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Priority Substances List
Assessment Report

Inorganic Fluorides

Government of Canada
Environment Canada
Health Canada

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Synopsis

Inorganic fluorides are used in Canada and emitted into the Canadian environment both from anthropogenic (estimated releases of approximately 23 500 tonnes/year) and natural sources (amounts released are not known). The main anthropogenic sources of inorganic fluorides in Canada include phosphate fertilizer production, chemical production, and aluminum smelting. Approximately 23%, 58%, and 19% of the total inorganic fluorides reported to enter the Canadian environment from anthropogenic sources are released to the air, water, and land, respectively. Gaseous inorganic fluorides (e.g., hydrogen fluoride and sulphur hexafluoride) are primarily released into the atmosphere, whereas particulate compounds (e.g., sodium fluoride and calcium fluoride) are released into the aquatic and terrestrial environments. Inorganic fluorides have been measured in ambient air, freshwater (including groundwater), seawater, aquatic sediments, soil, and biota throughout Canada, as a result of both natural and anthropogenic sources.

The mean concentrations of inorganic fluoride in ambient air at several locations across Canada (in the vicinity of anthropogenic sources) are within the range of the effects threshold for several sensitive terrestrial plant species. The mean concentrations of inorganic fluoride in the majority of freshwaters and marine waters in Canada in the vicinity of known anthropogenic sources are equal to, or exceed the lowest estimated effects threshold for, freshwater and marine species. The levels of fluoride in vegetation near certain industrial sources are similar to those that may induce adverse effects in sensitive wildlife populations.

Inorganic fluoride compounds (except sulphur hexafluoride) are not expected to remain in the troposphere very long or migrate to the stratosphere. Although sulphur hexafluoride is long-lived enough to migrate into the stratosphere, its contribution to the depletion of stratospheric ozone is considered minimal. Owing to the lack of relevant data, it is not possible to determine the contribution of inorganic fluorides to global climate change.

Based on data on the levels of inorganic fluoride in ambient air, drinking water, food, soil, and household products, the total average daily intakes of inorganic fluoride by various age groups of the general population of Canada have been estimated. These average daily intakes are at least 20% less than the level at which adverse effects upon the skeleton (the end-point considered most sensitive on the basis of available data) are anticipated, derived on the basis of studies in humans.

Based on these considerations, it has been concluded that inorganic fluorides are entering the environment in quantities or under conditions that may be harmful to the environment. There is insufficient information to conclude whether sulphur hexafluoride is entering the environment in quantities or under conditions that may constitute a danger to the environment on which human life depends. It has been concluded that inorganic fluorides (i.e., the fluoride ion derived from such inorganic substances) are not entering the environment in quantities or under conditions that may constitute a danger to human life or health.

1.0 Introduction

The *Canadian Environmental Protection Act* (CEPA) requires the federal Ministers of the Environment and of Health to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents, and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" as defined in section 11 of the Act, which states:

> "...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions
>
> (*a*) having or that may have an immediate or long-term harmful effect on the environment;
>
> (*b*) constituting or that may constitute a danger to the environment on which human life depends; or
>
> (*c*) constituting or that may constitute a danger in Canada to human life or health."

Substances assessed as "toxic" according to section 11 may be placed on Schedule I of the Act, and considered for possible development of regulations, guidelines, or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport, and ultimate disposal.

The assessment of whether "inorganic fluorides" are "toxic", as defined under CEPA, was based on the determination of whether they **enter** or are likely to enter the Canadian environment in a concentration or quantities or under conditions that could lead to **exposure** of humans or other biota at levels that could cause adverse **effects**.

Data that form the basis for an assessment of the effects of inorganic fluorides on human health were derived from studies of humans and laboratory animals exposed to different forms of these compounds. Individuals may be occupationally exposed to aluminum fluoride [AlF_3], calcium fluoride (CaF_2), calcium phosphate fluoride ($3Ca_3[PO_4]•CaF_2$), sodium aluminum fluoride ($3NaF•AlF_3$), and sodium silicofluoride (Na_2SiF_6). Hydrofluosilicic acid (H_2SiF_6), sodium fluoride (NaF), and sodium silicofluoride are commonly used in the fluoridation of drinking water. Sodium fluoride, stannous fluoride (SnF_2), and sodium monofluorophosphate (Na_2FPO_3) are used in dentifrices and mouthrinses. In clinical studies, humans are administered sodium fluoride, and in most toxicological investigations, laboratory animals are

exposed to sodium fluoride. Most of the long-term health effects resulting from exposure to various forms of inorganic fluorides may be attributed to the actions of the fluoride ion *per se*. Moreover, in general, available data on human exposure refer to the levels of fluoride ion in environmental media, foodstuffs and household products. Consequently, the assessment of whether inorganic fluorides are "toxic" to human health as defined under paragraph 11(*c*) of CEPA, is based on the effects of the fluoride ion derived from inorganic substances. Unless otherwise specified, in the health-related sections, "inorganic fluoride" refers to the fluoride ion derived from inorganic compounds. With respect to the effects of fluoride on human health, neither dental fluorosis nor the beneficial effects of fluoride in the prevention of dental caries have been assessed in this report.

On-line databases, including HSDB, RTECS, MEDLINE, TOXLINE, TOXLIT, IRIS, NIOSH, CCRIS, CHRIS, DOBIS, AQUAREF, CODOC, MICROLOG, and ELIAS, were searched (from 1965 through 1992) in order to identify data relevant to the assessment of health effects. Reviews on the toxicity of inorganic fluoride that were also consulted include those published by the U.S. Agency for Toxic Substances and Disease Registry (ATSDR, 1991), the U.S. Department of Health and Human Services (U.S. DHHS, 1991), the U.S. Environmental Protection Agency (U.S. EPA, 1985), the World Health Organization (WHO, 1984), and an unpublished review of the health effects of inorganic fluorides prepared under contract by Hilcon Consultants, Inc. (Hill and Hill, 1991). Information was also supplied by Alcan Smelters and Chemicals Ltd. (Montréal, Quebec), and the Procter & Gamble Company (Cincinnati, Ohio). Data relevant to the assessment of whether inorganic fluorides are "toxic" to human health obtained after July 1993 were not considered for inclusion.

In this report, the assessment of whether inorganic fluorides are "toxic" to the environment as defined under CEPA focused principally on four inorganic fluorides: hydrogen fluoride (HF), calcium fluoride (CaF_2), sodium fluoride (NaF), and sulphur hexafluoride (SF_6). These compounds were considered the most relevant of the inorganic fluorides on the basis of quantities released to the Canadian environment, environmental concentrations, and toxicological effects on biota. Data relevant to the assessment of whether inorganic fluorides are "toxic" to the environment were identified through searches of commercial and government databases, including: ENVIROFATE, TOXLINE, BIOSIS, MEDLARS II, CAB Abstracts, ELIAS, MICROLOG, ENVIROLINE, AQUAREF, ASFA, BIOSIS Previews, NTIS, AQUIRE, CESARS, PHYTOTOX, AGRICOLA, SWRA, RTECS, CA SEARCH, Soviet Science and Technology, Pollution Abstracts, and Hazardous Substances Databank. Information including data on the production, importation, releases, storage, and use of inorganic fluorides in Canada was obtained from industry through a mandatory request for information under section 16 of CEPA. Data relevant to the assessment of whether inorganic fluorides are "toxic" to the environment obtained after April 1993 were not considered for inclusion.

