larch and white birch displayed severe symptoms of fluoride injury up to a distance of 8 km from the source. Moderate symptoms were observed between 8 and 9 km, light symptoms from 9 to 12 km, and no symptoms beyond 12 km (Sidhu, 1979). At the end of the 1976 growing season, maximum fluoride concentrations in the foliage of these tree species in the zone between 0 and 12 km from the plant were 265, 96, 411, and 357 $\mu\text{g g}^{-1}$ DW, respectively. Beyond 12 km, the fluoride concentrations in the foliage of the same tree species were less than 20 $\mu\text{g g}^{-1}$ DW. Air monitoring, using sodium-formate plates, gave a calculated maximum fluoride level of about 5 $\mu\text{g m}^{-3}$ (6.1 ppb) at a distance of 0.7 km from the source. Beyond 12 km, the calculated level was 0.20 $\mu\text{g m}^{-3}$ (0.24 ppb) or less.

During another investigation of forest damage at Long Harbour in the summer of 1977, it was observed that over 80% of the

dominant balsam fir and black spruce trees within 5 km north of the phosphorus manufacturing plant had been killed (Linzon, 1978a). Chemical analyses of samples collected from balsam firs showed fluoride foliage levels over 100 times higher at a distance of 2 km from the source than at 20 km. Considerable amounts of fluoride could be washed off the affected foliage, suggesting that both particulate and gaseous fluorides were present in the area's fluoride emissions.

Fluoride levels in the lichens *Cladina raniferina* and *Cladina stellaris* correlated inversely with distance from the phosphorus reduction plant at Long Harbour, following the direction of the prevailing NE winds (Roberts and Thompson, 1980). Fluoride concentrations in the lichens ranged from 2,830 $\mu\text{g g}^{-1}$ DW in the severely damaged area to 15.5 $\mu\text{g g}^{-1}$ DW in the lightly damaged area to 6.4 $\mu\text{g g}^{-1}$ DW in controls. Trace damage occurred at concentrations of 25 $\mu\text{g g}^{-1}$ DW. Symptoms consisted of discolouration and loss of structure. The fluoride concentration in lichens was twice that of the soil humus and half that of bryophytes at the sample locations.

The effects of fluoride emissions on the flowering and fruit production of blueberries and raspberries, and on the foliage, cones and seeds of balsam fir, black spruce and larch were studied at six sites downwind from the Long Harbour plant in the summer of 1982 (Sidhu and Staniforth, 1986; Staniforth and Sidhu, 1984). Fluoride levels, using sodium-formate plates, ranged from 11.38 $\mu\text{g F m}^{-3}$ at 1.4 km to 0.08 $\mu\text{g F m}^{-3}$ at 18 km. The highest levels occurred in July during the flowering of the blueberries and raspberries. Flower mortalities were 89% for blueberries and 78% for raspberries at the

highest fluoride site with a 21- and 10-fold reduction in seed production respectively, as well as a significant decrease in size, quantity and dry weight. Fluoride levels in the foliage ranged from 403 and 216 $\mu\text{g g}^{-1}$ DW to 8 and 9 $\mu\text{g g}^{-1}$ DW for raspberry and blueberry, respectively. Fluoride injury was observed on the raspberry foliage. At the same six locations, chlorosis, necrosis, needle damage and defoliation to balsam fir, black spruce and larch occurred when the fluoride concentration of the foliage exceeded 20 $\mu\text{g g}^{-1}$ DW. Injury occurred where airborne fluoride levels exceeded 0.85 $\mu\text{g F m}^{-3}$. Reduction in seed size, germination rate, number of seeds per cone, number of cones per tree, number of fertile trees, and size reduction, distortion, or mortality of cones occurred under the same fluoride gradient as for the blueberry and raspberry. Seed production on the windward side of the trees was significantly less than on the leeward side. Reproduction failure and past mortality of fluoride damaged conifers have resulted in their being replaced by the more tolerant hardwoods, birch and alder. It is important to note that the calculation of airborne fluoride levels (in $\mu\text{g F m}^{-3}$) from the sodium-formate plate data is specific for only this study, and represents total fluoride levels, rather than gaseous HF levels.

4.3.2 Phosphorus Fertilizer Production Port Maitland, Ontario

Inorganic fluoride emissions from a phosphorous fertilizer facility in Port Maitland, Ontario, was associated with damage to conifers and deciduous trees facing the prevailing winds (Hall et al., 1968). The Ontario Ministry of the Environment conducted extensive terrestrial assessment

surveys around the facility from 1969 until 1985, one year after it ceased manufacturing operations in July 1984 (McLaughlin, 1981, 1986). Forage was collected biweekly during the growing season from 1975 to 1980 as part of a control order that would result in the temporary shutdown of the facility if the average fluoride content of the foliage exceeded 80 ppm (80 $\mu\text{g g}^{-1}$ DW, unwashed material) for any one-month period, 60 $\mu\text{g g}^{-1}$ DW for any two-month period, or 35 $\mu\text{g g}^{-1}$ DW over the growing season. After 1980, collections were made on a one-month basis. In 1984, at a location 2,300 m east of the plant fluoride levels ranged from 17 ppm $\mu\text{g g}^{-1}$ DW in April to 40 $\mu\text{g g}^{-1}$ DW in August and back down to 11 $\mu\text{g g}^{-1}$ DW in October. Similar levels and seasonal pattern had been observed at the same location in 1979 and 1980. During the same period, 4,600 m east of the plant, fluoride levels in foliage ranged from 2 to 5 $\mu\text{g g}^{-1}$ DW and there was no seasonal pattern. In 1985, fluoride levels in foliage dropped to 7 to 14 $\mu\text{g g}^{-1}$ DW at the first location and <1 to 2 $\mu\text{g g}^{-1}$ DW at the second location, with no seasonal trend observed. The pattern of fluoride levels in forage near the gypsum setting ponds over a seven year period, as old ponds were capped and new ponds brought on line, showed that these ponds were a significant localized source of fluoride emissions.

Fluoride levels (unwashed) and injury evaluations of maple foliage (red, silver, sugar and Manitoba) were determined at 30 locations within 6 km of the plant in September of each year. The highest fluoride level in 1984 was 67 $\mu\text{g g}^{-1}$ DW, 500 m east of the plant and 26 $\mu\text{g g}^{-1}$ DW, 600 m south of the plant. Both stations had levels of 400 $\mu\text{g g}^{-1}$ DW in 1982 and 1983, and 840 $\mu\text{g g}^{-1}$ DW and 1,270 $\mu\text{g g}^{-1}$ DW,

respectively, in 1979. There was a steady increase in the fluoride levels of maple foliage throughout the growing season. In 1979, 500 m east of the facility, fluoride levels were $50 \mu\text{g g}^{-1}$ DW in June, $255 \mu\text{g g}^{-1}$ DW in July and $840 \mu\text{g g}^{-1}$ DW in September. Injury on maple foliage in 1983 was observed up to 3.2 km NE of the facility. In 1984, it was limited to two sites within 500 m, and there was no injury in 1985. Wild grape, a fluoride-sensitive species, was used to delineate the zone of fluoride injury around the operation. In 1983, the injury zone extended 5 km NE of the plant and covered an area of 23.6 km^2 . This zone remained unchanged (24.2 km^2) in 1984 and decreased to 1.4 km^2 in 1985.

4.3.3 Aluminum Reduction Cornwall Island, Ontario

Studies were started in 1969 on Cornwall Island, Ontario, to document the effects of fluorides emitted from an aluminum reduction plant located immediately to the south, in Massena, New York (Linzon, 1971). At a sampling station about 1.6 km NE of the plant, eastern white pine needles had accumulated $135 \mu\text{g g}^{-1}$ DW fluoride. The pines displayed an orange-red terminal necrosis on their needles, showing severe injury; many were dead. Trembling aspen trees had $495 \mu\text{g g}^{-1}$ DW fluoride in injured foliage and displayed reddish-brown marginal lesions. At a control location about 6.4 km NE of the source, eastern white pine and trembling aspen foliage displayed no injury and contained less than $20 \mu\text{g g}^{-1}$ DW. Since 1959, the aluminum company had emitted 139 kg F hr^{-1} until abatement measures in 1972 reduced the emissions to about 34 kg F hr^{-1} . The eastern white pines on Cornwall Island demonstrated a

remarkable recovery in the radial growth following the abatement measures (McLaughlin and Emerson, 1984), and little or no fluoride injury has occurred on the new growth of needles (Linzon, 1986). The levels of fluoride in maple foliage and injury to sensitive species has remained relatively constant since 1978 (Emerson, 1994b). In 1993, the highest level of fluoride in unwashed maple foliage was $155 \mu\text{g g}^{-1}$ DW at the site 1.6 km NE of the facility, and fluoride levels decreased rapidly with increasing distance.

A dendroecological study was conducted on nine tree species found on Cornwall Island in order to determine sensitivity ranking based on annual tree ring-growth reduction and to determine if reduction in growth occurred in the absence of foliar injury (McLaughlin, 1991). The study looked at growth over three periods: pre-operation of the aluminum smelter, 20 years of high, uncontrolled fluoride emissions and 12 years of reduced fluoride emissions. All species except green ash showed significant growth reductions during the period of high emissions. There was no growth reduction during the period of reduced emissions. During the period of high emissions, there was a deterioration in the relationship between climate and growth, and a consistent relationship between reduced growth and fluoride levels in vegetation and air. Based on growth reduction, the ranking of the nine species from most sensitive to least sensitive was: trembling aspen, sugar maple, eastern white pine, red oak, American beech, basswood, shagbark hickory, black cherry, and ash. Based on growth reduction, trembling aspen, red oak and sugar maple were more sensitive than the literature rankings based on foliar injury, while black cherry was more tolerant. The study concluded that foliar

injury is an unreliable indicator of the total effect of fluoride on forest trees.

4.3.4 Aluminum Reduction Arvida, Quebec

Studies were conducted on the effects of HF on epiphytic lichens and mosses near an aluminum reduction facility at Arvida, Quebec (Leblanc et al., 1971, 1972). Lichen and moss-bearing bark discs were cut from trees in an unpolluted area, fixed to trees at various sites near the aluminum facility, and left for periods of 4 and 12 months. At a distance of 1 km from the source, the lichens accumulated $990 \mu\text{g g}^{-1}$ DW fluoride in 4 months compared to $70 \mu\text{g g}^{-1}$ DW in a control area located 40 km from the source. During the same period, mosses accumulated $570 \mu\text{g g}^{-1}$ DW fluoride in compared to $20 \mu\text{g g}^{-1}$ DW in the control area. Both species accumulated fluorides even at a distance of 15 km from the aluminum plant ($190 \mu\text{g g}^{-1}$ DW in lichens after 4 months, and $78 \mu\text{g g}^{-1}$ DW in mosses after 12 months). They also calculated an index of atmospheric purity (IAP) which was based on the number of epiphytes, frequency of coverage and the resistance factor of each epiphyte found on *Populus balsamifera* at 42 sites covering an area of 250 km^2 within 15 km of the facility. While a total of 54 epiphytes, 9 bryophytes and 45 lichens were recorded within the study area, none was found within one kilometre of the facility. IAP values ranged from 0, indicating no epiphytes found, near the plant to 103 away from the facility. The IAP values increased with increasing distance from the facility, suggesting that fluoride emissions from the facility were affecting both the density and frequency of epiphytes on *Populus balsamifera*.

4.3.5 Aluminum Manufacturing Kitimat, British Columbia

A study of the effects of atmospheric fluorides on tree growth in the vicinity of an aluminum manufacturer at Kitimat, British Columbia, was started in 1973 (Bunce, 1984, 1985). A grid pattern containing 64 permanent sample plots was established, increment cores were taken from the trees to measure tree growth, and foliage was collected for chemical analysis of fluoride content. The forest area surrounding the smelter was segregated into an inner zone (high effect), an outer zone (low effect), and a surrounding zone (no effect). Hemlock forests were severely damaged in the inner zone to a distance of about 8 km from the smelter. The growth rate of the forests from 1954 to 1973 was reduced by 28% in the inner zone and by 19% in the outer zone compared to growth rates before the smelter began operation in 1954. Fluoride in hemlock foliage in 1974 measured $271 \mu\text{g g}^{-1}$ DW in the inner zone, and $163 \mu\text{g g}^{-1}$ DW in the outer zone. Abatement measures were taken at the smelter in 1974, and from 1974 to 1979, the rate of fluoride emission was reduced by 64% of pre-1974 emissions (from $5,500 \text{ kg day}^{-1}$ to $2,000 \text{ kg day}^{-1}$). The tree growth reduction of $2,800 \text{ m}^3$ per year declined to 620 m^3 during 1974–79. The fluoride content of hemlock foliage in the inner zone decreased to $87 \mu\text{g g}^{-1}$ DW in 1979, and to $29 \mu\text{g g}^{-1}$ DW in the outer zone. The basal area decrease in forest growth remained high in the inner zone for the period 1974–79, but a small positive increase in forest growth occurred in the outer zone.

4.3.6 Aluminum Engine Casting Windsor, Ontario

Fluoride accumulation in silver maple foliage and grass was found around a large aluminum engine casting plant in Windsor, Ontario (Gizyn, 1994). Fluoride injury was limited to trace amounts on wild grape within 400 m of the plant. Fluoride levels in unwashed grass ranged from 183 $\mu\text{g g}^{-1}$ DW 100 m east of the plant, to 2 $\mu\text{g g}^{-1}$ DW 1 km west of the plant. Fluoride levels in unwashed silver maple foliage ranged from 188 to 20 $\mu\text{g g}^{-1}$ DW. The pattern of elevated fluoride levels in grass and maple was correlated with the prevailing wind patterns.

4.3.7 Uranium Processing Port Hope, Ontario

Since 1974, the Ontario Ministry of Environment and Energy has conducted annual assessment surveys to monitor the impact of emissions from a uranium processing plant on the local terrestrial ecosystem (McLaughlin, 1988). The facility in Port Hope, Ontario, produces uranium hexafluoride and uranium dioxide; fluoride and uranium are emitted into the atmosphere during production. In 1986, trace to light injury (<1% to 10% injury to individual leaves) was observed on Manitoba and silver maple (moderately sensitive to fluoride) within distances of 300 to 750 m. In 1987, the same zone was rated at moderate (11–35%) to severe (>35%) injury. Trace injury was observed up to 1,100 m downwind of the facility. In 1987, fluoride injury was also observed on the fluoride sensitive plants tulip, hosta, canna lilies, *Gladiolus*, wild grape and St. John's wort to a distance of 1.5 km NE of the facility. Fluoride levels in unwashed maple foliage from 12 sites around the facility were the second lowest

since 1974. The levels ranged from a maximum of 46 $\mu\text{g g}^{-1}$ DW in Manitoba maple 300 m west of the facility, to 4 $\mu\text{g g}^{-1}$ DW 750 m west of the facility, with a consistent gradient of decreasing fluoride levels with increasing distance. Levels varied significantly from year to year depending on uranium production. At the site 300 m east of the facility, fluoride levels in maple foliage ($\mu\text{g g}^{-1}$ DW) ranged from a low of 20 in 1984 and 1986 to 1,075 in 1980 and 1,330 in 1977.

4.3.8 Tile Manufacturing Niagara, Ontario

Soft suture disorder of peaches was reported from three orchards within one-half mile of a facility manufacturing field drainage tile in the Niagara Peninsula of Ontario (Drowly et al., 1963). Early maturing varieties of peaches were the most susceptible to soft suture disorder. In two of the orchards, severe leaf drop occurred in June, with characteristic fluoride injury on the leaves. Monthly collections were made of peach leaves during the summers of 1960 and 1961. Fluoride levels in unwashed peach leaves from the affected orchards averaged 40 to 50 $\mu\text{g g}^{-1}$ DW compared to 27 $\mu\text{g g}^{-1}$ DW from control orchards. There was no significant difference between the washed and unwashed leaves, suggesting that the emissions were mainly gaseous. The application of lime sprays to the peach trees reduced the incidence of soft suture.

4.3.9 Brick Manufacturing Southern Ontario

Investigations of fluoride injury to and the accumulation of fluoride in vegetation have been carried out around a number of

brickworks in southern Ontario since the early 1970s (Emerson, 1977, 1984, 1994a). The zones of influence are generally localized around these operations, with injury on sensitive species such as wild grape, eastern white pine and Manitoba maple being moderate (11–35% injury on some leaves) up to 300 m downwind and light (2–10% injury on some leaves) up to 500 m downwind. Fluoride levels in unwashed maple foliage within 300 m of the brickworks range from 100 to 360 $\mu\text{g g}^{-1}$ DW, between 300 and 700 m downwind were 25 to 90 $\mu\text{g g}^{-1}$ DW, and drop off to 5 to 15 $\mu\text{g g}^{-1}$ DW at 1 km from the brickworks. The levels of fluoride in washed foliage is marginally lower or no different than unwashed foliage, indicating that the majority of the fluoride emissions from these brickworks are gaseous in nature.

4.3.10 Fibreglass Manufacturing Guelph, Ontario

Fluoride and boron injury to natural vegetation and in *Gladiolus* biomonitoring plots were studied around a fibreglass manufacturing facility in Guelph, Ontario, from 1969 to 1976 (Temple et al., 1978). Fluoride and boron were used as a component of the flux in the four glass-melting furnaces. Fluoride emissions went from being uncontrolled in 1969 through a series of control measures to total elimination of fluoride from the manufacturing process in 1972. In 1969, severe fluoride injury on Manitoba maple, silver maple and buckthorn leaves was observed 150 m from the facility, with light injury extending for another 150 m. In 1971, with the reduction of fluoride but not boron emissions, the extent of injury remained the same, but boron injury became more

prominent in addition to fluoride marginal necrosis. By 1972, when fluoride emissions had been eliminated, fluoride injury symptoms had been totally replaced by boron injury. At the sampling station closest to the facility, seasonal average fluoride concentrations ($\mu\text{g g}^{-1}$ DW) in washed silver maple foliage went from 613 in 1969 and 1,600 in 1970 to 21 in 1973 and 26 in 1974. Manitoba maple and buckthorn at other locations showed a similar pattern. In 1969, fluoride accumulation in foliage, as defined by a seasonal average fluoride concentration of greater than 50 $\mu\text{g g}^{-1}$ DW, extended 2,000 m downwind of the facility. This distance was reduced to 250 m in 1972 and less than 30 m by 1974. There was no significant difference between the washed and unwashed fluoride content in the leaves of all three species, indicating the emissions were primarily gaseous.

4.3.11 Oil Refining Mississauga, Ontario

The sudden appearance of injury on Scot's pines up to 5 km from an Ontario oil refinery was investigated (Linzon, 1978b). The maximum amount of fluoride found in severely injured Scot's pine needles was 16.3 $\mu\text{g g}^{-1}$ DW, while the lowest amount of fluoride found in the needles of control Scot's pines was 1.3 $\mu\text{g g}^{-1}$ DW. In addition, eastern white pine, spruce, larch, plum, and Manitoba maple displayed both marginal necrosis and bifacial lesions in the central portions of the leaves. A histopathological study was conducted on the injured Scot's pine needles (Linzon and Tung, 1976). Cellular damage included collapsed mesophyll cells, hypertrophied transfusion parenchyma cells in the stele, a compressed phloem and collapse of the endodermal ring

of cells surrounding the stele. The combination of symptomatology, resistance, and sensitivity of different species, the chemical analysis results, and the histopathological findings confirmed that the injuries had been caused by an acute HF fumigation.

4.4 INTERACTIVE EFFECTS OF HF WITH OTHER GASEOUS POLLUTANTS

Marcross corn that was fumigated continuously with $0.56 \mu\text{g m}^{-3}$ and $191 \mu\text{g m}^{-3}$ SO_2 for 12 days developed injury symptoms that were greater than the sum of the effects of the two contaminants acting independently (Mandl et al., 1975). Similar results were obtained by Murray and Wilson (1988a), who reported that HF (up to $1.05 \mu\text{g m}^{-3}$) and SO_2 (up to $271 \mu\text{g m}^{-3}$) synergistically increased visible leaf injury in some species of *Eucalyptus*. In a second series of experiments, HF ($0.38 \mu\text{g m}^{-3}$) and SO_2 ($267 \mu\text{g m}^{-3}$) applied through the growing season were antagonistic on leaf area, having less of an effect than either compound alone (Murray and Wilson, 1988b). However, the effects of these compounds on stem weight and above-ground plant weight were synergistic. Applied together, HF (1 or $3 \mu\text{g m}^{-3}$) and SO_2 (260 or $780 \mu\text{g m}^{-3}$) both delayed the development of common blight on red kidney bean and resulted in smaller disease lesions (Laurence and Reynolds, 1986).