Review articles were consulted where appropriate; however, original studies that form the basis for the determination of "toxic" under CEPA were critically evaluated by staff of Health Canada (human exposure and effects on human health) and Environment Canada (entry and environmental effects). The following officials contributed to the preparation of the report:

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W. Dormer of Health Canada also contributed to the consolidation of the Assessment Report.

In this report, a synopsis that will appear in the *Canada Gazette* is presented. A summary of the technical information that is critical to the assessment, and which is presented in greater detail in unpublished Supporting Documentation, is presented in Section 2.0. The assessment of whether inorganic fluorides are "toxic" as defined under CEPA is presented in Section 3.0.

As part of the review and approvals process established by Environment Canada, the environmental sections of this report were reviewed by Dr. L. Weinstein (Cornell University), Dr. P.D. Warrington (British Columbia Ministry of Environment), and Dr. S.S Sidhu (Forestry Canada). Sections of the Assessment Report and unpublished Supporting Documentation related to the effects on human health were reviewed by Dr. M. Grynpas (Mount Sinai Hospital), Dr. J. Siemiatycki (Institut Armand Frappier), Dr. W.C. Sturtridge (Toronto General Hospital), Dr. G. Whitford (Medical College of Georgia), and BIBRA Toxicology International (Surrey, U.K.), and approved by the Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazards of Health Canada. The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

Copies of this Assessment Report and the unpublished Supporting Documentation are available upon request from the:

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2.0 Summary of Information Critical to Assessment of "Toxic"

2.1 Identity, Properties, Production and Uses

Under standard conditions of temperature and pressure, fluorine is a halogen that exists as a light yellow-green, pungent, acrid gas of F_2 molecules. Fluorine has the Atomic Number 9 and a molecular weight of 19.0 g/mol. It is the most electronegative and has the highest chemical reactivity of all elements in the Periodic Table (Neumüller, 1981). Due to its high reactivity, fluorine is not present naturally in its elemental state; rather, it exists either as inorganic fluoride (i.e., ionic fluoride, [F^-], which is either free or matrix-bound in minerals or covalently bound in inorganic compounds such as hydrogen fluoride), or as organic fluoride (covalently bound in organic compounds) [Whitford, 1989]. The assessment of whether inorganic fluorides are "toxic" to the environment focused principally on hydrogen fluoride, calcium fluoride, sodium fluoride, and sulphur hexafluoride. These compounds were considered the most relevant on the basis of quantities released to the Canadian environment, environmental concentrations, and toxicological effects on biota.

At room temperature, hydrogen fluoride (HF; molecular weight, 20.01 g/mol; density, 0.991 g/L) is a colourless, pungent, acrid liquid or gas with a melting point of -83°C and a boiling point of 19.5°C. Hydrogen fluoride is highly soluble in many organic solvents and in water, in which it forms hydrofluoric acid (Weast, 1986; Neumüller, 1981). Hydrogen fluoride is an important industrial compound, with an annual world consumption in excess of 1 million tonnes (Greenwood and Earnshaw, 1984); in Canada, approximately 70 000 tonnes are used each year (Corpus Information Services, 1991). Hydrogen fluoride is manufactured from calcium fluoride and is used mainly in the production of synthetic cryolite, aluminum trifluoride, motor gasoline alkylates, and chlorofluorocarbons (CFCs) [Corpus Information Services, 1991]. The demand for CFCs is decreasing as a result of legislation restricting their use, thereby resulting in a decline in the demand for hydrogen fluoride. It was recently predicted, however, that the demand for hydrogen fluoride could rise in the latter part of this decade as a result of the production of alternatives to CFCs (Corpus Information Services, 1991). Hydrogen fluoride is also used in the synthesis of uranium tetrafluoride and uranium hexafluoride, both of which are used in the nucleur industry (Neumüller, 1981).

Calcium fluoride (CaF_2; molecular weight, 78.08 g/mol) is a colourless solid with a melting point of 1 403°C and a boiling point of 2 513°C. It is relatively insoluble in water and dilute acids and bases (Neumüller, 1981). Industrially, calcium fluoride is the principal fluoride-containing mineral, with a fluoride content of 48.5% (WHO,

1984). The annual Canadian consumption of calcium fluoride (as fluorspar) is 180 000 tonnes (Prud'homme, 1989). Calcium fluoride is used as a flux in steel, glass, and enamel production, and as the raw material for production of hydrofluoric acid and anhydrous hydrogen fluoride (Neumüller, 1981). Calcium fluoride is also used as a molten electrolyte for the separation of oxygen and alumina in aluminum production. Another important calcium- and fluoride-containing mineral is fluorapatite, which is used as a source of phosphates in the fertilizer industry (Neumüller, 1981).

Sodium fluoride (NaF; molecular weight, 41.99 g/mol) is a colourless to white solid that is moderately soluble in water, with high melting (988 to 1 012°C) and boiling points (1 695°C) [Neumüller, 1981]. Sodium fluoride is usually prepared from hydrofluoric acid and sodium carbonate or sodium hydroxide (Neumüller, 1981). Data on the total annual consumption of sodium fluoride in Canada were not identified. This substance is used in the "fluoridation" of drinking water, as a preservative in certain glues, in glass and enamel production, and as a flux in steel and aluminum production (Neumüller, 1981). Sodium fluoride is also registered for use as an insecticide and wood preservative in Canada, although data on the amounts currently used for these purposes were not identified (RIPP Database, 1993).

Sulphur hexafluoride (SF_6) is a colourless, odourless, tasteless, chemically inert, and non-flammable gas, with a molecular weight of 146.05 g/mol and a density of 6.16 g/L (at 20°C) [Neumüller, 1987]. Its melting and sublimation points are -50.5°C and -63.8°C, respectively (Weast, 1986; Neumüller, 1987). Sulphur hexafluoride is only slightly soluble in water, but is readily soluble in ethanol and bases (Weast, 1986). It absorbs strongly infrared radiation at wavelengths in the region of 10 μm (Chu, 1991). More than 110 tonnes of sulphur hexafluoride are imported into Canada annually (Environment Canada, 1993). This substance is used extensively as an insulation and current interruption medium in electrical switchgear, such as power circuit breakers, compressed gas transmission lines, in various components in electrical substations (James, 1992; Environment Canada, 1993), and as a protective inert gas over molten metals such as magnesium and aluminum (Neumüller, 1987). Over 90% of the total amount of sulphur hexafluoride imported into Canada is used in the production of magnesium; the remainder is used in electronic switchgears (Environment Canada, 1993). These two uses are considered to be both non-destructive to sulphur hexafluoride and ultimately dispersive (Environment Canada, 1993).

Measurement of inorganic fluorides in environmental samples is restricted to the detection of the free anion (F^-), thereby limiting the ability to distinguish between different chemical species. The most common analytical method used to measure the free anion is the fluoride ion-selective electrode (F-ISE) [Neumüller, 1981; Harzdorf *et al.*, 1986; ATSDR, 1991]. Modifications in sample preparation and in the instruments themselves can influence the sensitivity and recovery, and therefore the detection limit. Typical detection limits of the F-ISE for inorganic fluorides range from

0.1 to 300 ng/m^3 (air) to 1 to 1 000 μg/L (water) to 0.05 to 20 mg/kg (organic tissues, wet weight) [Harzdorf *et al.*, 1986; ATSDR, 1991]. Other methods used to quantitate fluoride ion include colorimetry, ion chromatography, atomic absorption spectrophotometry, and photon activation (Neumüller, 1981; ATSDR, 1991).

2.2 Entry into the Environment

Inorganic fluorides are released into the environment naturally through the weathering of minerals, as emissions from volcanoes, and as marine aerosols (Symonds *et al.*, 1988; ATSDR, 1991). Estimates of the annual global release of hydrogen fluoride from volcanic sources (passive degassing and eruptions) range from 60 to 6 000 kilotonnes, of which approximately 10% are introduced directly into the stratosphere (Symonds *et al.*, 1988). Annually, approximately 20 kilotonnes may be released from marine aerosols (Symonds *et al.*, 1988). Data regarding natural releases of inorganic fluorides into the Canadian environment were not identified.

Anthropogenic sources of inorganic fluorides include aluminum smelting, steel production, phosphate fertilizer production, glass and enamel making, brick and ceramic manufacturing, glue and adhesive production, fluoride-containing pesticides, and fluoridation of some drinking water supplies (Burns and Allcroft, 1964; Neumüller, 1981; Fuge, 1988; Fuge and Andrews, 1988). A Notice issued under subsection 16(1) of CEPA was published in the *Canada Gazette* and sent to relevant industrial sectors in Canada to obtain data on emission rates, levels in the environment, and relevant toxicological data for inorganic fluorides. Data on the known releases of inorganic fluoride from the major commercial activities in Canada surveyed under CEPA are summarized in Table 1. Based on a comparison between reporting facilities and survey facilities (“coverage” in Table 1), the amounts released may be underestimated, particularly for the steel-producers and clay-products sectors. Based on the available data, aluminum smelting (> 4 000 tonnes; ≈ 75% of all reported releases to air), phosphate fertilizer production (≈ 11 000 tonnes; ≈ 80% of all reported releases to water), and chemicals production (> 3 000 tonnes; ≈ 70% of all reported releases to land) are the major sources of fluoride released into the Canadian environment. Collectively, these sources account for over 75% (≈ 18 100 tonnes) of the total inorganic fluoride estimated to be released into the Canadian environment based on this survey. The total amount of inorganic fluorides released from anthropogenic sources to the Canadian environment (air, land, and water) is estimated to be in excess of 23 500 tonnes (Environment Canada, 1993). At least 5 500 tonnes of inorganic fluorides are released in atmospheric emissions (predominately as hydrogen fluoride), while over 13 500 tonnes are released in effluents. Releases of inorganic fluoride to land are estimated to exceed 4 500 tonnes. Data on the amounts of inorganic fluoride released from the glass and enamel production sector (a known consumer of calcium and sodium fluoride), or on the release of individual fluorides (i.e., HF, NaF, CaF_2, and SF_6 in Canada) were not identified. Information on the

release of inorganic fluoride from the fluoridation of drinking water in Canada was not identified. Groth (1975) estimated that for every 100 million people supplied with "fluoridated" drinking water in the United States, approximately 20 kilotonnes of inorganic fluorides (mostly sodium fluoride) are released into the aquatic environment.

Table 1
Estimate of Anthropogenic Inorganic Fluoride Releases into the Canadian Environment (Environment Canada, 1993)[1]

		Annual Releases (in tonnes)			
Sector	Coverage[2]	Air	Water	Land	Total[3]
Oil Refining	3/3	24	100.1	783.7	907.8 (≈ 4%)
Phosphate Fertilizer Producers	5/6	107.6	10 959	74.7	11 141.4 (≈ 48%)
Steel Producers	6/12	238.9	253.5	429.6	922 (≈ 4%)
Primary Aluminum Producers	5/5	4 063.4	306.7	NR[4]	4 370.1 (≈ 19%)
Clay Products	3/9	24.9	NR	NR	24.9 (0.1%)
Chemical Producers	5/7	305.3	1 362.4	3 077.2	4 744.9 (≈ 20%)
Coal-burning Utilities	3/4	543.1	555.3	NR	1 098.4 (≈ 5%)
Primary Copper and Nickel Producers	2/3	26.4	3.6	185.9	215.9 (0.9%)
Magnesium Producers[5]	1/1	100	NR	NR	100 (0.4%)
Other[6]	1/2	–	0.69	2.4	3.1 (0.01%)
Total[3]		5 433.6 (′ 23%)	13 541.4 (′ 58%)	4 553.5 (′ 19%)	23 528.5

1. Some values may be underestimated.
2. Number of reporting facilities versus number of facilities surveyed.
3. Number in brackets refers to Percent of Total Inorganic Fluorides released (i.e., 23 528.5 tonnes) represented by sector or medium.
4. NR = Not Reported.
5. Released as sulphur hexafluoride.
6. Includes: motor vehicle manufacturing, glue and adhesive production.

At least 110 tonnes of sulphur hexafluoride can potentially be released into the Canadian atmosphere from anthropogenic sources each year. This amount represents approximately 1% to 3% of the annual global atmospheric release of sulphur hexafluoride, which is estimated to range from 5 000 to 8 000 tonnes (based on data obtained in 1990) [Environment Canada, 1993].

2.3 Exposure-related Information

2.3.1 Fate

The fate of inorganic fluorides in the atmosphere is primarily influenced by vaporization, aerosol formation, wet/dry deposition, and hydrolysis. In water, the transport and transformation of inorganic fluorides is influenced by pH, hardness, and the presence of ion-exchange materials (e.g., clays). Factors that influence the mobility of inorganic fluorides in soil are pH and the formation of aluminum and calcium complexes. The fate of inorganic fluorides in biota is primarily determined by the route of exposure, levels of bioavailable inorganic fluorides, and uptake/excretion kinetics.

Globally, hydrogen fluoride and inorganic fluoride particulates (sodium and calcium fluoride) account for approximately 75% and 25%, respectively, of inorganic fluorides present in the atmosphere (Health Council of the Netherlands, 1990). Hydrogen fluoride may combine with water vapour to produce an aerosol or fog of aqueous hydrofluoric acid. Nonvolatile inorganic fluoride particulates are removed from the atmosphere via condensation or nucleation processes. Most inorganic fluoride particulates emitted into the atmosphere are stable (CPHA, 1979). Based upon available data, inorganic fluoride compounds, with the exception of sulphur hexafluoride, are not expected to remain in the troposphere for long periods or migrate to the stratosphere. Due to their low to moderate water solubility, the particulates usually return to earth by dry deposition, unlike gaseous species, which are returned primarily by wet deposition (Murray, 1981). Based on data from other countries, seasonal climatic conditions are expected to influence the rate and mode by which atmospheric fluorides are deposited, with wet deposition dominating during winter (high precipitation) and dry deposition dominating during summer (low precipitation) [Low and Bloom, 1988]. Estimates of the residence time of sulphur hexafluoride in the atmosphere range from 500 to several thousand years (Ramanathan *et al.*, 1985; Chu, 1991).

In areas of extreme acidity and alkalinity, inorganic fluorides may leach from fluoride-containing minerals into surface water or groundwater (Coker and Shilts, 1979). Solubilization of inorganic fluorides from minerals may also be enhanced by the presence of ion-exchange materials (e.g., bentonite clays and humic acid) [Pickering *et al.*, 1988]. Once dissolved, inorganic fluorides remain in solution under

conditions of low pH and hardness, and in the presence of ion-exchange material (Coker and Shilts, 1979; Sahu and Karim, 1989). Soluble inorganic fluorides may also form aerosols at the air-water interface or vaporize into the atmosphere (Brimblecombe and Clegg, 1988), whereas undissolved species generally undergo sedimentation (Drury *et al.*, 1980).