Simultaneous fumigation of soybean plants with $0.26 \mu\text{g HF m}^{-3}$ and $277 \mu\text{g SO}_2 \text{ m}^{-3}$ did not reduce bean yield to the extent of SO_2 fumigation alone (Murray and Wilson, 1990). The same treatments applied to maize resulted in lower cob dry weights, although kernel yield was not affected

relative to SO_2 treatment alone. HF ($0.27 \mu\text{g m}^{-3}$) reduced peanut yield, while SO_2 ($279 \mu\text{g m}^{-3}$) reduced the number of pods and kernels per plant without significantly reducing total yield. The interactive effect on plant productivity of the two fumigants was less than additive. Navy bean yield increased at $141 \mu\text{g SO}_2 \text{ m}^{-3}$; this stimulatory effect was removed by treatment with $0.25 \mu\text{g HF m}^{-3}$. Overall, Murray and Wilson (1990) concluded that the effects of HF and SO_2 are often antagonistic since HF reduced the effects induced by SO_2 exposure; however, the actual responses are species-specific.

In wheat and barley, as in the experiments outlined above, the responses to joint treatment with HF ($0.38 \mu\text{g m}^{-3}$) and SO_2 (130 or $267 \mu\text{g m}^{-3}$) were complex, but mostly antagonistic (Murray and Wilson, 1988c). The effects of SO_2 alone were often counteracted by treatment with HF.

Fumigation of Marcross corn with HF ($1.5 \mu\text{g m}^{-3}$) and NO_2 ($2,280 \mu\text{g m}^{-3}$), with a total dose of $2,280 \mu\text{g HF days m}^{-3}$ (which approximates a 24-day treatment period) resulted in less leaf damage than exposure to the same HF dose alone (Amundson et al., 1982). This was attributed to the increased leaf resistance induced by NO_2 , which likely resulted in reduced HF uptake through the stomates.

Co-exposure to HF ($1.0 \mu\text{g m}^{-3}$ for 4 hours every second day over 8 days) and O_3 ($0.06 \mu\text{l L}^{-1}$ for 4 hours every second day over 8 days, alternating with the HF treatment) resulted in protection of 21-day-old corn plants from HF damage (chlorophyll loss and membrane leakage), relative to ozone treatment alone (MacLean, 1990). Fluoride accumulation was enhanced in both the HF alone and HF + O_3 treatments;

however, HF alone had no effect on chlorophyll levels or membrane integrity.

The complexity of responses of plants to simultaneous or intermittent fumigations by HF and other pollutants makes it impossible

at this time to derive reference levels for HF in the presence of other gases. As shown by the experiments discussed above, these gases may act antagonistically, additively, or synergistically even within the same plant, depending upon the endpoint measured.

5 EFFECTS ON LIVESTOCK AND WILDLIFE

Review of the literature revealed a dearth of information concerning the effects of hydrogen fluoride on livestock and wildlife which are exposed to hydrogen fluoride mainly by the respiratory route. Some dermal exposure may occur when hydrogen fluoride mixes with water to form hydrofluoric acid. Indirect exposure may occur through ingestion of fluoride deposited on vegetation.

Generally, it was found that mammals are less sensitive to the effects of hydrogen fluoride than are plants. The difference in sensitivity is approximately 1,000 times, depending on the duration and manner of exposure. For this reason, it is suggested that the adverse effect on plants be used to derive the reference level.

Airborne fluorine compounds will eventually be deposited on and incorporated into, or contaminate the surface of, plant tissues eaten by animals. Indirect exposure to airborne fluorine compounds is generally more significant than direct exposure; that is, ingestion is more pivotal than inhalation in fluorosis. Therefore, consideration of an ambient air guideline to protect livestock and wildlife from the adverse effects of fluorine or HF must take into account the inhaled portion of the total dose of fluoride, the portion ingested in food and water and the portion absorbed through the skin.

This review approaches evaluation of the effects of HF in terms of its pharmacokinetic effects (the effect of the body on the chemical) and its pharmacodynamic effects (the effect of the chemical on the body). There were insufficient data available to create a table showing effects following a 24-hour exposure to livestock and wildlife.

5.1 PHARMACOKINETICS

HF has the potential to cause significant injury due to the unique toxicity of the dissociated fluoride ion (Bertolini, 1992). Upon contact with water, HF gas rapidly forms hydrofluoric acid. This acid readily gives up the reactive fluorine atom which, with cations, forms a fluoride salt. Calcium is rapidly altered to form calcium difluoride, an almost insoluble fluoride salt. These two chemical reactions account for the toxicity of HF:

- acidic burns caused by hydrofluoric acid;
- sequestration of calcium as calcium fluoride resulting in hypocalcemia;
- alteration of the calcium containing hydroxyapatite crystal in bone, resulting in fluorosis.

No pharmacokinetic studies of HF were found for livestock and wildlife. However, the kinetics of sodium fluoride (NaF) were studied in a group of three adult ewes which had been given NaF intravenously at three dose levels (0.15, 0.375, and 0.75 mg kg⁻¹ body weight). Data were analyzed using both compartmental and non-compartmental approaches. A three-compartment open model was selected to describe the data. Comparison of the different parameters indicated the absence of change with dose level, suggesting that fluoride behaved linearly at the doses under study. The half-life of the elimination was 2.57 ± 1.28 hours, the steady-state volume of distribution was 0.26 ± 0.5 l kg⁻¹, and the body clearance was 0.105 ± 0.26 l kg⁻¹ h⁻¹.

Dermal absorption has not been described in animals, but probably occurs in whole-body

exposure studies. As hydrofluoric acid, dermal absorption is rapid and can be fatal in humans (Bertolini, 1992) and possibly animals. As a concentrated acid, hydrofluoric acid causes burns. However, burns may take several hours to develop at concentrations of 20 to 50%. During this time, a large dose of fluoride ions has been absorbed. These patients may die of hypocalcemia, a critical situation caused by sequestration of calcium by fluoride. This cationic imbalance can cause death by heart failure in a manner similar to the disease “milk fever” (hypocalcemia) seen in periparturient cows in veterinary medicine.

No studies on tissue distribution of fluoride were found that dealt with HF; however, the fluoride atom would be distributed primarily in tissues high in calcium. Because of its affinity to calcium, fluoride concentrations are highest in bones and teeth following chronic administration (Schupe et al., 1992). Acute administration results in it binding to blood calcium, hence the use of sodium fluoride as an anticoagulant.

No elimination studies could be found; however, most fluoride is eliminated by the kidneys (Bartik and Piskac, 1981).

5.2 PHARMACODYNAMICS

In the real-world situation, acute poisoning by fluorine, or HF, is rarely encountered in domestic animals. Acute poisoning by fluorides and hexafluoroplumbic salts, used as pesticides, is more common (Bartik and Piskac, 1981). There are a few reports of accidental or intentional exposure to HF. For the purposes of this review, they will be classified by their temporal nature.

5.2.1 Acute Toxicity

The acute toxicity of HF in livestock and wildlife has been poorly described. In a toxicologic pathological study mainly based on rodent exposure, dogs and rabbits were exposed to concentrations of 6% to 50% of the LC₅₀ (median lethal concentration) concentrations for rats (Rosenholz et al. 1963). Rat LC₅₀ concentrations had been established following exposure periods of 5, 15, 30, and 60 minutes to be 4,074 mg HF m⁻³ (4,970 ppm), 2,205 mg HF m⁻³ (2,690 ppm), 1,672 mg HF m⁻³ (2,040 ppm), and 1,074 mg HF m⁻³ (1,310 ppm), respectively. The methodology did not describe the method of exposure in enough detail to determine whether whole-body or nose-only exposure had occurred. The eye irritation would indicate that probably whole-body exposure had occurred.

Clinically, animals exposed to near-lethal concentrations showed signs of conjunctival and nasal irritation. Extensive nasal secretions, lacrimation, pawing at the nose and sneezing were noted. Non-lethal exposures also revealed clinical abnormalities. Rabbits (n=5) exposed to 50% of the rat (n=20) LC₅₀ showed respiratory distress lasting a few hours following exposure, lacrimation, nasal discharge, pawing at the nose, and reddened conjunctivae. Pawing at the nose continued for several hours following exposure. The animals appeared depressed and weak for at least 24 hours and appeared sluggish for an additional day. Signs of nasal and conjunctival irritation usually were not seen after about four days (Rosenholz et al., 1963).

Dogs (n=2) were exposed to approximately 25% of the rat LC₅₀ concentrations and

showed blinking, periodic sneezing, coughing, and signs of general discomfort during the exposure. After removal from the chamber, the dogs rubbed their noses and bodies on grass, suggesting some skin irritation (also indicating probable whole-body exposure). No skin lesions were noted. Although the cough disappeared within two days, it reappeared upon exercise. All coughing ceased after a week to ten days. Haematological data did not show any changes compared with pre-exposure data and normal ranges for dogs (Rosenholz et al., 1963).

The pathologic portion of the Rosenholz et al. (1963) study was confined to the rats exposed to HF. It should be noted that the clinical signs seen in the rabbits and dogs occurred at doses 1,000,000 times the proposed ambient air quality reference level for HF.

5.2.2 Chronic Toxicity

Chronic HF toxicity has not been well characterized owing to the nature of the reactive molecule, which does not remain in the body as HF very long. For all intents and purposes, chronic HF toxicity should be considered as chronic fluoride toxicity. Chronic fluoride toxicity has been well reviewed elsewhere and will not be for the core of this review (Agency for Toxic Substances and Disease Registry, 1993; U.S. National Academy of Sciences, 1974).

A case report of HF toxicosis in camels is found in Karram and Ibrahim (1992). These workers evaluated the hemograms from 114 camels at various distances from a super-phosphate factory in Egypt. The authors took and analyzed blood sera and whole blood to determine fluoride levels and

haematological parameters, and state that elevated mean corpuscular volume (MCV) values correlated with levels of sodium fluoride. They also claim that decreased total erythrocytes (RBC), haemoglobin (Hb), packed cell volume (PCV), and mean corpuscular haemoglobin (MCH) levels were associated with the elevated MCV values. Evaluation of the data showed that the MCV values were elevated in comparison to control animals, when mathematically compared. However, there were no groups that fell out of the normal range for each parameter, indicating that the mathematical differences were not biologically significant. Serum fluoride levels of the camels that received the greatest exposure (1.56 mg m^{-3} ; 1.90 ppm) were seen to be ten times that of the control group (0.09 mg m^{-3} ; 0.11 ppm). The assay methodology is not detailed, nor are the exact criteria for the definition of fluorosis in the camels. For these reasons, this paper should not be considered in the reference level derivation for ambient HF concentrations.

5.2.3 Developmental Toxicity, Reproductive Effects and Carcinogenesis

No studies were found that dealt with the developmental, teratological, reproductive or carcinogenic effects of HF in livestock and wildlife.

5.2.4 Fluorides

Fluoride salts are present in most animal foods and occur naturally in many water supplies (Schupe et al., 1992). Fluoride salts enter the mammalian body mainly through ingestion, and may be passed on to the fetus (Schupe et al., 1992). Usually only small

quantities enter via the respiratory tract as dusts (Ontario Ministry of Labour, 1983). Absorption of fluoride salts through the skin is insignificant (Cass, 1961). The U.S. Environmental Protection Agency (cited in World Health Organization, 1984) lists the most common sources of excessive fluoride salts for livestock as follows:

- forage crops, usually the major source of an animal's diet, which have been contaminated by HF and fluoride salt emissions, or wind-blown or rain-splashed soil with a high fluoride salt content;
- water with a high fluoride content;
- feed supplements and mineral mixtures that have not been properly defluorinated;
- forage crops grown in soils with a high fluoride salt content.

The first of these sources is of primary interest in the present context. The most frequent causes of excessive fluoride salt concentration in vegetation are industrial emissions of HF and other fluoride salts. Volcanic eruptions releasing HF can also result in high concentrations of fluoride salts in plants (Kessabi et al., 1984). The earliest report of this phenomenon is from Icelandic literature following volcanic eruptions about a 1,000 years ago (Roholm, 1937), but similar effects were reported following the eruptions of Mount Hekla in 1963. Eruptions in the Lonquimay volcanic complex in the Andes were the cause of bovine fluorosis in the southern part of Chile (Araya et al., 1990). The fluoride content of the ash was 75 to 100 $\mu\text{g g}^{-1}$ and fluoride contaminated forage was the main route of cattle intoxication. Wildlife, such as deer, are also at risk of contamination by fluoride-containing industrial emissions, often detected by

changes in the skeletal system (Machoy et al., 1991).

One of the more aggressive forms of intoxication is the inhalation and ingestion of dust containing fluoride, since this causes an abrasive local action on the respiratory and digestive systems in addition to the usual systemic effects (Bartik and Piskac, 1981).

Injury caused by fluoride salts (fluorosis) in livestock develops progressively when total fluoride dietary concentrations exceed 20 to 30 $\mu\text{g g}^{-1}$ (U.S. National Academy of Sciences, 1974). Here the fluorine atom binds to calcium, rendering the calcium atoms unavailable for their normal bodily functions. Diagnosis of fluorosis is based on clinical observations, especially of dental and skeletal lesions, lameness, biopsy of tail bones, determination of fluoride in the total diet, effects on appetite, decreased milk production or body growth and, where applicable, post mortem examination. The simultaneous administration of aluminium

sulphate has been reported to alleviate dose-related fluorosis (Kessabi et al., 1986). Fluoride crosses the bovine placenta, which acts as a partial barrier (Schupe and Bagley, 1992). Pharmacokinetics of fluoride (see section 7.1) have been determined in sheep (Joseph-Enriquez et al., 1990). The effects of fluorosis have been described in cattle (Schupe et al., 1992) and camels (Karram and Ibrahim, 1992).

Animals differ in their susceptibility to ingestion, as shown in table 7. Ingestion would represent the indirect route of exposure to airborne fluorine compounds. Based on the previous review, the lowest level of fluoride in forage or feed which appears to lead to adverse effects is 40 $\mu\text{g g}^{-1}$ DW in the most sensitive species. The atmospheric concentration of HF which would lead to such levels appear to be 0.33 to 1.3 $\mu\text{g m}^{-3}$ fluorides for 30 days.

Table 7 Susceptibility of animals to fluoride by ingestion	
Animal	Fluoride feed levels affecting performance ($\mu\text{g g}^{-1}$)
Beef or dairy heifers	40
Mature beef or dairy heifers	50
Finishing cattle	100
Feeder lambs	150
Breeding ewes	60
Horses	60
Growing dogs	100
Finishing pigs	150
Breeding sows	150
Growing or boiler chickens	300

Laying or breeding hens	400
Turkeys	400
Source: World Health Organization, 1984	

5.3 CONCLUSION

In addition to the dearth of information on effects at different exposure levels, time of exposure does not support the development of a 24-hour exposure reference level for the protection of livestock and wildlife. From the weak chronic study data, it appears as though a continual exposure on mammals should not exceed 7 mg m^{-3} . This concentration is more than three orders of magnitude greater than that recommended for the HF reference level based on the effects of HF on plants.

Airborne fluorine compounds will eventually be deposited on and incorporated into, or

contaminate the surface of, plant tissues eaten by animals. Indirect exposure to airborne fluorine compounds is generally more significant than direct exposure; that is, ingestion is more pivotal than inhalation in fluorosis. Therefore, consideration of an ambient air guideline to protect livestock and wildlife from the adverse effects of fluorine or HF must take into account the inhaled portion of the total dose of fluoride, the portion ingested in food and water, and the portion absorbed through the skin.

HF gas is a potent, acute toxicant when animals are exposed to large quantities directly via the respiratory route. The chemical properties of the compound

accounts for its pharmacodynamic properties: it mixes with water to form a strong acid resulting in burns, and it binds to calcium resulting in sequestration of calcium and alteration of bone calcium (chronic exposure). As HF rapidly becomes a fluoride salt, the majority of the toxicity issues can be considered under the evaluation of the toxicity of fluorides. No chronic exposure studies were available for HF.

It is concluded that while plants are more likely to be affected at lower concentrations of HF than livestock and wildlife, protection of farm and wild animals from fluorosis can be achieved by implementing a maximum level of fluorides in feed and forage.

6 EFFECTS ON EXPERIMENTAL ANIMALS

There are a number of reports on the effects of hydrogen fluoride on experimental animals, usually rodents.

6.1 ACUTE TOXICITY

This section includes results from studies where animals were exposed to HF for 24 hours or less. HF and other gaseous fluorides such as tetrafluoride induce respiratory tract damage. If this damage is not in itself lethal, systemic intoxication may follow (World Health Organization, 1984).

Five guinea pigs and five rabbits died in 0.5 and 1.5 hours, respectively, after exposure to 540 mg m^{-3} HF (660 ppm). When five guinea pigs and five rabbits were exposed to 205 mg m^{-3} HF (250 ppm), they died within 1.0 and 3.0 hours. All animals showed severe signs of irritation from the start of the experiment, with increasingly laboured breathing. Autopsy showed ulceration of the upper respiratory tract and of the cornea of the eyes. The lungs were hyperaemic and edematous. At 40 mg m^{-3} (50 ppm), five guinea pigs died in two hours, whereas the five rabbits displayed severe signs of physical distress after three hours of exposure. At a concentration of 25 mg m^{-3} (30 ppm), guinea pigs died after a day, while rabbits were in such poor condition that they were sacrificed. Continuous exposure at 8 mg m^{-3} (10 ppm) for 5 days was not fatal to either species. In addition to laboured breathing, the guinea pigs showed only slight irritation of the eyes (Ronzani, 1909, cited in Heitman, 1976).

Machle et al. (1934) reported that exposure to 1,000 to 1,500 mg HF m^{-3} for five minutes caused death in a significant proportion of

the rabbits and guinea pigs exposed.

Damage to liver, kidneys and lungs was observed in animals exposed to 245 mg m^{-3} . Dipasquale and Davis (1971) reported the lethal concentration for 50% of the exposed population (LC_{50}) for a five-minute exposure to HF for rat and mouse to be 14,400 and 5,000 $\text{mg F}^{-} \text{ m}^{-3}$, respectively.

The 60-minute LC_{50} values for rats and mice were reported to be 1,100 and 270 $\text{mg F}^{-} \text{ m}^{-3}$, respectively (Wohlschlagel et al., 1976). When rats were exposed through inhalation to HF for 5, 15, 30, or 60 minutes, the LC_{50} s were 4,060, 2,200, 1,670 and 1,070 mg HF m^{-3} , respectively. The LC_{50} for guinea pigs with an exposure time of 15 minutes was 3,540 mg HF m^{-3} . Irritation of the mucous membranes of the eyes and nose, weakness, and a decrease in body weight was observed in the HF-exposed animals (World Health Organization, 1984). Acute inflammation and focal necrosis of the nasal mucosa, irritation of the skin, necrosis of the renal tubular epithelium, congestion of the liver and vacuolisation of its cells and myeloid hyperplasia of the bone marrow were found histologically (World Health Organization, 1984).

The HF LC_{50} value is three to five times higher than the fluorine LC_{50} value in rats. In general, the gradient of susceptibility in laboratory rodents is mice>rats>guinea pigs (Rosenholtz et al., 1963; Agency for Toxic Substances and Disease Registry, 1993).

Sub-lethal inhalation exposure of rats and mice to fluorine or HF affects the respiratory system (mild congestion, disperse), liver (coagulation necrosis and cloudy swelling), kidney (coagulation and necrosis) and mucous membranes (irritation of eyes and

nose) (Keplinger and Suissa, 1968). In this study, rats, mice and guinea pigs, rabbits and dogs were exposed to fluorine for 5 minutes at 820 mg m^{-3} (1,000 ppm), 15 minutes at 57 mg m^{-3} (70 ppm), 30 minutes at 45 mg m^{-3} (55 ppm), or 60 minutes at 37 mg m^{-3} (45 ppm). This non-linear effect illustrates the difficulty in extrapolating to 24-hour ambient concentrations. These sublethal concentrations did not result in any significant differences in haematological parameters. Gross evaluation of the animals sacrificed serially after exposure showed that the lungs had the greatest change of any organ (the nasal passages were bypassed). Lesions seen included congestion, petechiation, and diffuse consolidation. These lesions decreased in severity with time after exposure. The interpretation of these lesions was not given by the authors, although their appearance is typical of diffuse bronchiolar and alveolar damage. Histopathology revealed that coagulation necrosis was present in the lower airways and the alveoli, consistent with hydrofluoric acid damage. The explanation for the hepatic coagulation necrosis is more difficult since the zonal nature of the lesion was not given. If hydrofluoric acid had been swallowed in substantial quantities, then absorption of the compound into the portal tree could have resulted in zonal coagulation necrosis. The anticipated distribution of this necrosis would be periportal in nature.