During weathering, some fluoride minerals (e.g., cryolite [Na_3AlF_6]) are rapidly broken down, especially under acidic conditions (Fuge and Andrews, 1988); fluorapatite ($Ca_5[(F,Cl,OH)|(PO_4)_3]$) and calcium fluoride (CaF_2) dissolve slowly (Kabata-Pendias and Pendias, 1984). In more acidic soils, concentrations of inorganic fluoride are considerably higher in the deeper horizons. The low affinity of inorganic fluorides for organic material results in leaching from the more acidic surface horizon, and increased retention by clay minerals and silts in the more alkaline deeper horizons (Davison, 1983; Kabata-Pendias and Pendias, 1984). This distribution profile is not observed in either alkaline or saline soils (Gilpin and Johnson, 1980; Davison, 1983). The results of numerous studies have indicated that soils rich in calcium carbonate or amorphous aluminum-hydroxides may bind inorganic fluoride by forming insoluble calcium fluoride or aluminum-fluoro-hydroxide complexes, thus limiting leaching from the soil and uptake by plants (Flühler *et al.*, 1982). Other cations (e.g., iron) also contribute to the fixation of fluoride (Murray, 1983, 1984), while soil phosphate may contribute to the mobility of inorganic fluoride (Kabata-Pendias and Pendias, 1984). The fate of inorganic fluorides released to soil also depends on their chemical form, rate of deposition, soil chemistry, and climate (Davison, 1983).

Uptake and subsequent absorption of inorganic fluorides by aquatic and terrestrial animals appears to be greater from water than from food (Hemens and Warwick, 1972; Fleming *et al.*, 1987). Terrestrial plants may accumulate inorganic fluorides following airborne deposition and uptake from the soil (Davison, 1983). Inorganic fluorides tend to accumulate preferentially in the skeletal tissues of vertebrates, exoskeletons of invertebrates, and cell walls of plants (Ledbetter *et al.*, 1960; Michel *et al.*, 1984).

Limited available evidence indicates that biomagnification of inorganic fluoride does not occur in aquatic or terrestrial food chains (ATSDR, 1991); however, some aquatic and terrestrial biota bioaccumulate soluble inorganic fluorides (Hemens and Warwick, 1972; Barbaro *et al.*, 1981; ATSDR, 1991). In samples obtained near a reclaimed fluorspar-mining site, the levels of inorganic fluorides in plants, invertebrates, and small mammals were higher than those in samples obtained from a control site (Andrews *et al.*, 1982). Twenty-four hours after sodium fluoride was released into an experimental pond, the concentration of fluoride in aquatic vascular plants was increased 35-fold, and uptake was also increased in algae (14-fold), mollusks (12-fold), and fish (7-fold) [Kudo and Garrec, 1983].

2.3.2 Concentrations

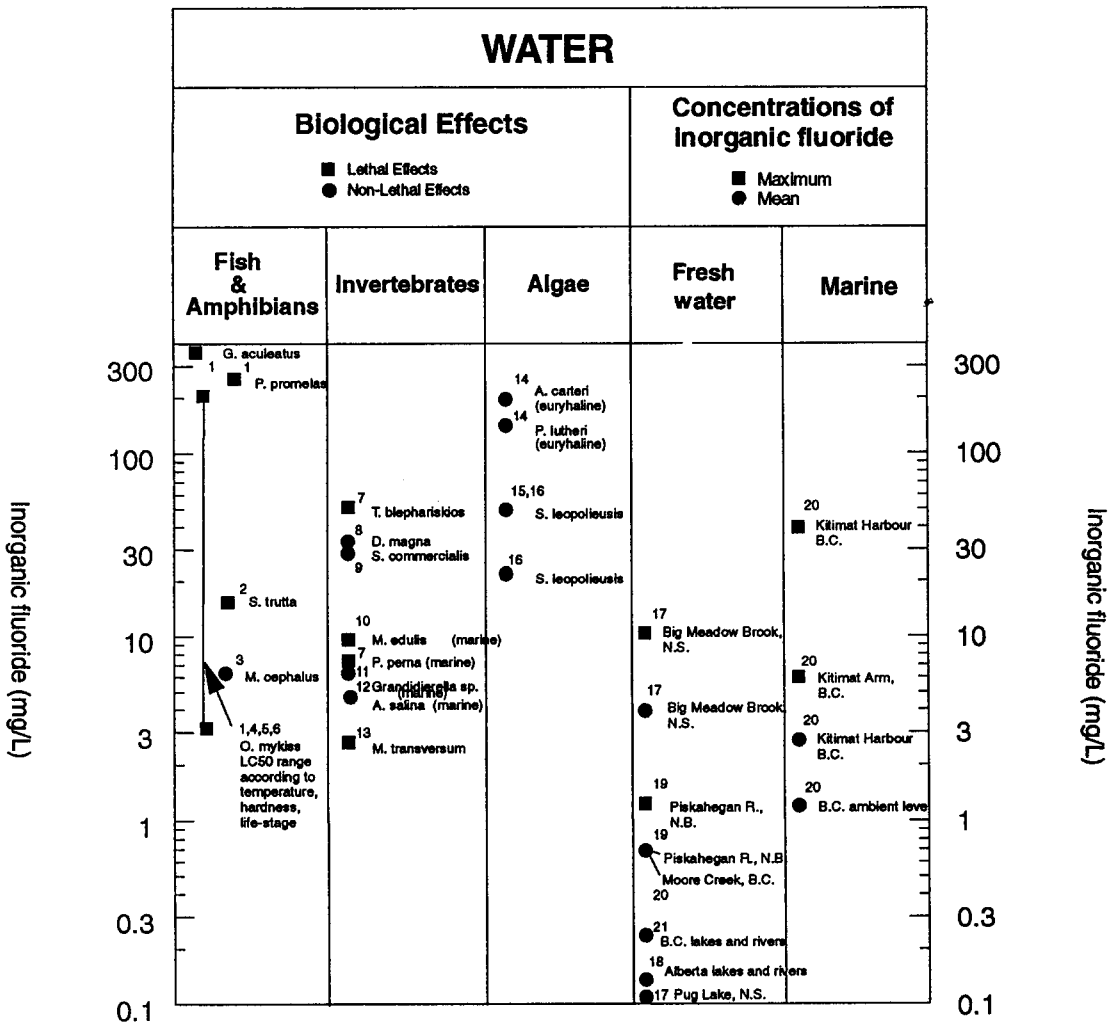
The concentration of inorganic fluoride has been quantitated in samples of ambient air, freshwater, seawater, groundwater, aquatic sediments, soils, and biota in various regions of Canada, although data for the latter 4 media are very limited. Data on the concentrations of inorganic fluoride in surface waters and ambient air (near industrial facilities) are presented in Figures 1 and 2, respectively.

The levels of inorganic fluoride in air are usually measured as total, gaseous, or particulate fractions of hydrogen fluoride and sulphur hexafluoride, and are usually reported as "fluoride". Information on the concentration of individual species of inorganic fluorides is presented when available.

The levels of fluoride in ambient air in most parts of Canada are generally low or undetectable (i.e., < 0.05 μg/m^3) [FPACAQ, 1991], 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 (analyzed between January 1981 and July 1981) was 0.03 μg/m^3 (detection limit not specified) [McGrath, 1983]. A mean concentration of fluoride of < 0.05 μg/m^3 was reported for 4 411 samples of ambient air (detection limit = 0.05 μg/m^3) 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) while the concentration of fluoride in urban air (n = 3 687) ranged from < 0.05 to 1.65 μg/m^3 (Thompson *et al.*, 1971). No information on the concentration of fluoride in the indoor air of homes within Canada was identified.

Mean concentrations in the vicinity of industrial sources can be up to an order of magnitude higher than in ambient air. The mean levels of inorganic fluoride in air near emitting industries in Canada generally range from 0.01 to 1.0 μg/m^3 fluoride (see Figure 2). The mean level of inorganic fluoride (predominately hydrogen fluoride) in air at distances up to 8 km from 5 aluminum smelters in Quebec ranged from 0.1 to 0.71 μg/m^3 fluoride (Environment Canada, 1993). The mean level of inorganic fluoride in the air near a steel plant in Hamilton, Ontario, in 1991 was 0.20 μg/m^3 fluoride (levels ranged from 0.17 to 0.24 μg/m^3 fluoride) [Environment Canada, 1993]. The mean levels of inorganic fluoride in the air within 5 km of a phosphate fertilizer plant in British Columbia in 1990 and 1991 were 0.43 and 0.59 μg/m^3, respectively (Environment Canada, 1993). The mean concentration of fluoride in 171 samples of outdoor air collected between April 1987 and October 1987 at Cornwall Island, Ontario, 1.65 km N.E. from an aluminum plant located in Massena, New York, was 0.79 μg/m^3 (detection limit not specified) [Environment Canada, 1988]; the mean concentration in 152 samples of air collected from the same location 1 year later (April 1988 to October 1988) was 0.85 μg/m^3 (Environment Canada, 1989c). The mean concentration of inorganic fluoride in 158 samples of air collected between

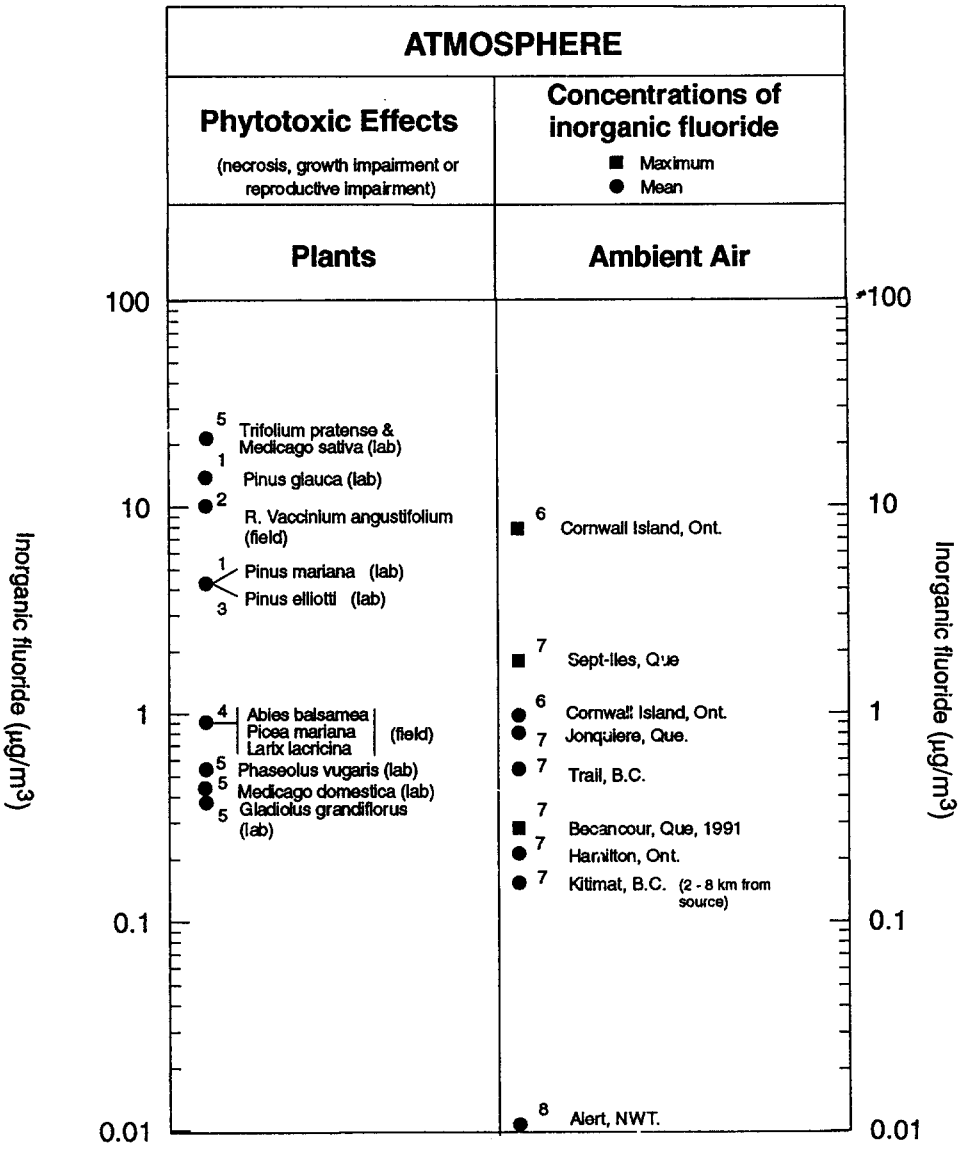
Figure 1. Inorganic fluoride (F) concentrations in Canadian waters and concentrations causing adverse effects to biota.



1. Smith *et al.* 1985.
2. Wright, 1977.
3. Hemens *et al.*, 1975.
4. Angelovic *et al.*, 1961.
5. Pimental and Bulkley, 1983.
6. Neuhold and Sigler, 1960.
7. Hemens and Warwick, 1972.
8. Fieser *et al.*, 1986.
9. Nell and Livanis, 1988.
10. Wright and Davidson, 1975.
11. Connell and Airey, 1982.
12. Pankhurst *et al.*, 1980.
13. Sparks *et al.*, 1983.
14. Antia and Klut, 1981.
15. Hekman *et al.*, 1984.
16. Nichol *et al.*, 1987.
17. Parker, 1992.
18. Alberta Environment, 1992.
19. Gauthier, 1992.
20. Warrington, 1992.
21. B.C. Environment, 1991.

Note: All species are freshwater unless otherwise indicated

Figure 2. Inorganic fluoride (F) concentrations in the Canadian atmosphere and concentrations causing adverse effects to plants.



1. McCune *et al.*, 1990.
2. Staniforth and Sidhu, 1984.
3. Doley, 1989.
4. Sidhu and Staniforth, 1986.
5. Hill and Pack, 1983.
6. Environment Canada, 1991.
7. Environment Canada, 1992.
8. Barrie and Hoff, 1982.

between April 1988 and October 1988 at Cornwall Island, 4.0 km N.E. of the aluminum plant, was 0.43 μg/m^3 (Environment Canada, 1989c). The average ambient mean air level at 2 rural locations on Cornwall Island between May and October 1991, was 0.68 μg/m^3 (Environment Canada, 1991). The mean concentrations of fluoride in samples of air collected between December 1980 and June 1981, 0.8 km from a brick manufacturing plant in Toronto, or within 1 km of a brick manufacturing plant in Brampton, Ontario, were 0.07 μg/m^3 and 0.73 μg/m^3, respectively (McGrath, 1983). The mean concentrations of inorganic fluoride in samples of air collected in 1982 and 1989 in the vicinity of a phosphorus plant in Newfoundland were approximately 0.15 and 0.14 μg/m^3, respectively (Newfoundland Department of Environment, 1989).