The acute toxicity of five-minute exposure to HF was studied also by Higgins et al. (1972) in rats and mouse in an observational period of seven days. The five-minute LC_{50} was $14,900 \text{ mg m}^{-3}$ HF (18,200 ppm) and for mice $5,120 \text{ mg m}^{-3}$ HF (6,247 ppm). The same LC_{50} s for mice and rats were also reported by McEwen and Vernot (1971). For a 60-minute exposure, the LC_{50} values for mice

and rats were 374 mg m^{-3} and 792 mg HF m^{-3} , respectively (Vernot et al., 1977). McEwen and Vernot (1971) reported that, following a 5-minute exposure to HF, most of the exposed animals experienced pulmonary edema of varying severity, and pulmonary haemorrhage was a common finding in animals that died during or shortly after exposure to HF at levels above the LC_{50} value.

Inhalation of HF constitutes the most common route of exposure; however, there are data to suggest that absorption does not only occur at the level of the alveolar epithelium. In a study of the regional disposition and absorption of inhaled HF (36 to 176 mg F m^{-3}) in male Long-Evans rats, it was seen that virtually all inhaled HF was deposited in the upper respiratory tract. Less than 0.1% was found to pass into the lungs thus leaving 99.7% absorbed in the upper respiratory tract. The authors concluded that although the upper respiratory tract serves to protect the lower respiratory tract in rats, most of the absorption into the blood stream results from absorption at the lower site (Morris and Smith, 1982).

In another experiment (Stavert et al., 1991), biologically significant damage to the middle and lower airways occurred when male Fischer-344 rats were forced to breathe approximately $1,066 \text{ mg m}^{-3}$ (1,300 ppm) of HF vapour for five minutes. These animals were intubated with endotracheal tubes, thus bypassing the nasal cavity. It is clear from the above experiments that the nasal cavity protects the lower airways from the corrosive effects of gaseous HF, and acts as the major site of absorption of this compound.

The pathology seen in the rats acutely exposed to HF can be attributed to the

corrosive nature of the compound, once it comes into contact with the water associated with the exposed epithelium and forms hydrofluoric acid. In the upper respiratory tract severe epithelial necrosis, fibrinopurulent exudate and submucosal inflammation indicate that a full thickness epithelial burn had occurred in the nasal cavity of rats treated with $1,066 \text{ mg m}^{-3}$ (1,300 ppm) HF for 30 minutes (Stavert et al., 1991).

Mild suppurative tracheitis was present in the proximal trachea of these treated animals (Stavert et al., 1991). This less severe lesion decreases in severity the more distal it is from the nose. This may indicate a decrease in the concentration of HF as it is removed from the air space higher up the airway. The lungs also showed mild irritation, characterized by infiltration of neutrophils in the alveoli. There was no description of necrosis of alveolar epithelium, known for its exquisite sensitivity to insult.

6.2 SHORT-TERM TOXICITY

The only gaseous fluoride exposure studies that have been reported are for HF, and of those few reports the exposure durations were one day to one year.

Fifteen rabbits, 21 guinea pigs and four pigeons were exposed to HF at 8 mg m^{-3} (10 ppm) for two 3-hour periods per day for 31 days. During this period, two rabbits, seven guinea pigs and one pigeon died. At autopsy, opacity of the cornea with ulcerations, lesions of the nasal mucous membranes, emphysematous lungs, bronchopneumonitis, and interstitial pneumonitis were found. The autopsy of one of the rabbits surviving the exposure periods showed similar, but less severe, pathologic

findings. All surviving animals had lost up to 23% of their original weight and had severe anemia. After five HF-exposed guinea pigs had been immunized, they showed a marked decrease in the production of specific antibodies, and their resistance to bacterial infection in the lungs was reduced. While exposed to HF, the animals were less resistant than controls to the effects of inoculation with diplococcus and tuberculous bacilli; the opposite was true for anthrax (Ronzani, 1909, cited in Heitman, 1976). Nevertheless, these results seem to indicate an immunotoxic effect of airborne HF. Further studies by Ronzani (1909, cited in Heitman, 1976) using HF concentrations of 6, 4, and 2.5 mg m^{-3} (7.5, 5, and 3 ppm) established 2.5 mg m^{-3} (3 ppm) as the NOAEL (No Observable Adverse Effect Level), because in a 30-day study with 16 rabbits, 20 guinea pigs and 3 pigeons, exposure to HF did not cause any pathologic changes.

Machle and Kitzmiller (1935) reported that no externally obvious adverse effects were noted in rabbits, guinea pigs and Rhesus monkeys exposed to $15.2 \text{ mg HF m}^{-3}$ for a total of 309 hours (six to seven hours per day over about 10 weeks, observed for up to eight more months post-exposure). Two guinea pigs became sick and died after 134 and 160 hours of exposure. Both of these animals showed liver and lung damage (one had pulmonary haemorrhage), and one had kidney damage. The surviving animals were normal in behaviour and appearance, but had decreased growth rates. Some had decreased erythrocyte counts. At necropsy, these rabbits and guinea pigs exhibited varying degrees of lung, liver and kidney damage. The Rhesus monkeys revealed kidney damage only. The authors indicate that the lower limit of toxic HF concentrations

in air lies between 30 and 2.5 mg m⁻³ based on older studies (Ronzani, 1909, cited in Heitman, 1976; Flury and Zernik, 1931).

Stokinger (1949) performed a toxicity study in which 29 rats, 20 mice, 20 guinea pigs, 18 rabbits and 4 dogs were exposed to gaseous HF at concentrations of 25 and 7 mg m⁻³ for six hours per day, six days per week for five weeks. A second group of animals (15 rats, 20 mice, 10 guinea pigs, 10 rabbits and 5 dogs) were exposed to 7 mg HF m⁻³ for the same period. Subcutaneous haemorrhages, particularly around the eyes and on the feet, were observed in rats and, to a lesser degree, in mice. In dogs, an inflammation of the scrotal epithelium was seen after three days' exposure. These effects were observed mainly at the 25 mg HF m⁻³ exposure level, although haemorrhagia to lesser extent was also noticed on the feet of rats exposed to 7 mg HF m⁻³. Death occurred only at 25 mg HF m⁻³ in all rats and mice. Deaths occurred in rats throughout the entire exposure period, while all mice died by 17 hours of exposure. At the 25 mg HF m⁻³ concentration, rats showed pronounced weight loss; rabbits showed a slight loss, dogs showed none while guinea pigs, after a consistent gain, lost weight following the third week of exposure. No species showed any significant effects on weight at the 7 mg m⁻³ level. No effects were noted on blood-calcium alkaline phosphatase or serum proteins in dogs and rabbits. There was a significant increase in blood fibrogen level in dogs and rabbits exposed to 25 mg HF m⁻³, while the prothrombin level remained normal. At autopsy, 27 out of 44 animals exposed to 25 mg HF m⁻³ showed haemorrhages and edema of the lungs. Degenerative testicular changes and ulcerations of the scrotum were found in four dogs. In rats, renal

cortical degeneration and necrosis were noted in 27 of 30 animals. At the 7 mg HF m⁻³ level, localized haemorrhagic areas in the lungs were observed only in one dog. A progressive increase of fluoride in the animal bones was detected at the 25 mg HF m⁻³ exposure level, from 25 to 95 hours. The fluoride concentration in the rats' teeth increased 300%. A somewhat smaller increase was found in the femur. In maxillary and mandibular bone of the dogs, increases of fluoride concentrations ranged from 200 to 300%. The fluoride concentration of animal bones exposed to 7 mg HF m⁻³ for 166 hours was somewhat lower than that of in the high exposure level. According to Heitman (1976) for this study at almost equal HF concentrations times exposure time (HF dose), the fluoride deposition in bone and teeth was approximately the same. In this study of Stokinger (1949) a distinct NOAEL (No Observable Adverse Effect Level) could not be established, as some slight haemorrhagic changes in the lung were still observed at the lowest level tested (7 mg HF m⁻³). Stokinger et al. (1950) reported the effects of airborne HF on 29 rats exposed 6 hours per day, 5 days per week at an average concentration of 8 mg HF m⁻³ for total of 124 hours (approximately 4 weeks). In this study no adverse effects due to exposure to HF were observed, indicating that the NOAEL could be 8 mg HF m⁻³ at that exposure regime for 4 weeks. However, no higher exposure level were tested in this study.

Changes in the lipid, cholesterol and total lipid content in the lungs and liver have been studied in 4 series of experiments on 337 white rats, exposed to HF, H₂S and SO₂ for 4 hours daily during 4 months. Isolated and combined effects of these gases induced phasic changes of varying degree,

depending on the gas concentration. The lipid content in the lungs was reduced under the effect of gas in low concentrations, and in the liver it increased under the effect of HF

(and decreased under the effect of H₂S). A NOAEL in this study is not indicated (Aitbaev, 1984).

Inhaled HF (10 mg m⁻³ for 14 days) increases plasma cholesterol levels very significantly in normal guinea pigs and in guinea pigs with chronic latent vitamin C deficiency. Ascorbic acid deficiency significantly increased plasma cholesterol levels in exposed animals and controls. But ascorbic acid deficiency produced an increase in cholesterol less important than HF inhalation. These results showed that vitamin C deficiency and HF inhalation both produce an increase of cholesterol level, but they do not interact. The mechanism of cholesterol increase has been investigated. In HF inhalation, the activity of cholesterol 7 alpha-hydroxylating system containing cytochrome P₄₅₀ does not decrease in the liver microsomes (Dousset et al., 1984).

Two experiments studied the effect of HF inhalation on lipid metabolism in guinea pigs (Phillibert et al., 1991). In the first experiment, control was established before guinea pigs were exposed to 7 mg HF m⁻³ for 96 hours, following which the effects were measured on their plasma cholesterol, non-esterified fatty acids and cyclic AMP. Exposed guinea pigs showed no weight change, but their plasma fluoride concentration increased significantly, from 8.5 to 203.2 µmol L⁻¹. Mean plasma cholesterol and free fatty acids also increased significantly. As well, plasma cAMP had increased, which could be the cause of changes in lipid parameters. However, experiments with theophylline showed that the increase in plasma cholesterol was mediated by the increase of plasma.

The second experiment consisted of three groups with 14 guinea pigs per group: a control group, a group treated with orally administered simvastatin (a drug inhibiting the activity of beta-hydroxy beta- methyl glutamyl CoA {HMG-CoA-reductase}, which regulates the biosynthesis of cholesterol), and a group exposed to 7 mg m⁻³ for 96 hours. These studies provide no information to establish NOAEL. It was demonstrated that inhaled HF modifies the biosynthesis regulation of cholesterol by an effect on the HMG-CoA reductase activity.

6.3 LONG-TERM TOXICITY AND CARCINOGENICITY STUDIES

There are very few long-term toxicity studies of gaseous HF. The studies involve exposures for periods greater than one year.

In one study, guinea pigs and rabbits were exposed to as little as 24.5 mg HF m⁻³ for six hours daily for a total of 41 hours; they were autopsied 18 hours post exposure. There were no deaths among the animals left alive and observed for one year (Machle and Kitzmiller, 1935; Machle et al., 1934).

In a long-term inhalation study, 50 guinea pigs were exposed to an atmosphere varying from 125 to 203 µg HF m⁻³ for 18 months in order to study the effects on the metabolism of myocardial cells and biochemical serum parameters indicative for cardiac cell damage. An unexposed group of guinea pigs served as control. In the study there were also interim kills at six and 12 months. After six months of exposure to HF a significant increase in the oxygen consumption of myocardial cells, whereas a strong significant decrease in oxygen consumption was observed after 12 and 18 months of exposure. In addition, after 12 and 18

months of HF exposure an increase in both total lactate dehydrogenase (LDH) and creatinine-kinase (CK) and in the myocardial LDH and CK-MB isoenzymes was detected. (Bourbon et al., 1979). From these results, it is indicated that a long-term exposure to 125 to 203 µg HF m⁻³ will cause cardiotoxic effects, and thus a NOAEL cannot be established.

In another long-term inhalation study, 50 guinea pigs were subjected to an atmosphere containing 150 µg HF m⁻³ for 18 months in order to evaluate the histological and biochemical effects on kidney functioning. Unexposed guinea pigs were used as a control group. In this study there were also interim kills at six and 12 months. The only effect observed in the HF-exposed guinea pigs was a transient increase of calciurea and phosphaturia. The authors concluded that inhaled HF did not cause any alteration of kidney function in either the biological or histological parameters of the kidney and its function (Rioufol et al., 1982). This study did not provide a real NOAEL.

No animal bioassays have been reported on the potential carcinogenicity of inhaled fluorides (Thiessen, 1988).

Because of the nature of the compound, chronic low-level exposure to HF can be treated as being equivalent to fluoride salts. Table 8 lists reported NOAELs and LOAELs (Lowest Observable Adverse Effect Levels) for mice and rats. More detailed information about fluoride salts can be found in Agency for Toxic Substances and Disease Registry (1993), National Research Council (1971) and Drury et al. (1980). Longer-term effects of HF have been investigated in rats, mice, guinea pigs, rabbits and dogs. All species were exposed to 7 or 24 mg m⁻³ HF for six hours per day, six days per week for 30 days

(Stokinger, 1949). Marked species differences were noted. All rats and mice exposed to 24 mg m⁻³ died, but no guinea

pig, rabbit or dog exposed at this concentration died. No animal of any species died following exposure to 7 mg m⁻³.

	NOAEL (mg F ₂ m ⁻³)		LOAEL (mg F ₂ m ⁻³)	
	Mice	Rats	Mice	Rats
Mean + SD*	106 + 67	75 + 31	153 + 75	146 + 65
Range	23 - 263	42 - 132	45 - 303	71 - 263

Source: Agency for Toxic Substances and Disease Registry, 1993
* Standard deviation

No Observable Adverse Effect Levels (NOAELs) and Lowest Observable Adverse Effect Levels (LOAELs) for rats and mice have been estimated (Agency for Toxic Substances and Disease Registry, 1993), and are presented in table 8. These data refer to lethality. The NOAELs quoted are for the following endpoints:

- rat, rabbit and dog haematology (24 mg m⁻³ for 6 hours per day, 6 days per week),
- renal disease in rats (7 mg m⁻³ for 6 hours per day, 6 days per week),
- neurological effects (0.03 mg m⁻³ for 5 months undisclosed exposure), and
- testicular degeneration (7 mg m⁻³ for 6 hours per day, 6 days per week for 30 days).

The equivalent information is not available for livestock or other animals. The latter raises the issue of robustness of the reported concentrations because of changes in chemical methods.

The use of lethality data from experimental animals may overestimate the practical threshold of the effects of fluorine and HF since the slopes are steeper than for irritation

and other biological endpoints (Alexeeff et al., 1993).

6.4 REPRODUCTIVE TOXICITY, TERATOLOGY AND GENOTOXICITY STUDIES

With the exception of a study in *Drosophila*, no specific genotoxicity experiments with airborne HF or other fluorides are reported.

Several authors have suggested the potential mutagenicity of either HF or sodium fluoride (NaF) to lower (bacteria, yeasts) and higher plants (*Drosophila*) or mammals (Caspary et al., 1987; Cole et al., 1986; Gerdes, 1971; Gerdes et al., 1971; Mitchell and Gerdes, 1973; Mohamed, 1977; Mohamed and Kenner, 1969; Tsutsui et al., 1984 a, 1984b, 1984c; Voroshilin et al., 1973, 1975). On the other hand, Leonard et al. (1977) found no increase in chromosome aberrations in the leucocytes of cattle with chronic fluoride poisoning, nor did Voroshilin et al. (1973) or Obe and Slasic-Erben (1973) in human leucocytes treated *in vitro* with 18 and 54 mg L⁻¹ NaF. Temple and Weinstein (1978) were unable to demonstrate mutagenicity of HF in tomato plants. Martin

et al. (1979) found no evidence for increased

chromosome aberration in mice following exposure to NaF administered orally, nor did they find NaF to be mutagenic in a bacterial (*Salmonella*) mutagenesis assay and it did not induce gene inversion in *Sacheromyces cerevisiae*. A review by the International Agency for Research on Cancer (1982) found that NaF is not mutagenic in *Salmonella* or *Drosophila*, and both the US EPA (Federal Register, 1985) and the Safe Drinking Water Committee (1977) concluded that the mutagenicity of fluoride in humans has not been demonstrated (Thiessen, 1988). Little or no effect was noted on chromosomes when mouse oocytes were exposed *in vitro* to a fluoride concentration of 200 mg L⁻¹ in media for up to 14 hours. Sheep and cow oocytes were unaffected by a concentration of 100 mg L⁻¹ in media for 24 hours (Jagiello and Lin, 1974). Mohamed and Chandler (1977) reported that the number of cells from bone marrow or spermatocytes with chromosomal abnormalities increased in mice with a fluoride dose in drinking-water of 1 mg L⁻¹ or more. Owing to various inconsistencies and lack of proper double-blind procedures, the results of Mohamed and Chandler (1977) have been questioned (Victoria Committee, 1980; World Health Organization, 1984).

6.5 CONCLUSION

With the paucity of data in experimental animals, it becomes difficult to establish air quality objectives. Furthermore, the chemical analytical procedures used in the older references (i.e., pre-1950s) may not be as precise or accurate as today's methods. At best, the conclusions can only address acute exposure to HF. Human sensory levels may be more sensitive than animal studies in establishing tolerable levels for brief human

exposures (Rosenholz et al., 1963). For example, it appears that humans (Largent, 1961; Machle et al., 1934) might be more sensitive than rats (Keplinger and Suissa,

1968; Wohlschlagel et al., 1976) to the irritant effects of fluorine or HF, perhaps by an order of magnitude.

7 EFFECTS ON HUMAN HEALTH

Acute exposure to gaseous fluoride is rare in a non-occupational setting. Hydrogen fluoride and fluorine are extremely toxic, posing immediate danger to health and life. Both gases can cause severe respiratory damage or skin burns on contact. Skin burns and respiratory damage caused by hydrogen fluoride are the only toxic effects of hydrogen fluoride that are not attributable solely to the action of the fluoride ion. Systemic fluoride poisoning usually occurs from hydrogen fluoride absorbed via the lungs or the skin (Thiessen, 1988).

Following exposure to gaseous fluorides and hydrogen fluoride by either inhalation or dermal contact, systemic effects are based on the fluoride absorbed and in circulation in the body. Under these circumstances, systemic toxicity parallels the toxicity of ingested fluoride. Where possible, this discussion is limited to aspects of the toxicity of gaseous hydrogen fluoride. A more complete overview of fluoride toxicity can be found in several extensive reviews (World Health Organization, 1984; Thiessen, 1988; Government of Canada, 1993).

A comparison of the properties of hydrogen fluoride with those of other hydrogen halides indicates deviations from expected values because of polymerization of the hydrogen fluoride molecule. The degree of polymerization varies depending on the partial pressure of the hydrogen fluoride and the temperature. At airborne concentrations of hydrogen fluoride at or near the recommended limits in the workplace, the partial pressure will be low enough that the polymerization of hydrogen fluoride is negligible. In this situation, it is probable that the molecular weight of hydrogen fluoride is

20 (Heitman, 1976). To account for any uncertainty in the figures for hydrogen fluoride and other airborne fluorides, the environmental limits are expressed in mg m^{-3} instead of in ppm. Especially at high exposure levels, the best way to express the concentration for review of toxicological studies is in mg m^{-3} if possible (if given). When units for airborne hydrogen fluoride are converted from ppm to mg m^{-3} in this report, it is assumed that airborne hydrogen fluoride exists as a monomer. If it is clear that the data refer to hydrogen fluoride, a conversion factor can be applied, and these calculated figures are indicated in parentheses. If total gaseous fluoride is indicated, it is not possible to express the units other than as given, unless the molecular weight or a conversion factor is provided by the authors.

7.1 PHARMACOKINETICS

7.1.1 Absorption

Inhaled fluorides consist primarily of hydrogen fluoride and particulate fluorides, both of which can be deposited in the respiratory tract (World Health Organization, 1984). Hydrogen fluoride, which is highly soluble, is rapidly taken up in the upper respiratory tract (World Health Organization, 1984) and quickly absorbed into the system, either directly from the respiratory tract or following translocation to the gastrointestinal tract via nasal mucus (Morris and Smith, 1982). Close to 100% of inhaled hydrogen fluoride is absorbed (Machle and Largent, 1943; Thiessen, 1988). Absorption of inhaled fluorides is dependent on several factors,

including the chemical nature of the fluoride and of other substances that may have been co-ingested or co-inhaled. Fluoride from inhaled dust is absorbed as rapidly as from inhaled hydrogen fluoride, but the total fluoride is less than from gaseous fluorides (Collings et al., 1952). Hydrogen fluoride is readily absorbed through the skin of individuals accidentally exposed in the workplace, leading to hydrofluoric acid burns (Burke et al., 1973; Tepperman, 1980; World Health Organization, 1984).

Absorption of any fluoride appears to be a passive process (Drury et al., 1980). Fluoride from any source is thought to be transported across biological membranes primarily as molecular hydrogen fluoride (Whitford et al., 1976; Gutt knecht and Walter, 1981; Whitford and Pashley, 1984). At physiological pH (in blood, intracellular fluid or mucus), fluoride from any source exists primarily as the fluoride ion (F^-), although a small amount of molecular hydrogen fluoride exists in equilibrium with the ion. The fate and effects of absorbed inorganic fluorides are essentially independent of the fluoride source (Thiessen, 1988).

7.1.2 Distribution

Once absorbed by the human body after inhalation, fluoride is transported through the body via the bloodstream and is then retained in the tissues, predominantly the skeleton, or excreted, mainly in the urine (World Health Organization, 1984). About 75% of the fluoride in blood is present in the plasma; the rest is found mainly in or on the red blood cells (Carlson et al., 1960a, 1960b; Hosking and Chamberlain, 1977; World Health Organization, 1984; Thiessen, 1988). Both the uptake of fluoride in calcified tissues and urinary excretion are fast

processes (Collings et al., 1952; Charkes et al., 1978; World Health Organization, 1984; Thiessen, 1988). Approximately 35–48% of systemically absorbed fluoride from any source is retained in the human body (Hodge and Smith, 1965; World Health Organization, 1984; Thiessen, 1988). At low fluoride uptake levels (non-occupational, <4.0–5.0 mg/day), there may be very little cumulative storage of fluoride (McClure et al., 1945). Studies with radioactively labelled fluoride suggested that the body retains about 60% of intravenously injected fluoride (Charkes et al., 1978; World Health Organization, 1984). The half-life for uptake by bone tissue is very short, about 13 minutes; both blood and extracellular fluid levels decrease rapidly. Approximately 99% of fluoride in the body is found in the skeleton. The remaining portion is distributed between the blood and soft tissues (World Health Organization, 1984; Thiessen, 1988).

Fluoride in human serum exists in both ionic and nonionic forms (Taves, 1968a, 1968b; World Health Organization, 1984). At least half of the fluoride in the human body consists of organic fluoride (perfluorinated fatty acid derivatives containing 6–8 carbon atoms) and non-ionizable fluoride from F^- or hydrogen fluoride (Ophaug and Singer, 1977; Morris and Smith, 1983; World Health Organization, 1984; Thiessen, 1988). Guy et al. (1976) indicated that human serum contains much smaller quantities of uncharacterized organic fluorocarbons. The amount of non-ionic fluoride is related to the total fluoride intake or uptake (Ophaug and Singer, 1977; Morris and Smith, 1983; World Health Organization, 1984; Thiessen, 1988). However, if the fluoride intake or uptake is high, the ionic form may predominate (World Health Organization, 1984). For the general population at a steady-state exposure to

fluoride, the plasma concentration of inorganic (ionic) fluoride is directly related to the inorganic fluoride concentration of drinking water (World Health Organization, 1984). On the basis of the general pharmacological behaviour of fluorides, this relationship also holds for the uptake of gaseous fluorides.

In a group of rural Chinese, organic fluoride was found to contribute about 17% to serum fluoride (Belisle, 1981). The half-life of fluoride in plasma ranged from two to nine hours, depending on the dose level (Guy et al., 1976; Ekstrand et al., 1978; Singer and Ophaug, 1979; World Health Organization, 1984). For the same intake, plasma fluoride/ ion concentration increases significantly with age (Carlson et al., 1960a; Singer and Ophaug, 1979; World Health Organization, 1984). This might be explained by a faster uptake by younger bone tissue, which is less saturated with fluoride (Weatherell, 1966; World Health Organization, 1984). In addition, because of the accumulation of fluoride in the skeleton, increased amounts may be released by the bone remodelling process into the plasma of older individuals (World Health Organization, 1984).

The study of the distribution of fluoride from inhaled gaseous fluorides, including hydrogen fluoride, is complicated by fluoride taken up orally by drinking water or food and by absorption through skin. Animal studies with labelled gaseous fluorides would be the ideal source of information on the pharmacokinetics of gaseous fluorides (see section 6.1).

7.1.2.1 Bone

Fluoride ions are taken up by bone through replacement of hydroxyl ions in bone apatite.

The precise mechanism of fluoride incorporation into bone is not completely clear (Drury et al., 1980; Rioufol et al., 1983; World Health Organization, 1984). The general conclusion is that absorbed fluoride is incorporated into hard tissues primarily by an exchange process and by incorporation into the apatite during bone mineralization (Thiessen, 1988). It has been suggested that fluoride in extracellular fluid enters the apatite crystal by a three-stage ion exchange process. Hydroxyapatite of bone mineral exists as extremely small crystals surrounded by a hydration shell. Fluoride first enters the hydration shell, in which the ions are in equilibrium with those of the surrounding tissue fluids and those of the apatite crystal surface. The second-stage reaction consists of an exchange between fluoride from the hydration shell and the hydroxyl group at the crystal surface. Once it has entered the surface of the crystal, fluoride is more firmly bound. In the third stage, some of the fluoride may migrate deeper into the crystal as a result of recrystallization (World Health Organization, 1984).

The amount of fluoride present in bone depends on a number of factors, including fluoride intake, age, sex, bone type and the topography of the bone. About half of absorbed fluoride is deposited in the skeleton, where it has a long half-life. The concentration of fluoride in bone increases with age (Jackson and Weidmann, 1958; Smith et al., 1982; World Health Organization, 1984). Fluoride can be released from bone, as is evidenced by its appearance in the urine in increasing amounts after exposure has ceased or decreased (Largent et al., 1952; Grandjean et al., 1983; World Health Organization, 1984). Hodge and Smith (1970) suggested, on the basis of published data, that such

removal of fluoride takes place in two phases — a rapid process taking weeks and probably involving ion exchange in the hydration shell, and a slower phase with an average half-life of about eight years owing to osteoclastic resorption of bone. Human data suggest that 2–8% of absorbed fluoride is excreted during 18 days following the initial retention (Spencer et al., 1975, 1981). Because of a slower remodelling process, fluoride is released more slowly from compact bone such as iliac crest than from trabecular bone (Baud et al., 1978; World Health Organization, 1984).

7.1.2.2 Teeth

The factors controlling the incorporation of fluoride into dental structure have been reviewed by Weidmann and Weatherell (1970), who concluded that the situation is essentially the same as that pertaining to bone (World Health Organization, 1984). Cementum is more similar to bone than are enamel and dentine, but its fluoride concentration has been found to be higher than that of bone (Singer and Armstrong, 1962). However, unlike bone, which can continue to take up fluoride throughout an individual's lifetime, teeth incorporate fluoride only during the period of calcification, which is up to about age 12 in humans (Drury et al., 1980). Once formed, enamel and dentin differ from bone in that they do not undergo continuous remodelling. Fluoride concentrations in these tissues also vary with site, age and surface attrition, and they increase with systemic and topical exposure to fluoride (Weatherell et al., 1977; Schamschula et al., 1982; World Health Organization, 1984). In adults, fluoride concentrations measured in the surface layer of enamel range from 900 to 2,700 mg kg⁻¹ (Berndt and Stearns, 1979; World Health

Organization, 1984). The average concentration of fluoride in dentine is 2–3 times that in enamel and is affected by growth and mineralization. As with bone and enamel, dentin fluoride concentrations are higher in the surface regions than in the interior (U.S. National Academy of Sciences, 1971; World Health Organization, 1984).

7.1.2.3 Soft Tissues

The concentrations of fluoride in human soft tissues reported by different authors vary greatly (World Health Organization, 1984). In general, however, only very small amounts of fluoride are found in the normal soft tissues. The highest levels are seen in the kidneys (Hodge and Smith, 1965; U.S. Environmental Protection Agency, 1980; Heifetz and Horowitz, 1986; Thiessen, 1988). Fluoride has a relatively short biological half-life in these organs, and the soft tissue fluoride concentration is therefore practically in equilibrium with that in the plasma. Unlike fluoride in bone, the concentration does not increase with age or duration of exposure (Underwood, 1971; Drury et al., 1980; Thiessen, 1980; World Health Organization, 1984).

7.1.2.4 Transplacental Transfer

Fluoride crosses the placenta. A study by Armstrong et al. (1970) measured fluoride from maternal uterine vessels and the umbilical vein and artery at caesarean section in human patients. The authors did not find any significant gradient between maternal and foetal blood levels, indicating that there is no placental barrier for fluoride. At higher fluoride levels, a partial barrier may exist (Gedalia, 1970). The fluoride content of the foetal skeleton and teeth increases with the age of the foetus and with the fluoride

concentration in the mother (Gedalia, 1970; World Health Organization, 1984).

7.1.3 Excretion

The principal route of fluoride excretion is via the urine. Some excretion takes place through sweat and faeces, and fluoride also appears in saliva. Fluoride crosses the

placenta, but it rarely seems to be excreted in milk to any extent (World Health Organization, 1984).

7.1.3.1 Urine

Approximately half of absorbed fluoride is excreted in urine (Drury et al., 1980; World Health Organization, 1984). Urinary excretion is the major route of fluoride clearance from the blood and from the body. Fluoride clearance is less than that of creatinine (approximately 0.15 L kg^{-1} body weight per hour; Ekstrand et al., 1977b). Fluoride appears rapidly in the urine after absorption. Intravenously injected fluoride is excreted even more rapidly (Ekstrand et al., 1977b; Charkes et al., 1978; World Health Organization, 1984). Renal fluoride ion excretion involves glomerular filtration followed by pH-dependent tubular reabsorption. Reabsorption occurs by non-ionic diffusion of hydrogen fluoride (Whitford et al., 1976) and therefore is greater in acidic urine than in alkaline urine (i.e., fluoride removal from the body is greater in alkalosis than in acidosis) (Reynolds et al., 1978; Whitford et al., 1979). Several factors may influence the urinary excretion of fluoride, such as total current exposure, previous exposure, age, urinary flow, urine pH and kidney status (Whitford et al., 1976; Ekstrand et al., 1978, 1982; Schiffel and Binswanger, 1980; World Health Organization, 1984).

Urinary excretion of fluoride is decreased in cases of renal failure or dysfunction, and retention (i.e., bone deposition) of fluoride increases accordingly (Gerster et al., 1983; Kono et al., 1984a, 1984b). People with renal dysfunction are therefore at a higher risk for adverse health effects due to fluoride. Some of the fluoride excreted originates from fluoride released during bone

remodelling. Thus, excretion rates may increase slightly with age, but no sex difference in fluoride excretion has been found (Toth and Sugar, 1976; Van de Putte et al., 1977; World Health Organization, 1984). Younger persons who are actively forming bone minerals excrete less fluoride (i.e., a lower proportion of the absorbed dose) than do adults. In situations in which humans attain extremely high plasma levels of fluoride, acute kidney dysfunction may ensue, with decreased clearance of fluoride (World Health Organization, 1984).

average individual exposures were between 1.2 and 3.9 mg m⁻³, six hours per day. No

7.1.3.2 Faeces

Some fluoride is also excreted in the faeces. Fluoride in the faeces is primarily ingested fluoride that was not absorbed, and fluoride excreted into the gastrointestinal tract does not appear to be a major source of faecal fluoride (Machle and Largent, 1943). This implies that the concentration of fluoride in the faeces will be low after dermal or inhalation exposure to fluoride. The proportion of the ingested fluoride that is eliminated in the faeces varies depending on circumstances (U.S. Environmental Protection Agency, 1980; Maheswari et al., 1981; Spencer et al., 1981; World Health Organization, 1984). In persons not occupationally exposed to fluoride and not using fluoridated water, the faecal elimination of fluoride is usually less than 0.2 mg/day (U.S. National Academy of Sciences, 1971). That some fluoride can be excreted into the gastrointestinal tract is suggested by the findings of Largent (1961), who found that the faecal fluoride content of human volunteers increased (2.5- to 6.7-fold, highest amount was 0.70 mg/day) during a period (2–4 weeks) of hydrogen fluoride inhalation (2.5–8.1 mg m⁻³, or 0.9–8.1 ppm). The

coincident increase in oral fluoride (food or water) was noted that might have accounted for the observations.

7.1.3.3 Other Excreta

Usually, only a few percent of the fluoride taken up is excreted in perspiration. However, under conditions of excessive sweating, as much as 50% of the total fluoride excreted may be lost via this route. These conditions can occur in cases of very active persons or in people in hot climates and whose water intake is therefore very high (Crosby and Shepherd, 1957; World Health Organization, 1984; Thiessen, 1988). After five young men ingested 4.0–5.0 mg of fluoride per day, the fluoride concentration in their sweat was 0.3–1.8 mg L⁻¹; two weeks after cessation of the exposure, the concentration was 0.2–0.3 mg L⁻¹ (McClure et al., 1945).

Less than 1% of absorbed fluoride is reported to appear in saliva (Carlson et al., 1960a; Ericsson, 1969; World Health Organization, 1984). Salivary fluoride concentrations are proportional to plasma fluoride concentrations and were found to be about 65% of plasma levels (Ekstrand et al., 1977a; World Health Organization, 1984; Thiessen, 1988). In fact, saliva does not represent pure excretion, because most of the fluoride will be recycled in the body. However, the fluoride content of the saliva is of major importance for maintenance of fluoride levels in the oral cavity (World Health Organization, 1984).

The concentration of fluoride in human milk is quite similar to that in plasma (Ekstrand et al., 1981), and significant exposure to fluoride through human milk is therefore very unlikely (World Health Organization, 1984). Observed fluoride levels in human milk are

between 2 and 8 µg L⁻¹, less than those in most milk substitutes (Thiessen, 1988).

7.1.4 Monitoring Exposure to Gaseous Fluoride by Pharmacokinetic Parameters

Kono et al. (1987) measured urinary fluoride concentrations pre-shift and post-shift in 142 workers exposed to hydrogen fluoride in their workplace at a level of 3 ppm (2.5 mg m⁻³) and in 80 unexposed workers (ages 18–59). They reported a linear relationship between the mean urinary fluoride concentrations and the hydrogen fluoride concentration in the air. The mean urinary fluoride value was 4 mg kg⁻¹ for exposed workers.

Pre- and post-shift serum and urine samples of 142 hydrogen fluoride workers were compared with those of 270 unexposed workers (Kono et al., 1992). The pre-exposure levels of serum and urinary fluoride in hydrogen fluoride workers were found to be higher than the control values, suggesting that fluoride excretion from the body did not return to control levels in the inter-shift period (12 hours). The post-shift serum and urinary fluoride concentrations of hydrogen fluoride workers were significantly higher than the pre-shift concentrations. A good correlation was obtained between serum fluoride and urinary fluoride concentrations. There was a linear relationship between mean serum fluoride concentration and hydrogen fluoride concentration in the workplace. A mean serum fluoride concentration of 82.3 µg L⁻¹ was estimated to correspond to an atmospheric hydrogen fluoride concentration of 3 ppm (2.5 mg m⁻³). This is the maximum allowable environmental concentration recommended by the Japanese Association of Industrial Health (1964) and by the

American Conference of Governmental Industrial Hygienists (1967).

In a similar study, Kono et al. (1993) recorded hair, urine, and serum fluoride concentrations pre- and post-shift in workers exposed to hydrogen fluoride in the workplace. This study confirmed the linear relationship between serum and urinary fluoride concentrations and the hydrogen fluoride concentration in the workplace. The results support the speculation that fluoride is excreted in the hair after long-term exposure to hydrogen fluoride. The studies of Kono et al. (1987, 1992, 1993) suggest that actual exposure to hydrogen fluoride can be monitored by determining the serum, urinary and hair fluoride concentrations.

Ehrnebo and Ekstrand (1986) monitored individual plasma and urine fluoride concentrations pre- and post-shift in workers at an aluminum plant in Sweden. They concluded that when fluoride exposure and body burden are to be studied on an individual basis, the area under the plasma concentration–time curve and the amount of fluoride excreted give better quantitative information than urinary fluoride concentration measurements.

7.2 PHARMACODYNAMICS

Fluoride toxicity involves at least four categories of major functional derangements (Hodge, 1969; Gosselin et al., 1984; Thiessen, 1988): (1) inhibition of enzymes controlling glycolysis or other vital pathways; (2) hypocalcaemia, resulting from binding or precipitation of calcium by fluoride; (3) cardiovascular collapse caused by hypotension and circulatory shock; and (4) damage to specific organs, primarily the brain and the kidneys. Fluoride also has

effects on inorganic phosphate and potassium concentrations in serum (Boink, 1993).

The literature on the influence of fluoride on enzyme systems is extensive. Both activating and inhibiting effects on enzymes have been described. Fluoride (as F^- or as undissociated hydrogen fluoride) may exert a direct action on the enzyme itself. More frequently, however, the effect is indirect, involving complexation with a metal (e.g., Ca^{2+} or Mg^{2+}) associated with the enzyme (Edwards et al., 1984; World Health Organization, 1984; Anonymous, 1985; Thiessen, 1988).

Reviews of the literature (Hodge and Smith, 1965; Taves, 1970; Wiseman, 1970; Drury et al., 1980; Swedish Fluoride Commission, 1981) suggest that low concentrations (about $10 \mu\text{mol/L}$, i.e., 0.18 mg L^{-1}) of fluoride in serum (but still much higher than normal) will stabilize and activate several soluble and membrane-bound enzyme systems, including adenylyl cyclase (World Health Organization, 1984). Alkaline phosphatase activity may be increased by fluoride (Farley et al., 1983), but changes in serum activity levels of this enzyme, and in serum calcium and phosphate, have been found to be minimal in potroom workers with skeletal fluorosis (Boillat et al., 1979).

At higher serum fluoride concentrations (at least 0.3 mg L^{-1}), fluoride will inhibit many enzymes (World Health Organization, 1984). Pyrophosphatase, for instance, is inhibited by about 50% at 0.4 mg L^{-1} , a level that is higher than that found in the plasma of an individual with a skeletal fluoride content of $6,000 \text{ mg kg}^{-1}$ and exposure to fluoride levels of 19 mg L^{-1} in drinking water (Ericsson et al., 1973). In rats, fluoride ion has been shown to be a potent inhibitor of liver cytosolic

pyrophosphatase (Baykov et al., 1992), the equilibrium inhibition constant for this enzyme being an order of magnitude lower than that for enolase. Baykov et al. (1992) suggested that fluoride-induced inhibition of pyrophosphatase may lead to an increase in cellular pyrophosphatase, which in turn inhibits fatty acid oxidation, protein and nucleic acid synthesis and bone formation and growth.

Among the results of enzyme inhibition by fluoride are hyperkalaemia and metabolic acidosis (Gosselin et al., 1984; World Health Organization, 1984). In acute fluoride poisoning, inhibition of metalloenzymes involved in essential processes can cause vital functions such as the initiation and transmission of nerve impulses to cease. Fluoride has been shown to affect the metabolism of glucose, lipids, cholesterol and collagen in mammals, as well as the formation of bones and teeth, and many of these metabolic effects are probably due to the effects of fluoride on the enzymes involved (Watanabe et al., 1975; Aitbaev, 1984; Dousset et al., 1984; Drozd et al., 1981, 1984; Den Besten, 1986; Thiessen et al., 1988; Boink, 1993). In these cases, serum fluoride levels, when reported, were at least $50 \mu\text{g L}^{-1}$ (Thiessen et al., 1988). Studies in humans have shown minimal increases in urinary cyclic adenosine monophosphate excretion and unchanged plasma levels following an oral intake of about 7 mg fluoride, which resulted in peak plasma fluoride levels of about 0.3 mg L^{-1} (Mornstad and Van Dijken, 1982).

In the mineralization of bones and teeth, the proteoglycans and their constituent glycosaminoglycans form an integral part of the organic matrix of these tissues. Fluoride-induced changes in the formation of these

compounds could be part of a common mechanism for the skeletal and dental effects of fluoride. Studies on rats have shown that the proteoglycans undergo molecular changes, particularly in terms of decreased size, during the development of dental fluorosis (Smalley and Embery, 1980). In rabbits, glycosaminoglycans show major changes, with the novel appearance of dermatan sulphate, an iduroglycosaminoglycan in fluorotic bone (Jha and Susheela, 1982a, 1982b). The serum of patients with endemic fluorosis (both skeletal and dental) contains decreased concentrations of sialic acid and increased levels of glycosaminoglycans compared with controls. Parallel results have been reported for rabbits dosed with sodium fluoride at 10 mg kg^{-1} body weight daily for eight months (Jha et al., 1983).