Data on the levels of sulphur hexafluoride in the atmosphere were not identified; however, it is estimated that, based on information on world-wide production and release, the global concentration[1] of sulphur hexafluoride in ambient air ranges from 0.006 to 0.3 μg/m^3 (0.001 to 0.05 ppbv), with an average of approximately 0.0091 μg/m^3 (0.0015 ppbv) [e.g., Ramanathan *et al.*, 1985; Chu, 1991]. These estimates are about 300 to 3 000 times less than the levels of CFCs (combined global average concentration = 2.8 to 23.9 μg/m^3 (0.5 to 4.2 ppbv) [Ramanathan *et al.*, 1985], and about 10^8 times less than the levels of carbon dioxide (average concentration = 6.2 to 8.2 × 10^5 μg/m^3 [340 to 450 ppmv]) [Ramanathan *et al.*, 1985].

The concentration of inorganic fluoride in samples of freshwater across Canada ranged from 0.01 to 11.0 mg/L (n = 51 299); the mean concentration was 0.05 mg/L fluoride (GSC, 1991; Parker, 1992) [see also Figure 1]. In general, the higher concentrations were present in samples from water obtained in the vicinity of industrial activities. Although recent information indicates that phosphate fertilizer production activities are the main source of inorganic fluorides to the aquatic environment in Canada, data on the levels in freshwaters near such facilities were not identified. The levels of inorganic fluoride in the Piskahegan River (Mount Pleasant, New Brunswick), located 2.5 km downstream from an abandoned tungsten mine, ranged from 0.24 to 1.37 mg/L (mean = 0.758 mg/L fluoride) [Gauthier, 1992]. The mean concentration of inorganic fluoride in 48 samples of water obtained between 1988 and 1991 from Big Meadow Brook (East Kemptville, Nova Scotia) was 3.8 mg/L; the maximum levels ranged from 5.9 to 11.0 mg/L (n = 7). This river is located 4 km downstream from an open pit tin mine tailings pond (Parker, 1992). The levels of inorganic fluoride in the Kitimat River (downstream of effluent discharges from an aluminum smelter, a methanol plant, and a

1. Data have been converted to SI-derived units of concentration using air conversion factors of 1 ppbv = 6.06 μg/m^3 for sulphur hexafluoride, 1 ppbv = 5.68 μg/m^3 for CFCs (based on CFC-11), and 1 ppbv = 1.82 μg/m^3 for carbon dioxide, assuming an ambient environmental temperature of 20°C and a pressure of 101.3 kPa.

pulp and paper mill) ranged from below detection (0.1 mg/L fluoride) to 0.19 mg/L (n = 32) [Warrington, 1992]. The mean concentration of inorganic fluoride at 242 sites across Alberta was 0.12 mg/L; the levels ranged from 0.05 to 0.95 mg/L (n = 10 429) [Alberta Environment, 1992]. In British Columbia, the mean concentration of inorganic fluoride at 21 sites was 0.22 mg/L; the levels ranged from 0.10 to 0.71 mg/L (n = 543) [British Columbia Ministry of Environment, 1991].

The mean global concentration of inorganic fluoride in seawater is 1.3 mg/L (Dobbs, 1974). Data on the levels of inorganic fluoride in seawater in Canada are limited to one region; the concentration of dissolved inorganic fluoride in Kitimat Harbour (British Columbia) in 1989 ranged from 0.2 to 44.0 mg/L (mean = 2.8 mg/L; n = 40). These samples of seawater were collected at distances between 100 and 800 metres from an aluminum smelter effluent outfall (Warrington, 1992). The levels of inorganic fluoride in samples collected between 1988 and 1990 at different locations in Kitimat Arm (within 2 km of an aluminum smelter, a methanol plant, and a pulp and paper mill) ranged from less than the detection limit (i.e., 0.1 mg/L fluoride) to 1.3 mg/L (n = 69) [Warrington, 1992]; the mean level in samples collected in Kitimat Arm closer to an industrial outfall was 1.2 mg/L fluoride (levels ranged from 0.1 to 6.9 mg/L, n = 25).

Recent identified data on the levels of inorganic fluoride in groundwater are limited. The mean concentration of inorganic fluoride in samples of groundwater in the Madoc area of southeastern Ontario was 0.105 mg/L (levels ranged from 0.0021 to 1.8 mg/L, n = 200) [Lalonde, 1976]. Levels ranging from 0.10 to 3.52 mg/L fluoride have been measured in samples of well water from a number of locations in British Columbia (British Columbia Ministry of Environment, 1991).

In 1986 (the last year for which data are available), approximately 62% of the population of Canada received "non-fluoridated"[2] drinking water. Based on the results of studies conducted between 1984 and 1989 in Prince Edward Island (Environment Canada, 1989a), New Brunswick (New Brunswick Department of Environment, 1989; Environment Canada, 1989b), British Columbia (Greater Vancouver Water District, 1990), the Northwest Territories (NWT) [Government of the Northwest Territories, 1989, cited in Hill and Hill, 1991], and the Yukon (Health and Welfare Canada, Yukon Territory, 1989, cited in Hill and Hill, 1991), the mean concentration of fluoride in "non-fluoridated" drinking water supplies in Canada ranges from < 0.05 to 0.21 mg/L.

2. Refers to drinking water to which inorganic fluoride has not been *intentionally* added for the prevention of dental caries.

In 1986, an estimated 38% of the population of Canada was supplied with "fluoridated"[3] drinking water (Droste, 1987). Based on the results of studies conducted between 1986 and 1989 in Newfoundland and Labrador (Droste, 1987), Nova Scotia (Droste, 1987), Quebec (Quebec Ministry of the Environment, 1990), Ontario (Ontario Ministry of the Environment, 1990a), Manitoba (Droste, 1987; Senka, 1990), Saskatchewan (Droste, 1987), the Yukon (Droste, 1987), and Alberta (Droste, 1987; Alberta Environment, 1990), the mean concentration of fluoride in "fluoridated" drinking water supplies in Canada ranges from 0.73 to 1.25 mg/L.

Throughout Canada, there are a number of communities where sources (not specified in the cited account) of drinking water contain elevated levels of inorganic fluoride from natural sources; however, those identified communities represent only a very small proportion (0.8%) of the total population (Droste, 1987). The concentrations of inorganic fluoride in the drinking water of these communities were generally between the levels observed in communities receiving "non-fluoridated" and "fluoridated" drinking water; however, higher levels of inorganic fluoride have been observed in the drinking water supplies of individual communities in Alberta (4.3 mg/L), Saskatchewan (2.8 mg/L), and Quebec (2.5 mg/L) [Droste, 1987].

Fluoride is a natural component of most types of soil, with concentrations ranging from 20 to 1 000 ppm (μg/g) in areas without natural phosphate or fluoride deposits, and up to several thousand ppm (μg/g) in mineral soils with deposits of fluoride (Davison, 1983). The levels of inorganic fluoride in ambient soils in Canada range from 300 to 700 mg/kg fluoride (Bowman *et al.*, 1979). The mean concentration of inorganic fluoride in Canadian Soil Survey Committee (CSSC) reference soil samples (n = 23) obtained at a depth of 0 to 130 cm was 309 ppm (μg/g); the mean concentration of total inorganic fluoride in CSSC soil (n = 3) collected near the surface (i.e, at a depth of 0 to 15 cm) was 160 ppm (μg/g) [Schuppli, 1985]. The concentration of total inorganic fluoride in (forest) soil collected in Newfoundland was 6 ppm (μg/g) [Sidhu, 1982]. Data on the levels of inorganic fluoride in soil near industrial sources in Canada have also been identified. The levels of inorganic fluoride in surface soil (collected at a depth of 0 to 3 cm) obtained 0.7 km from an elemental phosphorous plant in Long Harbour, Newfoundland, ranged from 1 138 to 1 915 ppm (μg/g); soil collected 18.7 km from the plant contained 18.7 to 26.1 ppm (μg/g) fluoride (Sidhu, 1979). The concentration of water-soluble inorganic fluoride in samples of soil collected 0.7 km from the plant ranged from 9.7 to 60.2 ppm (μg/g); levels in soil obtained 18.7 km from the plant ranged from 0.93 to 1.9 ppm (μg/g) [Sidhu, 1979].

3. Refers to drinking water to which inorganic fluoride has been *intentionally* added for the prevention of dental caries.

Data on the levels of inorganic fluoride in sediments near anthropogenic sources are limited. Sediment sampling surveys were conducted between 1984 and 1992 in the vicinity of an aluminum smelter, a pulp and paper mill, and a methanol plant located in the Kitimat River basin (Warrington, 1992). The levels of inorganic fluoride in marine sediments collected in 1989 at sites 400 metres from the aluminum smelter outfall and next to the methanol plant were 220 μg/g and 350 μg/g (dry weight, n = 1), respectively (Warrington, 1992). The mean concentration of inorganic fluoride in samples collected in 1990 within 150 metres of the aluminum plant ship basin was 1 370 μg/g (the levels ranged from 149 to 3 460 μg/g fluoride, n = 9). The mean concentration of inorganic fluoride in samples of sediment collected in 1988 from 14 sites in Kitimat Arm (within 1 km of the industries, n = 14) was 336 μg/g (the levels ranged from 271 to 390 μg/g fluoride).

Data on the levels of inorganic fluoride in biota[4] are limited to those collected in the vicinity of industrial sources. The mean levels of inorganic fluoride in silage obtained up to 7 km from 6 aluminum smelters in Quebec ranged from 6.1 to 14.4 mg/kg in 1990, and 5.3 to 17.4 mg/kg in 1991 (Environment Canada, 1993). The levels of inorganic fluoride in silver maple (*Acer saccharinum)* and red ash (*Fraxinus pensylvanica)* located 0.3 to 1.4 km from an oil refinery in Ontario ranged from 9.0 to 65.0 mg/kg and 5.0 to 24.0 mg/kg, respectively (Environment Canada, 1993). In 1991, the mean levels of inorganic fluoride in silver maple and poplar (*Populus* sp.) located within 2 km of a hydrogen fluoride chemical plant in Ontario were 16.0 and 19.0 mg/kg, respectively. At this site, the levels of inorganic fluoride in silver maple have declined steadily since 1987, when the concentration was 65.0 mg/kg fluoride (Environment Canada, 1993). The mean level of inorganic fluoride in a variety of plants sampled within 6 km of an aluminum smelter located in Bécancour, Quebec, ranged from 2.7 mg/kg (strawberries, *Fragaria* sp.) to 4.5 mg/kg (chinese cabbage) fluoride (Environment Canada, 1993). In the vicinity of the same smelter, mean levels in several coniferous tree species were 3.3 mg/kg (cypress), 3.9 mg/kg (spruce, *Picea* sp.), and 3.7 mg/kg (fir, *Abies balsamae*), whereas in moss (species not known), the level was 13.0 mg/kg fluoride. The mean levels of inorganic fluoride in forage vegetation (hay) collected less than 1 km from the smelter ranged from 24.4 to 121.9 mg/kg; less than 3 km from the smelter, the levels ranged from 5.1 (in hay) to 8.6 (in red clover) mg/kg fluoride (Environment Canada, 1993). The average mean concentration of fluoride in red maple (*Acer rubrum*) foliage collected at 3 locations on Cornwall Island, Ontario, between May and August 1988 was 68 μg/kg (n = 8); the average mean concentration in forage plants used as cattle feed collected at 8 locations on Cornwall Island, between May and October 1987, was 14.5 μg/kg [n = 48] (Ontario Ministry of the Environment, 1990b).

4. Unless otherwise noted, the levels of inorganic fluoride in biota are reported as dry weight.

Most of the data on the levels of inorganic fluoride in wildlife (such as deer [*Odocoileus virginianus*], martens [*Martes americana*], beaver [*Castor canadensis*], fox [*Vulpes vulpes*], hare [*Lepus americanus*], and moose [*Alces alces*]) were obtained during the 1960s and 1970s (Karstad, 1967; Alcan, 1979). The only recent data are those for species from the area near Bécancour, Quebec, where the level in skeletal tissues from muskrats (*Ondatra zibethicus*) was 12.0 mg/kg fluoride (the levels ranged from 7.0 to 22.0 mg/kg fluoride). The whole-body level of inorganic fluoride in sunfish (*Lepomus gibbosus*) collected from the Bécancour River was 2.5 mg/kg (the levels ranged from 0.06 to 7.4 mg/kg fluoride) [Environment Canada, 1993].

Recent information on the concentration of inorganic fluoride in foodstuffs consumed in Canada is limited to a single study of a wide range of (fresh and cooked) foods (Dabeka and McKenzie, 1993), with levels in other foods reported in studies conducted in the United States (Taves, 1983). Taves (1983) reported that food contains predominantly inorganic fluoride; however, Singer and Ophaug (1983) indicated that only between 34% and 79% of the total fluoride content of food is inorganic. The concentrations[5] of inorganic fluoride in 109 individual food items comprising the various composite groups routinely consumed by the population of Canada (Environmental Health Directorate, 1992) range from 0.01 to 0.80 μg/g in dairy products, 0.12 to 1.02 μg/g in cereal products, 0.01 to 0.58 μg/g in fruit, 0.01 to 0.68 μg/g in vegetables, 0.04 to 4.57 μg/g in meat, fish, and eggs, 0.05 to 0.13 μg/g in fats, 0.11 to 0.35 μg/g in nuts and legumes, 0.02 to 0.86 μg/g in foods containing primarily sugar, and 0.41 to 0.84 μg/g in soups, with 4.97 μg/g in tea (Dabeka and McKenzie, 1993; Taves, 1983). The levels of inorganic fluoride in (canned) fish, and shellfish (fresh or frozen) purchased in Canada were 4.57 μg/g and 3.36 μg/g, respectively (Dabeka and McKenzie, 1993).

Information on the levels of inorganic fluoride in infant formula are limited to samples collected in Canada in 1975 (Dabeka *et al.*, 1982) and 1980 (Dabeka and McKenzie, 1987); however, since that time, manufacturing processes in Canada have been adopted that reduce the level of fluoride in infant formula. The mean concentrations of fluoride in ready-to-use, milk-, and soy-based formula sold more recently in the United States were 0.127 and 0.305 mg/L, respectively (McKnight-Hanes *et al.*, 1988). The mean concentrations of fluoride in liquid milk- and soy-based concentrated formulas diluted with water containing 0.15 ppm (mg/L) fluoride were 0.196 mg/L and 0.317 mg/L, respectively; the mean concentrations in liquid milk- and soy-based concentrated formulas diluted with water containing 1 ppm (mg/L) fluoride were 0.621 mg/L and 0.742 mg/L, respectively. The mean concentrations of inorganic

5. The detection limits in Dabeka and Mackenzie (1993) ranged from 0.01 to 0.05 μg/g. Detection limits were not specified in Taves (1983).

fluoride in powdered milk- and soy-based formulas diluted with water containing 0.15 ppm (mg/L) fluoride were 0.170 mg/L and 0.200 mg/L, respectively; the mean concentrations in powdered milk- and soy-based formulas diluted with water containing 1 ppm (mg/L) fluoride were 0.825 mg/L and 0.854 mg/L, respectively (McKnight-Hanes *et al.*, 1988).