The strong affinity of fluoride for calcium results in hypocalcaemia. Fluoride intoxication following dermal exposure to hydrogen fluoride solutions or ingestion of fluoride salts is characterized by severe hypocalcaemia. Total calcium concentrations as low as 1 mmol/L (normal $2.2\text{--}2.6 \text{ mmol/L}$) have been found in the plasma of patients intoxicated with fluoride, whereas total protein, which binds approximately half of the calcium present in plasma, was normal (Boink, 1993). This fluoride-induced hypocalcaemia was accompanied by a rise in plasma parathyroid hormone, indicating that the normal physiological response to hypocalcaemia of the parathyroid gland is not affected by fluoride in humans or in animals (Simpson et al., 1980; Kono et al., 1982; Boink, 1993). It has been postulated that fluorapatite is responsible for the hypocalcaemia (Simpson et al., 1980; Boink, 1993). If the formation of fluorapatite is involved in the aetiology of hypocalcaemia,

its structural formula $[3\text{Ca}_3(\text{PO}_4)_2 \cdot \text{CaF}_2]$ suggests that the inorganic phosphate concentration in plasma will decrease during fluoride intoxication (Boink, 1993). This is indeed the case (Handler, 1945; Boink, 1993). Changes in serum inorganic phosphate concentrations are the result of a combination of (1) phosphate release from cells, (2) calcium mobilization from bone matrix, compensating for hypocalcaemia, during which process phosphate ions are released, (3) formation of fluorapatite, during which process phosphate ions are bound, and (4) impaired renal tubular phosphate metabolism (Boink, 1993). After intraperitoneal administration of sublethal doses of fluoride in rats, increased urinary phosphate excretion is observed (Kessabi et al., 1980).

Hypocalcaemia in cases of acute fluoride poisoning will often result in severe involuntary muscle contractions (tetany) (Gosselin et al., 1984). Many of the other effects of fluoride, including cardiac arrhythmias and other effects often associated with acute systemic fluoride poisoning, are thought to be caused by hypocalcaemia (Abkurah et al., 1972; Tepperman, 1980; Kono et al., 1982; Gosselin et al., 1984; Heifetz and Horowitz, 1986; Thiessen, 1988).

Fluoride-induced potassium leakage from erythrocytes has an absolute requirement for the presence of extracellular calcium (Lepke and Passow, 1968). McIvor and Cummings (1987) suggested that fluoride causes potassium leakage from erythrocytes by inhibiting Na^+, K^+ -ATPase, which in turn leads to a rise in intracellular sodium concentration and subsequent $\text{Na}^+ - \text{Ca}^{2+}$ exchange. In two fatal cases of fluoride intoxication of humans (Baltazar et al., 1980; McIvor et al., 1983)

and in experimental fluoride intoxication in dogs, rats and pigs, hyperkalaemia has been observed (Baltazar et al., 1980; Boink, 1993). Hyperkalaemia can result in ventricular fibrillation of the heart associated with

peaking of the T-waves in the electrocardiogram (Baltazar et al., 1980). Hypokalaemia has also been reported in one human case study (Abkurah et al., 1972).

Cardiovascular collapse is one of the two most common immediate causes of death in cases of acute fluoride poisoning (Gosselin et al., 1984). The hypotension and circulatory shock that are involved result from a combination of factors such as fluid and electrolyte losses (due to vomiting and diarrhoea or intragastric bleeding) and central vasomotor depression. Brain damage from acute fluoride poisoning can cause such symptoms as convulsions, lethargy, stupor and coma. Respiratory failure (the other leading cause of death in fluoride poisoning) is thought to be of central nervous system origin (Gosselin et al., 1984). Renal injury, including transient diabetes insipidus, may also result from acute fluoride poisoning, although it is probably not a major concern in cases of chronic fluoride exposure. Note that renal failure does not appear to be a cause of death in fluoride poisonings (Gosselin et al., 1984). More severe nephrotoxicity, also including diabetes insipidus, may occur from exposure to fluorine-containing anaesthetic agents such as methoxyflurane or enflurane (World Health Organization, 1984; Thiessen, 1988).

Because of the chemical similarities between the halogens iodine and fluorine, there has been much interest in the possible effects of fluoride on the thyroid (e.g., formation of goitre) (Day and Powell-Jackson, 1972; World Health Organization, 1984). Other investigations have failed to reveal any evidence that fluoride is responsible for any disorder of the thyroid (Demole, 1970; Royal College of Physicians, 1976; Sonneborn and Mandelkow, 1981).

7.3 EFFECTS IN HUMANS

A number of case reports on acute or chronic poisoning by inhalation or exposure of skin to airborne hydrogen fluoride have been published, some of which have already been reviewed by Heitman (1976), the World Health Organization (1984) and Thiessen (1988). Very little information from clinical studies is available on other gaseous fluorides. Most of the clinical cases of poisoning by hydrogen fluoride or other fluorides do not provide accurate quantitative data; at best, they provide some indication of the exposure levels leading to symptoms of toxicity.

Most case studies of acute or chronic intoxication by inhalation of hydrogen fluoride or skin exposure concern accidents in the work environment, whereas acute intoxication with liquid hydrogen fluoride or fluoride salts was associated with suicidal or accidental ingestion of fluoride-containing products used in the home (World Health Organization, 1984).

Gaseous fluoride compounds attack tissues much more vigorously than fluoride salts. The toxicity of some gaseous inorganic fluoride compounds decreases in the following order: F_2O , F_2 , HF, BF_3 and H_2SiF_6 (World Health Organization, 1984).

The odour threshold for hydrogen fluoride is reported to range from 0.02 to 0.22 $mg\ m^{-3}$ (0.02–0.27 ppm) (Sadilova, 1967; Lindberg, 1968).

7.3.1 Acute and Short-term Health Effects

In general, practically all the organs and systems are affected in acute fluoride poisoning after oral exposure to hydrogen fluoride or fluorides. The manifestations include vomiting (sometimes blood-stained), diffuse abdominal pain of spasmodic type, diarrhoea, cyanosis, severe weakness, dyspnoea, muscle spasm, pareses and paralyses, cardiovascular disorders, convulsions and coma (Hodge and Smith, 1965; World Health Organization, 1984; Thiessen, 1988). Although much has been reported on acute poisoning by hydrogen fluoride and other fluorides, the exact cause of death is not yet known (Boink, 1993). Massive impairment of the functioning of vital organs results in cell damage and necrosis. Terminally, there is a characteristic shock-like syndrome (World Health Organization, 1984).

Gaseous fluorides can trigger a local reaction, causing considerable damage to the skin, eyes and respiratory tract (World Health Organization, 1984). Hydrogen fluoride vapour was reported to also cause skin burn (Browne, 1974; Largent, 1961). At a concentration averaging 2.1–4.7 mg m⁻³ (2.6–5.7 ppm), hydrogen fluoride was reported to cause very slight irritation of the face and eyes; frequent cutaneous erythema was noticed; in one case, flaking of the epithelium, resembling sunburn, was seen.

Machle et al. (1934) reported the effects of airborne hydrogen fluoride on two human subjects. The highest concentration that the subjects were able to tolerate for more than one minute was 100 mg m⁻³. At this level, there was smarting of the exposed skin in less than one minute, and conjunctival and respiratory irritation was marked. At

50 mg m⁻³ (61 ppm), the same effects were noticed with the exception of the skin irritation, but tickling and discomfort in the larger air passages were noticeable with each inspiration. At 26 mg m⁻³ (32 ppm), eye and nose irritation was mild and could be tolerated for several minutes. There was no coughing or sneezing. The taste of hydrogen fluoride was reported at all three concentrations.

Largent (1952) listed the increasing intensity of acute effects of increasing concentrations of gaseous fluorides on the basis of controlled exposures of volunteers as follows: 2.1 mg m⁻³ (3 ppm) caused no local immediate effects; 7 mg m⁻³ (10 ppm) caused discomfort in many subjects; 21 mg m⁻³ (30 ppm) revealed complaints in all subjects and made them object to staying in the test environment; brief exposure to 42 mg m⁻³ (60 ppm) caused definite irritation of the conjunctiva and nasal passages and tickling and discomfort of the pharynx and trachea; and 84 mg m⁻³ (120 ppm), the highest concentration tolerated (less than one minute by two male subjects), resulted in the previously mentioned effects and smarting of the skin. Thus, the NOAEL in this experiment for local effects was 2.1 mg F⁻ m⁻³.

Elkins (1959) reported complaints of nosebleeds in workers engaged in the hydrogen fluoride etching process and in one plant where welders were exposed to fluoride at 0.4–0.7 mg m⁻³.

In an experimental inhalation study with hydrogen fluoride, five human volunteers were exposed six hours per day, five days per week, for 10–50 days, at average concentrations of 1.42–4.74 ppm hydrogen fluoride (1.16–3.89 mg m⁻³). Slight irritation of the nose was noticed in all subjects at

concentrations averaging 2.59–4.74 ppm hydrogen fluoride (2.12–3.89 mg m⁻³), ranging from 1.8–7.9 ppm (1.5–6.5 mg m⁻³). No signs or symptoms of liver toxicity or respiratory tract irritation were reported at these average concentrations (Largent, 1961). The NOAEL for skin and eye irritation in this study was 0.9 mg m⁻³ (1.1 ppm). A NOAEL for systemic effects could not be established.

Pulmonary exposure to gaseous hydrogen fluoride may occur independently of or simultaneously with skin exposure. Continued inhalation of hydrogen fluoride results in coughing, choking and chills, lasting 1–2 hours after exposure. In the next one or two days, fever, coughing, chest tightness, rales and cyanosis may develop, indicating delayed pulmonary oedema (Dreisbach, 1971). The signs and symptoms progress for a day or two and then regress slowly over a period of a few weeks. At higher exposures to gaseous hydrogen fluoride, the delicate tissues of the lung may be intensely and even fatally irritated.

A report by Gaugl and Wooldridge (1983) suggested that pulmonary damage due to inhibition of surfactant synthesis may result from systemic fluoride poisoning, even if the fluoride was not inhaled. Death from acute fluoride poisoning, whether from hydrogen fluoride inhalation or burns from ingestion of fluoride salts, is usually from cardiac or respiratory failure and generally occurs within 24 hours (Heifetz and Horowitz, 1986; Thiessen, 1988).

As a result of an accident with the convection section of a hydrogen fluoride alkylating heater of an oil refinery, an estimated 24,000 kg of caustic hydrogen fluoride were released from a storage tanker. In total, 939 persons who were potentially

exposed to airborne hydrogen fluoride were examined for symptoms of intoxication, and their emergency room and hospital records were studied. Most persons present at the emergency room were female (56%) or black (60%), and their mean age was 33.9 years. The most frequently reported symptoms were eye irritation (41.5%), burning throat (21%), headache (20.6%) and shortness of breath (19.4%). Physical examination results were normal for 49% of the cases. Decreased pulmonary function was demonstrated by a pulmonary function test (42.3% < 80% of the predicted value for forced expiratory volume in the first second [FEV1]). Hypoxaemia (<80 mm Hg in 17.4%) and hypocalcaemia (<8.5 mg dL⁻¹ in 16.3%) were also noted. Ninety-four individuals were hospitalized, with an average stay of approximately two days, and more than 83% of all cases were discharged with a primary diagnosis of "hydrogen fluoride exposure." There were no fatalities. The ambient air concentration of hydrogen fluoride was not monitored (Vernon et al., 1991; Wing et al., 1991). Neither an effect level nor a NOAEL could be established.

Serum fluoride concentrations of 3–15.5 mg L⁻¹ have been associated with fatal cases of fluoride poisoning, from oral ingestion of fluorides, skin burns and inhalation of hydrogen fluoride (Greendyke and Hodge, 1964; Hodge and Smith, 1965; Yolken et al., 1976; Tepperman, 1980; Gosselin et al., 1984). One case was reported in which the serum fluoride level at autopsy was only 67 µg L⁻¹ (Burke et al., 1973), although one victim of oral fluoride (Na₂SiF₆) poisoning survived despite a serum fluoride concentration of 14 mg L⁻¹ six hours after ingestion (Yolken et al., 1976).

The major route of clearance of excess fluoride from the body following poisoning is the urinary system, and urinary fluoride levels as high as 87 mg L⁻¹ (3.5 hours after the poisoning accidents) have been reported (Burke et al., 1973; Yolken et al., 1976). Fluoride concentration also increased in soft tissues following fatal intoxication. Levels of 10.6 mg kg⁻¹, 4.6–11.6 mg kg⁻¹, 4.4–11.2 mg kg⁻¹ and 12.4–15.6 mg kg⁻¹ have been reported in heart, kidney, liver and lung tissue, respectively, following fatal intake of sodium fluoride (Hodge and Smith, 1965).

7.3.2 Chronic Health Effects

The clinical and epidemiological studies described in this section have been organized according to the predominant type of effect investigated or observed in each study.

7.3.2.1 Effects on the Respiratory System

Leidel et al. (1967) studied the effects of chemical irritations on exposed workers (305) in a chemical plant where hydrogen fluoride was only one of the primary chemicals produced. The control group consisted of 88 workers in a box plant. Twenty-eight samples of airborne hydrogen fluoride were taken, with sampling periods ranging from 10 to 30 minutes. The concentration of hydrogen fluoride ranged from 0.07 to 10.0 ppm (0.06–8.2 mg m⁻³), with a mean of 1.03 ppm (0.85 mg m⁻³). The samples for particulate fluoride were all under 0.5 mg m⁻³ (0.1–0.49 mg m⁻³). The mean age of the chemical plant workers was 44 years, 14 years older than that of the box plant workers. The observed values for forced vital capacity (FVC), one-second forced expiratory volume (FEV1) and FEV1/FVC for the total group were within

about 3% of the predicted normal values, with no significant difference between the chemical workers and the control group. The residual volume expressed as 5% of total lung volume was 30.8% in the chemical workers and 26.8% in the box plant workers, with both values within normal limits (35%, upper limit). This difference could be explained by the difference in average age of the two groups. If a correction were made for age and smoking, no effect of work-related exposure would be established. The urinary fluoride concentration before the shift in the exposed group ranged from 0.33 to 0.48 mg L⁻¹, compared with 0.95–26.6 mg L⁻¹ after the shift. For the control group, these ranges were 0.50–1.88 and 0.50–2.38 mg L⁻¹, respectively.

In a plant for the electrolytic extraction of aluminum, which began operating in 1973, 207 workers were medically examined in view of some complaints of respiratory symptoms, which they associated with occupational exposure. The exposures measured at different working places ranged between 0.27 (0.32 ppm) and 4.1 mg m⁻³ (5.0 ppm) for hydrogen fluoride, between 0.02 and 1.6 mg m⁻³ for particulate fluorides and between 0.08 and 4.0 mg m⁻³ for sulphur dioxide. The exposure levels were occasionally higher than the threshold limit values in Yugoslavia (1.7 mg m⁻³ [2.1 ppm] for hydrogen fluoride; 1 mg m⁻³ for fluoride expressed as F; and 10 mg m⁻³ for sulphur dioxide). The results of the study showed that only 4.9% of workers had symptoms defined as chronic bronchitis (87% of workers were <40 years of age). On the other hand, a rather large number (10.2%) complained of paroxysmal wheezing with dyspnoea. Out of 21 subjects with such complaints, 19 claimed that the broncho-constrictive symptoms appeared after they

had started to work in the potrooms. Only two of them had similar symptoms earlier. Pulmonary function tests revealed a slight decrease in the mean values (compared with the predicted values) of FVC and FEV1 and a higher decrease in the mean values of mean expiratory flow, particularly in those workers who complained of paroxysmal wheezing with dyspnoea. Owing to the technological process used in the plant, it is most likely that the respiratory effect is due to the action of hydrogen fluoride (and particulate fluoride). However, the mechanism of increased respiratory susceptibility remains to be clarified (Saric et al., 1979). The design of the study did not permit an exact identification of the toxic cause or the establishment of a NOAEL.

A group of 74 workers in a hydrogen fluoride plant who had been exposed to hydrogen fluoride (periodically severely) for an average of 2.7 years was studied. On a few occasions, there had been cases of upper respiratory tract irritation. Repeated chest X-rays over a five-year period did not reveal any visible evidence of lung changes and did not differ from those of unexposed workers. Periodic clinical examinations did not reveal any incidence of pulmonary infection in the exposed workers (Evans, 1940).

Johnson et al. (1973) conducted a study of an aluminum reduction facility for the primary purpose of collecting and analysing airborne dust, coal tar, pitch volatiles, fluorides, carbon monoxide and sulphur dioxide. Although obstructive airway changes had developed in some workers, the investigators concluded that it was not justified to link the changes to a particular exposure because of the many contaminants involved in the potroom area.

A study was carried out on 1,242 aluminum smelter workers to assess the impact on the lungs of exposure to multiple pulmonary irritants, including gaseous and particulate fluoride and sulphur dioxide. A pulmonary risk index was generated for each worker which accounted for the nature, intensity, duration and multiplicity of exposure. History and symptoms of pulmonary disease, spirometry and chest X-rays were performed on all 1,242 individuals, whereas single-breath diffusing capacity was tested in 460. The results were then compared in those at low, moderate and high pulmonary risk. Highly significant differences were observed between those with abnormal FEV1s and FEFs and a high pulmonary risk index. Twenty-nine percent of all the workers and 10% of the 460 in whom the diffusing capacities were tested were also found to be abnormal (Carnow and Conibear, 1978). No exposure levels were indicated, and no association could be drawn between the results and exposure to hydrogen fluoride alone (only an abstract was available).

Ernst et al. (1986) explored the relationship between respiratory symptoms and lung function and exposure to ambient air pollution consisting of particulate and gaseous fluorides. The subjects were 253 North American Indian children 11–17 years of age living on the Akwasasne reserve, which is adjacent to an aluminum smelter. Among boys, closing volume was increased in those raised closest to the smelter compared with those having lived most of their lives farthest from this source of air pollution. The ambient hydrogen fluoride concentration in the air was not reported. In both sexes, there was a significant linear relationship between increasing CV/VC% and the amount of fluoride contained in a spot urine sample. The authors concluded

that exposure to fluoride air pollution in the community may be associated with abnormalities in small airways. The implication of these abnormalities for future respiratory health is unknown. No fluoride concentrations in urine were included in this report.

Children living in the vicinity of a phosphate processing facility and exposed to fluoride concentrations ranging from about 100 to 500 $\mu\text{g m}^{-3}$ exhibited an impairment of respiratory function. It is noted, however, that it is unknown whether the concentrations were gaseous or total fluoride, and no other pollutants were recorded (Gezondheidsraad, 1981). In another study, no effects on respiratory function were observed at gaseous fluoride concentrations up to 16 $\mu\text{g m}^{-3}$ (Biersteker and Boleij, 1986).

The effects on the respiratory tract as observed in health assessments with regard to exposure were discussed by Wibowo and Zielhuis (1986). Occupational exposure to inorganic fluoride at concentrations of 500 $\mu\text{g m}^{-3}$ (200 $\mu\text{g/m}^3$ gaseous fluorides) was concluded to cause an increase in the incidence of irritations of the upper respiratory tract. However, these results may have been influenced by other air pollutants. In another study, exposures to considerably higher levels of gaseous hydrogen fluoride (1,700 $\mu\text{g m}^{-3}$, or 2,074 ppb) were reported not to cause any appreciable effect on the respiratory tract (Wibowo and Zielhuis, 1986).

Lung function and bronchial reactivity were measured in 38 aluminum potroom workers with no airway symptoms and in 20 healthy referents (office workers). All participants were non-smokers. The magnitude of exposure to airborne dust (alumina) and fluorides was determined. The mean

exposure values were 1.77 (0.49–4.5) mg m^{-3} for total dust and 0.31 (0.1–0.5) mg m^{-3} for total (gaseous and particulate) fluorides. The "worst-case" estimates showed mean values for gaseous fluorides of up to 3.13 mg m^{-3} during work with gas skirt exchanges. The aluminum potroom workers had obstructive lung function impairment with a significant decrease in expiratory flow and an increase in residual volumes. Diffusing capacity was found to be lower than in the controls. No bronchial hyperreactivity was found in the aluminum potroom workers. The exposure to inhaled alumina and particulate and gaseous fluorides in the plant was low, 15–20% of the Swedish exposure limits (10 mg m^{-3} for alumina and 2 mg m^{-3} for fluorides). The finding of only modest lung function alterations with no bronchial hyperreactivity in the aluminum potroom workers is not consistent with the results of other investigators. This discrepancy can probably be explained by the fact that the exposure to inhaled contaminants in the investigated aluminum plant was low (Larsson et al., 1989).

Golusinski et al. (1973) examined the mucosa in 130 aluminum plant workers exposed to hydrogen fluoride. Monitoring of hydrogen fluoride concentrations in the atmosphere of electrolytic halls showed that the concentration of hydrogen fluoride often considerably exceeded 0.5 mg m^{-3} (0.6 ppm, the Polish threshold limit value). In 30% of these workers, chronic inflammatory changes, either hypertrophic or atrophic rhinitis, were observed in the nasal mucosa. Biopsy specimens of septal mucosa were examined histologically. In the patients with hypertrophic rhinitis, numerous inflammatory infiltrates, consisting of mononuclear cells, were observed. The blood vessels were dilated, and extravasations of erythrocytes

were noted. The connective tissue stroma showed evidence of oedema and hyperactivity of the sero-mucous glands. In the atrophic mucosa, fibrosis and hyalinization of connective tissue stroma were seen associated with moderate inflammatory infiltrates and evidence of hypoactivity of the glands.

Burr et al. (1990) studied the health situation of workers in a glass company as related to exposure to noise and a number of air pollutants, such as organic solvents and hydrogen fluoride. The exposure to hydrogen fluoride ranged from 0.34 to 3.0 mg m⁻³ (0.41–3.66 ppm). As well as the 171 workers' complaints of occupational pneumoconiosis, hearing loss and cumulative disorders were also diagnosed. The authors concluded that the workers were potentially exposed to cumulative trauma, acid mists and noise. No specific associations between hydrogen fluoride exposure and toxic symptoms could be concluded, owing to multiple exposures.

Following an accident at an oil refinery in Texas City, Texas, which released about 40,000 pounds of hydrogen fluoride (Vernon et al., 1991; Wing et al., 1991), a population-based epidemiological study was conducted to evaluate the impact of the accident on the health of the surrounding community (Dayal et al., 1992). Exposure assessment was done using a multipronged approach through a door-to-door survey of 10,811 individuals. A symptom survey resulting in 1,994 completed interviews was conducted with a stratified random sample selection. The results showed a strong relationship ($p < 10^{-4}$) between the exposure (not given in the publication) and symptoms reported following the accident and two years later, most notably breathing and eye symptoms. However, substantial improvement in health

was reported over the two-year period, regardless of the exposure level. Although the authors recognized that recall bias and behavioural sensitization possibly led to an overestimation of the effect, they concluded that it was difficult to dismiss the interpretation that hydrogen fluoride exposure indeed caused health problems in the community that continued for at least two years after the accident. No hydrogen fluoride or other gaseous fluoride concentrations in ambient air were reported.

A case report describes the symptoms of a 57-year-old worker who had been working for 10 years, eight hours a day, in the alkylation unit of an oil company, where volatile fluorides were possibly released to the atmosphere during loading and unloading and where tar residues that liberated fluoride fumes on exposure to air were frequently produced. The worker was possibly exposed to variable and unknown concentrations of hydrogen fluoride, either from ambient air or from fumes. Episodes of obvious acute poisoning were not uncommon, when immediate contact with the fumes caused symptoms and signs of intense eye irritation, tearing, blurred vision and marked dyspnoea with severe respiratory tract pain and coughing. If he could not get quickly away, the worker developed nausea, epigastric pain, vomiting and sudden weakness. Such apparent acute episodes occurred approximately 10–15 times a year. The noxious and irritating odour of hydrogen fluoride was stated to have been identified. Within 1–2 years after starting this work, the worker began having rectal incontinence with diarrhoea. He developed severe headaches, increasing weakness upon exertion and pain in the lower back. Leg and back pain became so severe that medical consultation was

necessary after eight years. The symptoms progressed, and intellectual dysfunction was also diagnosed. Finally, osteoarthritis of the spine was diagnosed, abnormalities in the bladder were detected and lung function was decreased considerably (Waldbott and Lee, 1978). No accurate exposure levels were measured.

7.3.2.2 Effects on Bones and Teeth

Roentgenological examinations of the lumbar spine of hydrogen fluoride workers showing high urinary fluoride concentrations (4.31–26.6 mg L⁻¹) did not show any skeletal fluorosis. In a follow-up study of four workers two years later, one worker showed a slight first-degree osteosclerosis, which was not associated with disability. This worker had been employed for 11 years in a hydrogen fluoride plant (Leidel et al., 1967).

Peperkorn and Kahling (1944) performed clinical and radiological examinations of 47 workers exposed to airborne hydrogen fluoride, hydrofluoric acid and cryolite. No quantitative exposure data were given. Nearly all of the workers complained of mild to moderate back pain and stiffness, with pain in the cervical spine in some cases. Some complained of pain in the thighs and knees. The majority of the men reported shortness of breath on exertion. There was little evidence of cough, expectoration or asthmatic conditions. Except for a few cases of skin burns, physical and chemical clinical findings were normal. Seventy-two percent of the workers showed osteosclerotic changes varying from first degree to third degree. Characteristics of first-degree osteosclerosis included increased bone density and thickened and misshapen structure of the trabeculae, with the marginal contours of the bones exhibiting slight blurring. In second-

degree osteosclerosis, the findings were more pronounced. The outer boundaries of the bones had become more irregular, insertions of the tendons had started to calcify and the cortical substance of the long bone was widened, restricting the medullary canal. In third-degree osteosclerosis, the bone had become radiographically opaque and the insertions of tendons, ligaments and interosseous membranes were calcified. The first evidence of changes was found in the pelvis and lumbar spine. As the process advanced, the changes spread to the rest of the spinal column and the ribs, with extremities affected last. The degree of radiological changes increased with the duration of employment. No exposure data were given.

A case of intoxication by long-term exposure (15 years) to airborne hydrogen fluoride of a 40-year-old worker in a hydrogen fluoride plant was reported by Peperkorn and Kahling (1944). After seven years of employment, the worker began to have "rheumatic pains," which, over the years, increased until he became totally disabled. He complained of stiffness in all joints, except hands and feet. He had difficulty breathing when walking or climbing. He was prematurely aged, emaciated and pale, had a stiff posture and walked with small steps. Chest expansion was limited, as were movements of the spine, hips and shoulders. Red and white blood cell counts, sedimentation, blood calcium and urinalysis were all reported normal. No urinary fluoride levels were obtained. X-rays of the skeletal system showed third-degree osteosclerosis (Heitman, 1976). Exposure levels of airborne hydrogen fluoride were not determined.

A clinical study was carried out on a group of workers exposed intermittently to hydrogen

fluoride and, to a lesser degree, calcium fluoride dust in a hydrofluoric acid manufacturing plant, during an observation period of five years. The exposure took place during repair, and concentrations ranged from 11 to 21 mg F⁻ m⁻³ (13–26 ppm). The mean urinary fluoride excretion of exposed workers was 3.65 mg L⁻¹ (ranging from 4 to 24 mg L⁻¹). No significant effects on chest X-ray, haemoglobin or red and white blood cell counts were detected. Roentgenological examinations of the pelvis and spine of 10 men working with the greatest potential exposure did not show skeletal fluorosis after five years of intermittent exposure (Machle and Evans, 1940).

Dale and McCauley (1948) provided data on the medical and dental conditions of workers engaged in the production of hydrofluoric acid for 2–33 years. Eleven unexposed office and warehouse workers served as controls. No workplace airborne hydrogen fluoride levels were determined, but it was reported that window glass in a building housing the hydrofluoric acid retorts corroded in a few months' time and had to be replaced periodically. Some workers in close proximity to the retorts experienced transitory hyperaemia of the exposed skin. The skin of the faces and hands appeared dehydrated, roughened and irritated in the majority of the workers. Dental examinations showed fewer caries and fillings in the exposed group. In the trabecular pattern of the osseous structure of the upper and lower jaws, changes were seen in 24 of the 40 workers, and questionable changes in eight. The bone changes were characterized by an increase in the number and thickness of trabeculae and a corresponding decrease in the intratrabecular and canalicular species. The urinary fluoride excretion of 34 exposed

workers in spot samples ranged from 0.89 to 49.3 mg L⁻¹ (with a mean of 10.8 mg L⁻¹).

In a clinical study workers at a phosphoric acid producing plant, hydrogen fluoride and silicon tetrafluoride were released, but the airborne fluoride concentration was maintained below 3 ppm and averaged 2.4 ppm gaseous fluoride. Medical and radiological examinations revealed no abnormalities. No consistent urinary fluoride excretion above 5 mg L⁻¹ was observed (Rye, 1961).

Derryberry et al. (1963) reported the prevalence of osteosclerosis in 74 workers in a fertilizer manufacturing plant in relation to fluoride exposure. Fluorides in the form of dust and gases in varying combinations and concentrations were produced throughout the process. A weighted airborne exposure was calculated for the period of employment of each worker. The individual exposure to fluoride was 0.50–8.32 mg m⁻³, with 1.78–7.73 mg m⁻³ being associated with increased bone density observed in workers. The difference in averages between the increased bone density group (average fluoride exposure 3.38 mg m⁻³) and the remainder of the exposed group, which showed significantly less bone density (average fluoride exposure 2.62 mg m⁻³), was evaluated by the National Institute for Occupational Safety and Health (1977). Within the group of workers with increased bone density, 60.9% of the urine samples contained fluoride at concentrations of 4.0 mg L⁻¹ or greater, compared with 47.5% of the samples submitted by the group of workers without increased bone density. This difference was significant (ranging from p < 0.02 to p < 0.08). The average fluoride concentrations in urine for the increased bone density group and the group without an

increase were 5.12 and 4.53 mg L⁻¹, respectively. These results demonstrate an association between increased fluoride concentrations in the urine and an increase in suspected cases of osteosclerosis.

Kaltreider et al. (1972) reported the results of roentgenographic examinations and urinary fluoride studies of potroom workers in two aluminum plants. In one plant, 76 of 79 potroom workers X-rayed revealed increased bone density. Forty-six (58.2%) were classified as having slight fluorosis, showing only accentuation of trabeculation and slight blurring of the bone structure; four (5.1%) had moderate diffuse structureless bone appearance; and 26 (32.9%) were classified as having marked fluorosis. Limited motion of the dorsolumbar spine was found in 22 (20.6%) of the entire group of 107 potroom workers and in none of the control group. The average fluoride exposure (eight-hour working day) for the potroom workers ranged from 2.4 to 6.0 mg m⁻³. The average urinary fluoride concentration in spot samples ranged from 8.7 to 9.6 mg L⁻¹. The average urinary fluoride excretion for the controls was 0.7 mg L⁻¹. The investigation in the second potroom plant revealed no useful information on possible toxic effects caused by exposure to airborne fluorides.

Massmann (1981) reviewed occupational epidemiological studies on fluorine and its inorganic fluorides. In Germany, the threshold limit values were reported to be 0.1 ppm for fluorine, 3 ppm for hydrogen fluoride (2.5 mg m⁻³) and 2.5 mg m⁻³ for fluoride. Exceedances of these threshold limit values 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. The most sensitive effect of

long-term exposure to fluoride at levels above the threshold limit value is skeletal alterations, or osteosclerosis. Following this effect, exostosis and calcinosis of the ligaments occur.

In Germany, fluorosis with skeletal alterations rarely occurs. In a study in which urine samples of individuals exposed to 2.4 ppm airborne fluoride for eight hours were measured, it was concluded that the fluoride concentration in urine increased in the first two hours from 0.5 to 4 mg L⁻¹ and in the next 10 hours to 8 mg L⁻¹; it then decreased in the next 12 hours to the initial concentration (Rye, 1961; Massmann 1981). Based on these observations, Massmann (1981) proposed a limit for fluoride of 7.0 mg L⁻¹ in a 24-hour urine sample.

In a study of 1,242 employees in an aluminum smelter using the Soderburg process, Carnow and Conibear (1981) reported that clinical musculoskeletal effects can occur before skeletal fluorosis becomes apparent radiologically. Questionnaire responses suggested an increased incidence of musculoskeletal diseases with increasing total fluoride exposure during employment. On the other hand, X-rays of the chest and lumbar spine failed to indicate any differences related to the exposure index. As recognized by the authors of this paper, this group of workers was heterogeneous, chemical exposures were mixed and ergonomic problems might have occurred. Unfortunately, the fluoride levels and the lengths of exposure were not reported, thus making a dose-response relationship impossible to determine. The employees of the same smelter were examined four years later by Chan-Yeung et al. (1983). The exposure levels were determined, and two control groups were examined. The fluoride

exposure level in the potroom was about 0.5 mg m^{-3} for the subgroup with the highest exposure. The authors were not able to confirm the finding of Carnow and Conibear (1981) that clinical musculoskeletal effects could occur before skeletal fluorosis becomes apparent radiologically.

It has been suggested that no discernible radiological or clinical signs of osteosclerosis will appear if the air concentrations of inorganic fluoride in the workplace remain below 2.5 mg m^{-3} and the urinary fluoride concentration of workers does not exceed 4 mg L^{-1} pre-shift (collected at least 48 hours after previous occupational exposure) and 8 mg L^{-1} post-shift over long periods of time (Dinman et al., 1976a; Hodge and Smith, 1977). U.S. recommendations for the threshold limit value for air fluoride have been established on the basis of these data (National Institute for Occupational Safety and Health, 1977). However, some countries recommend lower values. The former Soviet Union recommended 1.0 mg m^{-3} as the threshold limit value for air fluoride concentrations expressed as hydrogen fluoride (Gabovich and Ovrutskiy, 1969; International Labour Organization, 1980; U.S. Environmental Protection Agency, 1980). The correlation between fluoride levels in the ambient air, fluoride levels in the urine and the development of skeletal changes needs further documentation (World Health Organization, 1984).

In a few individual cases of human exposure to a high concentration of airborne hydrogen fluoride, mottling of the teeth was described (Heitman, 1976; World Health Organization, 1984). No other cases of dental fluorosis after exposure to airborne fluorides have been reported. The exposure levels at which these effects occur have not been provided.

7.3.2.3 Effects on Kidneys

There are no clear indications from clinical case studies or epidemiological studies that airborne hydrogen fluoride or other fluorides cause nephrotoxicity. Therefore, a NOAEL relating to potential nephrotoxicity for airborne hydrogen fluoride or other fluorides cannot be established. The information on potential nephrotoxicity comes from studies on humans exposed orally or parenterally to hydrogen fluoride, other fluorides or fluorine compounds.

In cryolite workers, Roholm (1937) found only insignificant haematuria and no albuminuria. A possible relationship between albuminuria and fluoride exposure was suggested by Derryberry et al. (1963), but Kaltreider et al. (1972) were unable to show any chronic effects on the kidney. No renal disorder has been related to fluoride in areas of endemic fluorosis (Jolly et al., 1969) or to cases of industrial fluoride exposure (Dinman et al., 1976b; Smith and Hodge, 1979). No cases of renal signs or symptoms are mentioned in connection with prolonged intake of fluoride in the treatment of osteoporosis and osteospongiosis (Causse et al., 1980; Schamschula, 1981; Dixon, 1983), although a thorough examination of kidney function may not have been carried out. No indications of increased frequency of kidney diseases or disturbed kidney functions have been recognized in areas with fluoride concentrations in water of 8 mg L^{-1} (Leone et al., 1954, 1955), $2.0\text{--}5.6 \text{ mg L}^{-1}$ (McClure, 1946; Geever et al., 1958) and 1.0 mg L^{-1} (Summens and Keitzer, 1975).

Although there are no reports of fluoride-induced chronic renal disorders in healthy individuals, several studies have dealt with the possible influence of fluoride on people with manifest kidney diseases. In patients

with kidney failure, fluoride excretion is decreased, and the ionic plasma fluoride concentration is higher than normal (Juncos and Donadio, 1972; Berman and Taves, 1973; Hanhijaervi, 1974). The capacity of the skeleton to store fluoride may provide a sufficient safety margin (Hodge and Smith, 1954; Hodge and Taves, 1970). On the other hand, it also seems plausible that an increased plasma fluoride concentration may result from fluoride liberation from the bone resorption process involved in certain kidney diseases. Patients with diabetes insipidus may absorb excess amounts of fluoride because of the large quantities of fluids ingested (World Health Organization, 1984; Thiessen, 1988).

In the case of fluoride-containing anaesthetic agents, nephrotoxic effects were discovered as a side-effect related to the metabolites of methoxyflurane or enflurane (Hagood et al., 1973; World Health Organization, 1984). Kidney damage is related to the high serum levels of fluoride and may show up days after anaesthesia.

Although peak fluoride levels associated with acute nephrotoxic effects have frequently been higher than $50 \mu\text{g L}^{-1}$, the total dose may be of more importance (Marier, 1982). Changes in kidney function have been reported at lower fluoride levels (Jarnberg et al., 1979). At serum fluoride levels averaging about $6 \mu\text{mol/L}$ after enflurane anaesthesia, no nephrotoxic effects were seen, but blood and urine levels of phosphorus changed considerably (Duchassing et al., 1982). It is not yet clear whether this circulating fluoride is directly related to the nephrotoxicity or whether fluoride is only indicative of metabolites of enflurane and methoxyflurane that formed during the biotransformation and that caused the nephrotoxicity. Therefore,

these data are difficult to apply to the case of exposure to airborne hydrogen fluoride or other fluorides and the possibility of induction of nephrotoxicity.

An important finding of the previous studies is that people already suffering from insufficient kidney function might be at risk from the toxic effects of fluorides owing to a decreased elimination of fluoride.

7.3.2.4 Carcinogenicity

No specific epidemiological evidence is available on the potential carcinogenicity to humans of hydrogen fluoride or other inhaled fluorides. Increased rates of cancer have been reported for workers in several occupations involving possible fluoride exposure, including aluminum production, fluorspar mining and stainless steel pickling (de Villiers and Windish, 1964; Ahlborg et al., 1981; World Health Organization, 1984; Grandjean et al., 1985). However, all these situations involved mixed exposures to several chemicals (e.g., radon in fluorspar mining, polycyclic aromatic hydrocarbons in aluminum production, and metal compounds and irritating acids in the stainless steel pickling house), and fluoride could not be specifically implicated as the cause of the cancers (de Villiers and Windish, 1964; Drury et al., 1980; Ahlborg et al., 1981; World Health Organization, 1984; Grandjean et al., 1985). A correlation has also been demonstrated between cancer rates and industrial pollution from steel mills, which emit fluoride among other things; again, no specific pollutant could be identified as the major cause of the increased cancer rates (Drury et al., 1980; Thiessen, 1988).

The possible carcinogenic potential of fluoride in drinking water has been investigated by comparing rates of cancer in

areas with artificially and naturally fluoridated water. The International Agency for Research on Cancer (1982) concluded that when "proper account was taken of the differences among population units, in demographic composition, and in some cases also in their degree of industrialization and other social factors, none of the studies provided any evidence that an increased level of fluoride in water was associated with an increase in cancer mortality." The U.S. National Academy of Sciences (1977) and the U.S. Environmental Protection Agency (1985) also agreed that the available information does not suggest that fluoride in drinking water has increased the rate of cancer mortality. The U.S. Environmental Protection Agency (1985) stated that "there is not enough information to conclude that fluoride presents a cancer risk to humans," but it has not officially classified fluoride or hydrogen fluoride with respect to carcinogenicity (Thiessen, 1988).

7.3.2.5 Reproductive Effects and Teratogenicity

Few reports are available concerning industrial fluoride exposure of women. The one available epidemiological study of female workers in a superphosphate plant found a higher incidence of gynaecological problems (e.g., menstrual irregularities, vaginal and uterine inflammation, toxicosis during pregnancy, untimely discharge of amniotic fluid) in production workers than in the control group of office workers and housewives (Hodge and Smith, 1977; Smith and Hodge, 1979). The production workers were exposed to dust concentrations of 5–57 mg m⁻³ and fluoride concentrations of 0.8–2.8 mg m⁻³ but specific information is not available on the possible correlation of gynaecological problems with fluoride concentrations in the workplace air or in the urine of the workers. No difference between groups was found in the numbers of pregnancies, miscarriages or births.

No reports of increased incidence of either spontaneous abortions or births of abnormal fetuses have come from communities in the United States with natural fluoride levels of 4 mg L⁻¹ or more in drinking water (Hodge and Smith, 1977; Smith and Hodge, 1979). The U.S. Environmental Protection Agency (1985) concluded that there is inadequate evidence to support an association between fluoride in U.S. drinking water and either reproductive or teratogenic effects (Thiessen, 1988).

7.3.2.6 Other Health Effects

Other effects of chronic fluoride exposure in humans have been reported occasionally, including thyroid injury, anaemia, hypersensitivity and dermatological reactions

(Spira, 1944; Hodge, 1960; Waldbott, 1961, 1973, 1980, 1981; McLaren, 1976; Waldbott and Lee, 1978). None of these effects has been convincingly established, particularly for fluoride concentrations likely to be encountered by the general public (Princi, 1960; Kaltreider et al., 1972; U.S. National Academy of Sciences, 1977; Smith and Hodge, 1979; World Health Organization, 1984; U.S. Environmental Protection Agency, 1985). The U.S. Environmental Protection Agency (1986) established an oral Reference Dose for fluoride of 0.06 mg kg^{-1} body weight per day for children, an intake that corresponds to a fluoride level of 1 mg L^{-1} (1 ppm) in water. Neither dental nor skeletal fluorosis occurs at this level. An inhalation reference dose is not available (Thiessen, 1988).

7.4 SUMMARY OF HEALTH EFFECTS OF INORGANIC FLUORIDES AS REPORTED BY CEPA

Inorganic fluorides, including gaseous fluorides, were assessed as part of the requirements of the Canadian Environmental Protection Act (CEPA) (Government of Canada, 1993). Carcinogenic effects of inorganic fluorides were reviewed in a large number of ecological studies, in studies with laboratory animals and in epidemiological studies. The CEPA report concluded that the available data are inadequate to assess carcinogenicity in humans. This conclusion supports earlier conclusions by the International Agency for Research on Cancer (1982), the World Health Organization (1984) and the U.S. Environmental Protection Agency (Thiessen, 1988).

There is evidence that fluoride is genotoxic, based on the outcome of *in vitro* and *in vivo* studies. Sodium fluoride induced recessive lethal mutations in *Drosophila melanogaster* and cytogenetic damage after intraperitoneal injections in rodents. Generally, however, in studies in which fluoride was administered to laboratory animals by routes of exposure similar to those by which humans are normally exposed (i.e., orally), fluoride had no effect upon the frequency of chromosomal aberrations, micronuclei, sister chromatid exchange, DNA strand breaks or sperm morphology. The mechanism by which sodium fluoride induces genetic alterations is not known; however, it is not likely due to an interaction between the fluoride ion and DNA. Rather, it may be a secondary effect of the actions of fluoride that results from its inhibition of enzymes involved in DNA synthesis and/or repair. (Government of Canada, 1993)

Because there are inconclusive data on the carcinogenic effects of inorganic fluoride and because inorganic fluoride is not directly genotoxic to DNA, the CEPA assessment (Government of Canada, 1993) based its toxicological evaluation on the NOAEL for the most sensitive phenomenon in long-term studies in both laboratory animals and humans. Based on the available data, it is evident that, following long-term exposure, skeletal effects in humans occur at dose levels of exposure lower than those associated with other adverse health effects, which is likely a consequence of the accumulation of inorganic fluoride almost exclusively in bone. Therefore, effects on the skeleton are considered to be the most relevant in assessing the toxicological effects of long-term exposure to inorganic fluorides. The lowest reported NOAEL for effects of fluoride on the skeleton in Sprague-Dawley

rats was 1.8 mg kg^{-1} body weight per day (and for Fischer-344 rats, 2.7 mg kg^{-1} body weight per day). However, rats are generally considered to be less sensitive than humans or larger animals to the toxicological effects of fluorides, owing to differences in toxicokinetics and skeletal development. Dogs and pigs are considered more appropriate models for the examination of the potential effects of various agents on the skeleton in humans. However, only short-term experiments with fluorides in dogs and pigs have been performed. Administration of fluoride at 0.32 and 2 mg kg^{-1} body weight per day to dogs and pigs, respectively, did not cause overtly pathological effects on the bone or on the general health of the animals.

Owing to the availability of data, although limited, on exposure–response relationships in humans and the interspecies variations in response to fluoride, the results of epidemiological studies on the effects of fluoride in humans were taken into account in the derivation of an effect level for inorganic fluoride. Case reports or descriptive ecological studies of skeletal fluorosis or osteosclerosis were not adequately documented. There is also limited quantitative information on exposure to inorganic fluoride and the development of skeletal effects in occupationally exposed workers (Government of Canada, 1993). Inconsistent results of inherently limited cross-sectional studies of small populations exposed to often unspecified concentrations of fluoride in the vicinity of industrial sources contribute little to an assessment of an exposure–response relationship for skeletal effects associated with exposure to fluoride. Information obtained from clinical studies, in which sodium fluoride was administered to patients for the treatment of osteoporosis, was considered to be inadequate, owing to

the limitations of the protocol and characteristics of the patients in these studies. Moreover, these clinical studies were undertaken to assess the considered beneficial effects. There are also limitations in the experimental design of epidemiological investigations. In addition, owing to the lack of data on individual exposures in epidemiological studies, it is difficult to derive meaningful conclusions concerning the exposure–response relationship for possible skeletal effects associated with exposure to fluoride.

Estimating an effects threshold for the development of skeletal fluorosis (or related changes) in humans exposed to inorganic fluoride is further complicated by differences in the radiological diagnosis of early-stage skeletal fluorosis among health care professionals, as well as by the multiplicity of factors that may influence the amount of fluoride deposited in bones. (Government of Canada, 1994)

Nevertheless, considering the limitations of human studies and complicating factors involved, when the results are evaluated collectively, the available data indicate that potentially adverse effects associated with skeletal fluorosis are likely to be observed at fluoride intakes greater than approximately $200 \text{ } \mu\text{g kg}^{-1}$ body weight per day. Although the relative risk of hip, wrist or spinal fracture was increased in some groups of women residing in an elevated fluoride community ($72 \text{ } \mu\text{g kg}^{-1}$ body weight per day) compared with control communities, the estimated intake of fluoride by these women was likely underestimated, and the calcium intake was only 25% from normal. It is concluded, therefore, on the basis of available data, that skeletal fluorosis is likely to be observed at intakes greater than approximately

200 $\mu\text{g kg}^{-1}$ body weight per day. Moreover, predicted concentrations of fluoride in bone resulting from a daily fluoride intake of 200 $\mu\text{g kg}^{-1}$ body weight per day or higher are within the range of those reported to be associated with effects on the skeleton (Government of Canada, 1993).

Based on the limited available data, adverse effects upon haematopoietic, hepatic or renal function are not expected to occur at this fluoride intake level of 200 $\mu\text{g kg}^{-1}$ body weight per day, but at fluoride levels of about 387 $\mu\text{g kg}^{-1}$ body weight per day or higher.

There are insufficient quantitative data available from studies in humans from which to conclude unequivocally that exposure to this level of inorganic fluoride would have adverse effects upon human reproduction and development or on the central nervous and immune systems (Government of Canada, 1993).

The CEPA report concluded that, based on available information, the estimated average daily intakes of inorganic fluoride, which range from approximately 0.5 to 160 μg fluoride by various age groups in the general population (or up to 167 μg fluoride/kg bw/day by those in the vicinity of point sources of inorganic fluorides) are less than the level (200 μg fluoride/kg bw/day) at which adverse effects upon the skeleton (most sensitive end-point on the basis of available data in humans) are anticipated. (Government of Canada, 1993)

relatively low and are not expected to pose a significant problem with respect to human exposure in the general population.

7.5 HUMAN EXPOSURE ASSESSMENT

Fluorides exist in both gaseous and particulate forms. In Canada, ambient concentrations of gaseous fluorides are

The levels of fluoride in ambient air in most parts of Canada are generally low or undetectable (i.e., $<0.05 \mu\text{g m}^{-3}$), although available data are limited. The average (monthly) mean concentration of fluoride in an unspecified number of samples of ambient air collected from a residential area in Toronto, Ontario (January 1981 – July 1981), was $0.03 \mu\text{g m}^{-3}$ (detection limit not specified) (McGrath, 1983). This is similar to the mean fluoride concentration of $<0.05 \mu\text{g m}^{-3}$ (detection limit $0.05 \mu\text{g m}^{-3}$) reported for 4,411 samples of ambient air collected in 1968 from 29 rural and 147 non-industrial urban locations throughout the United States; fluoride was not detected in any of the rural samples ($n=724$), whereas the concentration of fluoride in urban air ($n=3687$) ranged from <0.05 to $1.65 \mu\text{g m}^{-3}$, (Government of Canada, 1993).

For additional information on environmental levels of hydrogen fluoride in Canada, refer to section 3.4.

Higher ambient concentrations of gaseous fluorides may be observed in the immediate vicinity of industrial sources. Monitoring data indicate that ambient air concentrations measured in the vicinity of fluoride-emitting industries can be up to an order of magnitude greater than concentrations in ambient air sampled at other locations. Industrial sources found to release gaseous fluorides include aluminum smelters, steel plants and phosphorus plants. These sources have been monitored in 11 locations across Canada and are listed in table 5. Monitoring data for gaseous fluorides in air surrounding industries clearly show concentrations much higher than in rural and urban areas. Mean concentrations are approximately $1.0 \mu\text{g m}^{-3}$. Concentrations as high as $23.08 \mu\text{g m}^{-3}$ have also been

recorded (Environment Canada, 1988, 1989).

No information on the concentration of fluoride in the indoor air of homes within Canada has been identified (Government of Canada, 1993). It may be assumed that some gaseous fluorides enter the indoor air environment in conjunction with the infiltration of outdoor air.

The estimated upper bound of daily intake of gaseous fluorides from ambient air by five age groups of Canadians in several locations across the country are shown in table 9 (McGrath, 1983; Health and Welfare

Canada, 1992; Government of Canada, 1993; Government of Canada, Supporting Documentation, 1993; Environment Canada, 1994).

Table 9 Estimated upper bound of daily intake of gaseous fluorides

		Age and daily intake ($\mu\text{g}/\text{kg}$ body weight per day)				
Location	Mean conc. in air ($\mu\text{g m}^{-3}$)	0–6 months ^a	7 months – 4 years ^b	5–11 years ^c	12–19 years ^d	20+ years ^e
Ambient air ^f	0.03 ^g	0.01	0.01	0.01	0.01	0.01
Cornwall, Ont.	0.79	0.23	0.30	0.35	0.29	0.26
Cornwall, Ont.	0.85	0.24	0.33	0.38	0.31	0.28
Cornwall, Ont.	0.43	0.12	0.17	0.19	0.16	0.14
Toronto, Ont.	0.07	0.02	0.03	0.03	0.03	0.02
Brampton, Ont.	0.73	0.20	0.28	0.32	0.27	0.24
Long Harbour, Nfld.	0.15	0.04	0.06	0.07	0.06	0.05
Long Harbour, Nfld.	0.14	0.04	0.05	0.06	0.05	0.05
Trail, B.C.	0.59	0.17	0.23	0.26	0.22	0.19
Arvida, Que.	0.67	0.19	0.26	0.30	0.25	0.22
Grande Baie, Que.	0.10	0.03	0.04	0.04	0.04	0.03
Laterrière, Que.	0.14	0.04	0.05	0.06	0.05	0.05
Beauharnois, Que.	0.10	0.03	0.04	0.04	0.04	0.03

^a Assumed to weigh 7 kg and breathe 2 m³ air per day (Health and Welfare Canada, 1992).

^b Assumed to weigh 13 kg and breathe 5 m³ air per day (Health and Welfare Canada, 1992).

^c Assumed to weigh 27 kg and breathe 12 m³ air per day (Health and Welfare Canada, 1992).

^d Assumed to weigh 57 kg and breathe 21 m³ air per day (Health and Welfare Canada, 1992).

^e Assumed to weigh 70 kg and breathe 23 m³ air per day (Health and Welfare Canada, 1992).

^f See table 3, "Ambient Air," in Government of Canada (1993).

^g Based on a mean concentration of inorganic (gaseous and particulate) fluoride in ambient air of 0.03 $\mu\text{g m}^{-3}$, reported for Toronto, Ontario (McGrath, 1983), and assuming the concentration in indoor air is identical to that in outdoor (ambient) air.

7.6 SUMMARY AND CONCLUSION

Inhaled fluorides are rapidly absorbed in the upper respiratory tract; close to 100% of inhaled hydrogen fluoride is absorbed. The fate and effects of absorbed fluorides are

essentially independent of the fluoride source or the route of exposure. About 50% of absorbed fluoride is retained in the body. Approximately 99% of the fluoride in the body is found in the skeleton; the remainder is distributed in soft tissues. The half-life for

uptake by bone tissue is very short (about 13 minutes). A portion of circulating fluoride (50%) is inorganic fluoride, and the remainder consists of organic fluorides. The inorganic fluoride content increases with the fluoride exposure level. The other half of absorbed fluoride is rapidly eliminated from the body. The majority is excreted by urine, and only a few percent is excreted in faeces and sweat. Urinary excretion of fluoride is decreased in cases of renal dysfunction. In pregnant women, fluoride crosses the placenta. Measurement of fluoride in serum, urine or bone can under certain conditions serve to monitor exposure to gaseous fluorides.

The pharmacodynamics of fluoride are characterized by fluoride's effects on many enzyme systems and their complexing effect on metal ions. At high exposure levels, these properties result in several effects such as cardiovascular collapse, hypocalcaemia, hyperkalaemia and skeletal alterations.

Concentrations of gaseous fluorides in air that may pose a concern to human health have been reviewed in the CEPA Assessment Report for Inorganic Fluorides (Government of Canada, 1993), as well as a contract report on the health effects of gaseous fluorides prepared for Health Canada (Speijers, 1995). Health effects in experimental studies are generally observed at dose concentrations more than 100 times mean concentrations found in ambient air.

Studies in humans have revealed a NOAEL of 0.9 mg m^{-3} of airborne hydrogen fluoride for skin and eye irritation and a NOAEL of 2.1 mg m^{-3} as fluoride for irritation of the respiratory tract. The odour threshold for hydrogen fluoride ranges from 0.02 to 0.22 mg m^{-3} .

Clinical studies and most epidemiological studies on the inhalation of fluorides are not adequately designed to allow a NOAEL for systemic effects to be derived or a clear effect level to be identified. In many cases, individual exposures to fluorides in ambient air were not monitored. In workplace studies, people are exposed to many other potentially toxic compounds in addition to gaseous and particulate fluorides in the ambient air, making it impossible to establish an indicative NOAEL for gaseous fluorides. Only a few chronic epidemiological studies provide some quantitative information on exposure levels indicative of toxic effects on the skeleton (fluorosis and osteosclerosis) and the respiratory tract. In humans, no effects of chronic exposure to airborne hydrogen fluoride on kidneys, brain, thyroid or the haematopoietic system have been convincingly established at exposure levels considered to be representative of those normally encountered in ambient air or causing skeletal alterations or effects on the respiratory tract. No specific epidemiological data on the carcinogenic effects of airborne fluoride are available. A definitive NOAEL for airborne fluoride, including hydrogen fluoride, cannot be established from the available studies.

For intake of fluorides by other exposure routes, it has been concluded by several review bodies that there is insufficient evidence concerning any carcinogenic properties of inorganic fluorides. In addition, there is inadequate evidence to support an association between exposure to fluorides by different exposure routes and reproductive or teratogenic effects. As it is known from oral studies that, at least for skeletal alterations, rats are less sensitive than humans, it is prudent to rely mainly on the toxicological data in humans for a toxicological evaluation.

Both for laboratory animals and for humans, it can be concluded that adequate toxicological studies with gaseous fluorides (including hydrogen fluoride) are very limited.

From studies in occupationally exposed adults, it can be concluded that, in general, exposure to airborne hydrogen fluoride levels below 1.78–2.5 mg m⁻³ for an eight-hour work day will not cause skeletal alterations. The occupational exposure limit for fluoride of 2.0 mg m⁻³ per eight-hour shift corresponds to a fluoride intake of 286 µg kg⁻¹ body weight per day for a 70-kg adult exposed to an equivalent concentration in ambient air for 24 hours. This, then, is a NOAEL for skeletal effects. This can be compared with the CEPA report's conclusion (Government of Canada, 1993) that potentially adverse effects associated with skeletal fluorosis are likely to be observed at fluoride intakes above about 200 µg kg⁻¹ body weight per day. Pulmonary effects, the

most sensitive effect, are reported to appear in children, the most sensitive receptor, at gaseous fluoride concentrations above 200 µg m⁻³ (and 300 µg m⁻³ for particulate fluoride). This concentration can be considered a LOAEL for children (Turner et al., 1993).

The ambient air concentration of gaseous fluoride ranges from <0.05 to 1.65 µg m⁻³ in Canada and the United States. In most parts of Canada, the exposure levels are below 0.05 µg m⁻³. Ambient exposures range from 100 to 10,000 times less than the estimated effect level derived from human studies. Children, people with impaired kidney function, industrially exposed workers and persons living in the vicinity of a point source of fluoride emissions may be at somewhat greater risk than the general population, although all such groups are expected to be exposed to concentrations well below the effect level.

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APPENDIX HF REFERENCE DOSE DATABASE

Appendix HF Reference Dose Database

Study No.	Author(s)	Year	Journal	Vol.	pg	Species	Cultivar	Life Stage	Age	Conc. ($\mu\text{g m}^{-3}$)
1	Adams, D.F., C.G. Shaw, and W.D. Yerkes Jr.	1956	Phytopathology	46	587-591	<i>Gladiolus</i>	Ethyl Cave Cole	4th true leaf		0.85
1	Adams, D.F., C.G. Shaw, and W.D. Yerkes Jr.	1956	Phytopathology	46	587-591	<i>Gladiolus</i>	Ethyl Cave Cole	4th true leaf		1.46
1	Adams, D.F., C.G. Shaw, and W.D. Yerkes Jr.	1956	Phytopathology	46	587-591	Ponderosa Pine (<i>Pinus ponderosa</i>)		needles 50% exposed	5 yr	1.46
2	Solberg, R.A., D.F. Adams, and H.A. Ferchau	1955	Proceedings of the Third National Air Pollution Symposium		164-176	Ponderosa Pine (<i>Pinus ponderosa</i>)		4ft tall		0.61
2	Solberg, R.A., D.F. Adams, and H.A. Ferchau	1955	Proceedings of the Third National Air Pollution Symposium		164-175	Ponderosa Pine (<i>Pinus ponderosa</i>)		4ft tall		0.20
3	MacLean, D.C., R.E. Schneider, and D.C. McCune	1977	J. Amer. Soc. Hort. Sci.	102(3)	297-299	Green bean (<i>Phaseolus vulgaris</i> L.)	Tendergreen	life span		0.60
3	MacLean, D.C., R.E. Schneider, and D.C. McCune	1977	J. Amer. Soc. Hort. Sci.	102(3)	297-299	Tomato (<i>Lycopersicon esculentum</i>)	Fireball	life span		0.60
4	Zwiasek, J.J.	1994	Ontario Ministry of Environment and Energy, Research Technology Branch, PIBS 2807, ISBN 0-7778-0383-6			White pine (<i>Pinus strobus</i> L.)		seedlings	9 wks	0.61
4	Zwiasek, J.J.	1994	Ontario Ministry of Environment and Energy, Research Technology Branch, PIBS 2807, ISBN 0-7778-0383-6			White pine (<i>Pinus strobus</i> L.)		seedlings	9 wks	2.44
4	Zwiasek, J.J.	1994	Ontario Ministry of Environment and Energy, Research Technology Branch, PIBS 2807, ISBN 0-7778-0383-6			White pine (<i>Pinus strobus</i> L.)		seedlings	9 wks	0.61
5	MacLean, D.C., and R.E. Schneider	1981	Environmental Pollution (Series A)	24	39-44	Wheat (<i>Triticum aestivum</i> L.)	Olaf	anthesis		0.90
5	MacLean, D.C., and R.E. Schneider	1981	Environmental Pollution (Series A)	24	39-44	Wheat (<i>Triticum aestivum</i> L.)	Olaf	boot stage		0.90
6	MacLean, D.C., R.E. Schneider, and L.H. Weinstein	1982	Environmental Pollution (Series A)	29	27-34	Jerusalem cherry (<i>Solanum pseudo-capsicum</i> L.)			3 months	0.90
7	Madkour, D., and L.H. Weinstein	1987	Environmental Toxicology and Chemistry	6	627-634	Soybean (<i>Glycine max</i> L.)	Hodgson	veg. growth		0.70
7	Madkour, D., and L.H. Weinstein	1987	Environmental Toxicology and Chemistry	6	627-633	Soybean (<i>Glycine max</i> L.)	Hodgson	veg. growth		3.50
8	Coulter, C.T., M.R. Pack, and C.W. Sulzbach	1985	Atmospheric Environment	19 (6)	1001-1007	<i>Gladiolus</i>	Snow Velvet	2 to 3 leaf stage	31 days old	2.90
8	Coulter, C.T., M.R. Pack, and C.W. Sulzbach	1985	Atmospheric Environment	19 (6)	1001-1007	<i>Gladiolus</i>	T210	2 to 3 leaf stage	31 days old	2.90
8	Coulter, C.T., M.R. Pack, and C.W. Sulzbach	1985	Atmospheric Environment	19 (6)	1001-1007	<i>Gladiolus</i>	T210	2 to 3 leaf stage	31 days old	2.90
8	Coulter, C.T., M.R. Pack, and C.W. Sulzbach	1985	Atmospheric Environment	19 (6)	1001-1007	<i>Gladiolus</i>	T210	2 to 3 leaf stage	31 days old	2.90
8	Coulter, C.T., M.R. Pack, and C.W. Sulzbach	1985	Atmospheric Environment	19 (6)	1001-1007	<i>Gladiolus</i>	T210	2 to 3 leaf stage	31 days old	2.90

Note: Scientific Data Used to Derive the Reference Levels is Indicated in **Bold Face Type**

Appendix HF Reference Dose Database

Study No.	Duration (days)	Dose	Dose Period	Protocol	Endpoint Measured	Effect	Significant (p<=.05)	Variability	Comments
1	1.00	0.85	1	standard chamber	leaf necrosis, inj. index=0.7	Yes	-	-	Conc. in paper expressed as ppb (v/v?). Converted to $\mu\text{g m}^{-3}$ by x 1.22. Leaf injury index = % of leaf length injured.
1	1.00	1.46	1	standard chamber	leaf necrosis, inj. index=1.9	Yes	-	-	Conc. in paper expressed as ppb (v/v?). Converted to $\mu\text{g m}^{-3}$ by x 1.22. Leaf injury index = % of leaf length injured.
1	1.00	1.46	1	standard chamber	leaf necrosis, inj. index=0.5	Yes	-	-	Conc. in paper expressed as ppb (v/v?). Converted to $\mu\text{g m}^{-3}$ by x 1.22. Leaf injury index = % of leaf length injured.
2	6.60	4.03	7	standard chamber	time to first injury	Yes	-	20%	Conc. in paper expressed as ppb (v/v?). Converted to $\mu\text{g m}^{-3}$ by x 1.22. Duration is average time to first injury on 5 plants. Treatment concentrations not measured. Dose includes periods between exposures.
2	19.80	4.03	30	standard chamber	time to first injury	Yes	-	56%	Conc. in paper expressed as ppb (v/v?). Converted to $\mu\text{g m}^{-3}$ by x 1.22. Duration is average time to first injury on 5 plants. Treatment concentrations not measured. Dose includes periods between exposures.
3	43.00	25.80	30	standard open-top	25% (F.W.) marketable yield loss	Yes	0.01	-	
3	93.00	55.80	90	standard open-top	growth, fruiting, fruit production	No	-	-	
4	2.00	1.22	1	standard chamber	increased plasma membrane leakage	Yes	-	-	Conc. in paper expressed as ppb (v/v?). Converted to $\mu\text{g m}^{-3}$ by x 1.22.
4	5.00	12.20	7	standard chamber	first injury	Yes	-	-	Conc. in paper expressed as ppb (v/v?). Converted to $\mu\text{g m}^{-3}$ by x 1.22.
4	20.00	12.20	30	standard chamber	first injury	Yes	-	-	Conc. in paper expressed as ppb (v/v?). Converted to $\mu\text{g m}^{-3}$ by x 1.22.
5	4.00	3.60	7	standard open-top	yield loss	Yes	0.05	-	
5	4.00	3.60	7	standard open-top	yield loss	Yes	0.05	-	
6	1.00	0.90	1	standard chamber	leaf necrosis	Yes	-	-	Injury occurred when exposed in the dark and then brought into light. Lowest dose presented which caused an effect.
7	9.00	6.30	7	standard open-top	reduced C translocation	No	0.05	-	Non-sensitive endpoint.
7	9.00	31.50	7	standard open-top	reduced C translocation	Yes	0.05	-	Non-sensitive endpoint.
8	16 of 32 days	31.67	30	standard chamber	Overall average of 5.6% leaf area necrosis		-	-	Approx. $2 \mu\text{g m}^{-3}/48\text{hr}$ with 48hr no exposure for 32 days. No control (non-fumigated) for comparison and detection of a significant effect.
8	16 of 32 days	45.83 (average)	30	standard chamber	Overall average of 11.1% leaf area necrosis.		-	-	Approx. $2 \mu\text{g m}^{-3}/48\text{hr}$ with 48hr no exposure for 32 days. No control (non-fumigated) for comparison and detection of a significant effect.
8	16 of 32 days	45.63 (average)	30	standard chamber	Average of 10.8% leaf area necrosis.		-	-	Alternating 48 hr fumig. w/ 48 hr. non-fumig., total of 8 fumigations during the 32 day period. No control (non-fumig.), therefore, there's no way of knowing if the effect observed is statistically significant.
8	16 of 32 days	45.63 (average)	30	standard chamber	16.7% leaf area necrosis.	Yes	0.05	-	Alternating 96 hr fumig. w/ 96 hr non-fumig., total of 5 fumig. in 32 days. Sign. greater effect than in 24 and 48 hr fumigations in preceeding 2 lines. Therefore, this effect would be significantly greater than a control, even though a control is absent.
8	16 of 32 days	45.83 (average)	30	standard chamber	15.4% leaf area necrosis.	Yes	0.05	-	96 hr fumig., 192 hr non-fumig., 192 hr fumig., 192 hr non-fumig., 96 hr fumig., Sign. greater effect than in intermittent 24 and 48 hr fumig. above. Therefore, this effect would be significantly greater than a control, even though a control is absent.

Note: Scientific Data Used to Derive the Reference Levels is Indicated in **Bold Face Type**

Appendix HF Reference Dose Database

Study No.	Author(s)	Year	Journal	Vol.	pg	Species	Cultivar	Life Stage	Age	Conc. ($\mu\text{g m}^{-3}$)
8	Coulter, C.T., M.R. Pack, and C.W. Sulzbach	1985	Atmospheric Environment	19 (6)	1001-1007	<i>Gladiolus</i>	T210	2 to 3 leaf stage	31 days old	2.90
9	McCune, D.C., T.L. Lauver, and K.S. Hansen	1991	Canadian Journal Forest Research	21	756-761	White spruce (<i>Picea glauca</i> Moench.)		early summer	2 yr	2.63
9	McCune, D.C., T.L. Lauver, K.S. Hansen	1991	Canadian Journal Forest Research	21	756-761	White spruce (<i>Picea glauca</i> Moench.)		early summer	2 yr	5.14
9	McCune, D.C., T.L. Lauver, and K.S. Hansen	1991	Canadian Journal Forest Research	21	756-761	Black spruce (<i>Picea mariana</i> Mill.)		early summer	2 yr	2.29
10	Murray, F.	1983	J. Amer. Soc. Hort. Sci.	108(4)	526-529	Grapevine (<i>Vitis sinifer</i> L.)	Shiraz	early fruit to harvest	mature	0.17
10	Murray, F.	1983	J. Amer. Soc. Hort. Sci.	108(4)	526-529	Grapevine (<i>Vitis sinifer</i> L.)	Shiraz	early fruit to harvest	mature	0.28
10	Murray, F.	1983	J. Amer. Soc. Hort. Sci.	108(4)	526-529	Grapevine (<i>Vitis sinifer</i> L.)	Shiraz	early fruit to harvest	mature	0.28
11	Murray, F.	1984	Environmental Pollution (Series A)	36	337-349	Grapevine (<i>Vitis sinifer</i> L.)	Shiraz	growing season	mature	0.27
11	Murray, F.	1984	Environmental Pollution (Series A)	36	337-349	Grapevine (<i>Vitis sinifer</i> L.)	Shiraz	growing season	mature	0.27
11	Murray, F.	1984	Environmental Pollution (Series A)	36	337-349	Grapevine (<i>Vitis sinifer</i> L.)	Shiraz	growing season	mature	0.17
11	Murray, F.	1984	Environmental Pollution (Series A)	36	337-349	Grapevine (<i>Vitis sinifer</i> L.)	Shiraz	growing season	mature	0.27
12	Hitchcock, A.E., P.W. Zimmerman, and R.R. Coe	1962	Contributions from Boyce Thompson Institute	21	303-344	<i>Gladiolus</i>	numerous varieties	-	-	0.16
13	Pack, M.R.	1972	Journal of the Air Pollution Control Association	22(9)	714-717	Strawberry	Marshall	growing season		0.55
13	Pack, M.R.	1972	Journal of the Air Pollution Control Association	22(9)	714-717	Strawberry	Marshall	growing season		0.55
13	Pack, M.R.	1972	Journal of the Air Pollution Control Association	22(9)	714-717	Strawberry	Marshall	growing season		2.00
14	Mandl, R.H., L.H. Weinstein, and M. Keveny	1975	Environmental Pollution	9	133-143	Barley (<i>Hordeum vulgare</i> L.)	Dickinson	seedling	10 days	0.72
14	Mandl, R.H., L.H. Weinstein, and M. Keveny	1975	Environmental Pollution	9	133-143	Corn (<i>Zea mays</i> L.)	Marcross	seedling	10 days	0.63
15	Murray, F., and S. Wilson	1988c	Environmental Pollution	55	239-249	Barley (<i>Hordeum vulgare</i> L.)	Clipper	life span		0.38
15	Murray, F., and S. Wilson	1988c	Environmental Pollution	55	239-249	Wheat (<i>Triticum aestivum</i> L.)	Halberd	life span		0.38
16	Pack, M.R.	1971	Journal of the Air Pollution Controll Assoc.	21(3)	133-137	Green bean (<i>Phaseolus vulgaris</i> L.)	Tendergreen	life span		2.10
17	McCune, D.C., A.E. Hitchcock, and L.H. Weinstein	1966	Contrib. Boyce Thompson Inst.	23(8)	295-299	<i>Gladiolus</i>	Snow Princess	3 leaf stage	4 - 8 wks	2.10
18	Mohamed, A.H., J.D. Smith, and H.G. Applegate	1966	Can. J. Genet. Cytol.	8	575-583	Tomato (<i>Lycopersicon esculentum</i> Mill.)	309-7-1-2	pre-flowering		3.00
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B. Peterson, N.C. Leone		105-115	Alfalfa (<i>Medicago sativa</i> L.)	Ranger			2.50
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B. Peterson, N.C. Leone		105-115	Barley (<i>Hordeum vulgare</i> L.)	Bonneville			0.34

Note: Scientific Data Used to Derive the Reference Levels is Indicated in **Bold Face Type**

Appendix HF Reference Dose Database

Study No.	Duration (days)	Dose	Dose Period	Protocol	Endpoint Measured	Effect	Significant (p<=.05)	Variability	Comments
8	16 of 32 days	45.83 (average)	30	standard chamber	17.5% leaf area necrosis.	Yes	0.05	-	192 hr fumigation, 384 hr non-fumig., 192 hr fumig. Sign. greater effect than in intermittent 24 and 48 hr fumig. above. Therefore, this effect would be significantly greater than a control event though a control is absent.
9	2.08	5.48	7	standard open-top	apical necrosis		-	-	No control for comparison.
9	2.08	10.71	7	standard open-top	16% of trees with apical necrosis		-	-	No control for comparison.
9	3.25	7.44	7	standard open-top	30% of trees with apical necrosis		-	-	No control for comparison.
10	64.00	10.88	90	standard open-top	no necrosis	No	-	-	
10	64.00	17.92	90	standard open-top	no yield effect	No	-	-	
10	64.00	17.92	90	standard open-top	foliar necrosis on 5% of the leaves		-	-	Marginal response (5% necrosis). No statistical comparison to control. No effect on fruit yield or quality.
11	189.00	51.03	90	standard open-top	no yield effect	No	-	-	
11	189.00	51.03	90	standard open-top	no yield effect	No	-	-	
11	99.00	16.83	90	standard open-top	days to first injury	Yes	-	-	Well controlled experiment.
11	83.00	22.41	90	standard open-top	days to first injury	Yes	-	-	Well controlled experiment.
12	9.00	1.44	7	early chamber	2.5-6.0 cm tip burn		-	-	Poor statistical treatment of the data. Experiments inadequately controlled.
13	112.00	61.60	90	standard chamber	fruit wt.	No	0.05	-	No significant effect at this dose.
13	112.00	61.60	90	standard chamber	fruit development	Yes	0.05	-	Difficult to accurately calculate dose from the information given.
13	112.00	224.00	90	standard chamber	fruit wt.	Yes	0.05	-	Difficult to accurately calculate dose from the information given.
14	27.00	19.44	30	standard chamber	6.7% leaf necrosis	Yes	-	SD = 5.3%	
14	27.00	17.01	30	standard chamber	necrotic lesions on leaves increased	Yes	0.001	-	
15	90.00	34.20	90	standard open-top	no. of grains/ear decreased by 6.25%	Yes	0.05	-	Reduced no. of grains/ear offset by increased grain wt. and number of tillers.
15	90.00	34.20	90	standard open-top	yield components	No	-	-	Wheat is not a sensitive species.
16	90.00	189.00	90	standard chamber	less vigorous F1 progeny	Yes	-	-	This is not a sensitive endpoint. Statistical treatment of the data is weak.
17	7 of 49 days	14.70	90	standard chamber	40 mm leaf tip burn	Yes	-	-	
18	4.00	12.00	7	standard chamber	chromosomal abnormalities (mitosis and meiosis)	Yes	-	-	Treatments >4 days had effects as well. No leaf damage observed.
19	26.00	65.00	30	greenhouse fumigation	chlorosis, growth	No	-	-	
19	107.00	36.38	90	greenhouse fumigation	chlorosis, growth, yield	No	-	-	

Note: Scientific Data Used to Derive the Reference Levels is Indicated in **Bold Face Type**

Appendix HF Reference Dose Database

Study No.	Author(s)	Year	Journal	Vol.	pg	Species	Cultivar	Life Stage	Age	Conc. ($\mu\text{g m}^{-3}$)
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	Sugar beets				0.43
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	Bean (<i>Phaseolus</i> sp.)	Lima			0.64
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	Bean (<i>Phaseolus</i> sp.)	Lima			0.40
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	Celery				0.89
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	Celery				0.66
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	Corn (<i>Zea mays</i> L.)				0.41
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	Corn (<i>Zea mays</i> L.)				0.47
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	<i>Gladiolus</i>				0.66
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	<i>Gladiolus</i>				1.38
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	<i>Gladiolus</i>				0.36
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	<i>Gladiolus</i>				0.48
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	<i>Gladiolus</i>				0.44
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Shupe, H.B Peterson, N.C. Leone		105-115	<i>Gladiolus</i>				0.50
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	<i>Gladiolus</i>				0.41
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	Onion (<i>Alium</i>)		growing season		1.12

Note: Scientific Data Used to Derive the Reference Levels is Indicated in **Bold Face Type**

Appendix HF Reference Dose Database

Study No.	Duration (days)	Dose	Dose Period	Protocol	Endpoint Measured	Effect	Significant (p<=.05)	Variability	Comments
19	167.00	71.81	90	greenhouse fumigation	plant weight, size, root sugar content	No	-	-	
19	93.00	59.52	90	greenhouse fumigation	chlorosis, growth, yield	No	-	-	
19	69.00	27.60	90	greenhouse fumigation	chlorosis, growth, yield	No	-	-	
19	120.00	106.80	90	greenhouse fumigation	chlorosis, growth, yield	No	-	-	
19	118.00	77.88	90	greenhouse fumigation	chlorosis, growth, yield	No	-	-	
19	65.00	26.65	90	greenhouse fumigation	59% of leaves with chlorosis	Yes	-	-	
19	45.00	21.15	90	greenhouse fumigation	37% of leaves with chlorosis	Yes	-	-	
19	65.00	42.90	90	greenhouse fumigation	98% necrosis, 27% yield loss	Yes	-	-	
19	72.00	99.36	90	greenhouse fumigation	73% necrosis, 76% yield loss	Yes	-	-	Treatment dose far too high relative to known sensitivity of gladiolus to HF.
19	117.00	42.12	90	greenhouse fumigation	65% necrosis, 60% yield loss	Yes	-	-	
19	91.00	43.68	90	greenhouse fumigation	60% necrosis	Yes	-	-	
19	138.00	60.72	90	greenhouse fumigation	48% necrosis, 40% yield loss	Yes	-	-	
19	105.00	73.50	90	greenhouse fumigation	59% necrosis, 34% yield loss	Yes	-	-	
19	129.00	64.50	90	greenhouse fumigation	62% necrosis, 60% yield loss	Yes	-	-	
19	72.00	29.52	90	greenhouse fumigation	36% necrosis, 55% yield loss	Yes	-	-	
19	128.00	143.36	90	greenhouse fumigation	necrosis, growth, yield	No	-	-	

Note: Scientific Data Used to Derive the Reference Levels is Indicated in **Bold Face Type**

Appendix HF Reference Dose Database

Study No.	Author(s)	Year	Journal	Vol.	pg	Species	Cultivar	Life Stage	Age	Conc. ($\mu\text{g m}^{-3}$)
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	Peach (<i>Prunus</i>)				0.34
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	Peach (<i>Prunus</i> sp.)				0.41
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	Potato (<i>Solanum tuberosum</i>)		growing season		0.44
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	Prune (<i>Prunus</i> sp.)				0.89
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	Spinach				0.42
19	Hill, A.C., and M.R. Pack	1983	in "Fluorides, Effects on Vegetation, Animals, and Humans" ed. J.L. Schupe, H.B Peterson, N.C. Leone		105-115	Wheat (<i>Triticum aestivum</i> L.)				0.38
20	Murray F., and S. Wilson	1988b	Environmental and Experimental Botany	28	343-349	Eucalyptus (<i>Eucalyptus tereticornis</i>)			18 months	0.38
21	Murray F., and S. Wilson	1990	Journal of Experimental Botany	30	215-223	Soybean (<i>Glycine max</i> L.)	Dragon		50 days old	0.27
21	Murray F., and S. Wilson	1990	Journal of Experimental Botany	30	215-223	Maize (<i>Zea mays</i> L.)	QK 958		54 days old	0.26
21	Murray F., and S. Wilson	1990	Journal of Experimental Botany	30	215-223	Peanut (<i>Arachis hypogaea</i> L.)	Virginia Bunch		53 days old	0.27
21	Murray F., and S. Wilson	1990	Journal of Experimental Botany	30	215-223	Navy bean (<i>Phaseolus vulgaris</i> L.)	Gallaroy		26 days old	0.25

Note: Scientific Data Used to Derive the Reference Levels is Indicated in **Bold Face Type**

Appendix HF Reference Dose Database

Study No.	Duration (days)	Dose	Dose Period	Protocol	Endpoint Measured	Effect	Significant (p<=.05)	Variability	Comments
19	110.00	37.40	90	greenhouse fumigation	1% necrosis, 73% growth	Yes	-	-	
19	73.00	29.93	90	greenhouse fumigation	severe chlorosis, 1% necrosis	Yes	-	-	
19	138.00	60.72	90	greenhouse fumigation	necrosis, growth, yield	No	-	-	
19	51.00	45.39	90	greenhouse fumigation	necrosis	Yes	-	-	No description of results, and no quantitative description of necrosis.
19	38.00	15.96	30	greenhouse fumigation	necrosis, growth, yield	No	-	-	
19	88.00	33.44	90	greenhouse fumigation	necrosis, growth, yield	No	-	-	
20	90.00	34.20	90	open-top, field	specific leaf area (cm ² g ⁻¹)	Yes	0.01		Eucalyptus is not a Canadian species, nor are there close relatives. Therefore this data isn't used in the Ref. Level calculation.
21	91.00	24.57	90	open-top, field	Yield	No	-		No sign. effect on yield or yield components.
21	70.00	18.20	90	open-top, field	Yield	No	-		Sign. reduction in no. of immature kernels; no effect on yield or any yield component.
21	105.00	28.35	90	open-top, field	Yield	Yes	0.001		
21	49.00	12.25	90	open-top, field	Yield	No	-		Sign. reduction in avg. bean wt., compensated for by sign. increase in number of pods and beans per plant. No net effect on yield.

Note: Scientific Data Used to Derive the Reference Levels is Indicated in **Bold Face Type**