Available quantitative data on the concentration of fluoride in foods grown in areas in close proximity to industrial sources are limited to analyses of total fluoride content. Although the concentrations of total fluoride in unwashed or unprocessed foods grown in the vicinity of industrial sources (emissions) of inorganic fluoride in Japan (Muramoto *et al.*, 1991; Tsunoda and Tsunoda, 1986; Sakurai *et al.*, 1983) and the United Kingdom (Jones *et al.*, 1971) have been up to 100-fold greater than the levels observed in the same foods grown in other (non-industrially exposed) areas, it has been estimated that the average daily intake of fluoride from foods grown in the vicinity of industrial sources of inorganic fluoride is low, a consequence of the processing or washing of food products prior to their consumption (Sakurai *et al.*, 1983; Jones *et al.*, 1971).

More than 90% of dentifrice products commercially available in Canada (and the United States) contain inorganic fluoride (Beltran and Szpunar, 1988); concentrations range from 1 000 to 1 500 ppm (μg/g) [Whitford, 1987]. Topical mouthrinses marketed for daily home use contain between 250 to 500 ppm (mg/L) inorganic fluoride, while mouthwash products intended for weekly or biweekly use contain 1 000 ppm (mg/L) fluoride (Grad, 1990).

Inorganic fluoride has been detected in the breast milk of Canadian women. The overall mean concentration of inorganic fluoride in samples of breast milk collected from 210 women residing in communities served with “fluoridated” and “non-fluoridated” drinking water within Canada was 7.08 ng/g; (detection limit = 2.5 ng/g) [Dabeka *et al.*, 1986]. The mean concentration of inorganic fluoride in breast milk obtained from 32 women consuming drinking water containing < 0.16 ppm (mg/L) fluoride was 4.4 ng/g; the concentration in breast milk obtained from 112 women consuming water containing 1 ppm (mg/L) fluoride was 9.8 ng/g (Dabeka *et al.*, 1986).

2.4 Toxicokinetics

The absorption of inorganic fluoride is dependent upon solubility and varies considerably among fluoride-containing substances. Following absorption, bioavailable fluoride ion is rapidly distributed by the systemic circulation. Approximately 99% of the total body burden of inorganic fluoride is retained in bones and teeth (Hamilton, 1992; Kaminsky *et al.*, 1990; Grandjean and Thomsen, 1983). Fluoride becomes incorporated into the lattice of forming bone, by replacing hydroxyl ions (OH) within the unit cells of hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] producing

fluorapatite [$Ca_{10}(PO_4)_6(F)_2$] (Grynpas, 1990). In children with active bone growth or individuals not consuming "fluoridated" drinking water, up to 75% of the daily amount of fluoride absorbed may be incorporated into skeletal tissue (Hodge and Smith, 1965, cited in Caraicco *et al.*, 1983; U.S. DHHS, 1991). Fluoride retained in bone is gradually released from skeletal stores as a consequence of bone remodelling (McIvor, 1990; Spencer *et al.*, 1981, 1970; Grandjean and Thomsen, 1983; Boivin *et al.*, 1988). Under steady-state conditions, the long-term retention of a single dose of fluoride in mature bone is believed to be very small (Rao, 1984). In humans, fluoride crosses the placenta and is transferred from mother to foetus (Forestier *et al.*, 1990; WHO, 1984; Krishnamachari, 1987; Armstrong *et al.*, 1970; Caldera *et al.*, 1988).

2.5 Effects-related Information

2.5.1 Experimental Animals and In Vitro

In short-term studies, compared to unexposed controls, survival was reduced in male and female F344/N rats and in male, but not female, $B6C3F_1$ mice administered drinking water containing 363.2 mg/L fluoride for a period of 14 days (NTP, 1990). In other short-term studies, effects (compared to unexposed controls) on the skeleton included: an inhibition of (trabecular) bone mineralization in female Wistar rats administered drinking water containing 113.5 or 136.2 mg/L fluoride over a period of 5 weeks (Harrison *et al.*, 1984) [no-observed-effect-level (NOEL) = 12.7 mg/kg bw/day]; an inhibition of (endosteal) bone formation and a reduction in (cancellous) bone volume in male Holtzman rats administered drinking water containing 85.5 mg/L fluoride over a period of 21 days (lowest-observed-effect-level [LOEL] = 4.7 mg/kg bw/day) [Turner *et al.*, 1989]; delayed fracture healing and a reduction in collagen synthesis in male albino rats receiving 14 mg/kg bw/day fluoride for 30 days (Uslu, 1983); an increase in dermatan sulphate and chondroitin-6-sulphate in the bone (tibia) of male Sprague-Dawley rats receiving 17.5 mg/kg bw/day fluoride over a period of 1 to 2 months (Prince and Navia, 1983); and a 20% increase in bone-matrix formation in male C57BL/6 mice receiving 0.8 mg/kg bw/day fluoride for 4 weeks (Marie and Mott, 1986). Although male Swiss mice administered (orally) 5.2 mg/kg bw/day fluoride over a period of 35 days had reduced red blood cell counts and numbers of lymphocytes (39%), and increased numbers of monocytes, eosinophils, and basophils compared to controls (Pillai *et al.*, 1988), the levels of red blood cells, lymphocytes, neutrophils, monocytes, and eosinophils in male $B6C3F_1$ mice receiving 8.1 mg/kg bw/day fluoride (from drinking water for 24 weeks) were similar to those in controls receiving 0.6 mg/kg bw/day fluoride (NTP, 1990). Rabbits administered (intragastrically) 22.7 mg/kg bw/day fluoride for 45 days had alterations in the morphology of the diaphragm (Kaul and Susheela, 1976).

In sub-chronic studies, compared to unexposed controls, bone strength was increased (approximately 38%) or decreased (approximately 20%) in adult rats administered drinking water containing 16 ppm (mg/L), or 64 to 128 ppm (mg/L) fluoride, respectively, over a period of 16 weeks (lowest-observed-adverse-effect-level) [LOAEL] = 12.8 mg/kg bw/day) [Turner *et al.*, 1992], and altered bone remodelling (based on thickening of the osteoid seams in the tibia and femur) was observed in male and female $B6C3F_1$ mice administered water containing ≥ 22.7 and 45.4 mg/L fluoride, respectively, over a period of 6 months (LOEL = 4.5 mg/kg bw/day) [NTP, 1990]. Other effects (compared to unexposed controls) in animals administered drinking water containing fluoride for 6 months included: hyperplasia of the stomach and pathological effects (lymphocytic infiltration, hyperplasia, necrosis) in the glandular stomach of F344/N rats administered drinking water containing 45.4 mg/L and 136 mg/L fluoride, respectively (NTP, 1990); and reduced survival (82% and 44% in female and male $B6C3F_1$ mice, respectively), hepatic megalocytosis, renal nephrosis, mineralization of the myocardium, and necrosis/or degeneration of the seminiferous tubules in the testis of $B6C3F_1$ mice receiving water containing 272.4 mg/L fluoride (NTP, 1990). The daily intragastric administration of 22.7 mg/kg bw/day fluoride (as sodium fluoride) to rabbits for 136 days interfered with the maturation and metabolism of collagen (Sharma, 1982a). In studies in which rabbits were administered daily subcutaneous injections of sodium fluoride for 100 days, animals receiving ≥ 4.5 mg/kg bw/day fluoride had pulmonary haemorrhage, congestion and hyperplasia, histopathological changes (lymphatic tissue hypertrophy in the trachea and vacuolation and necrosis of tracheal epithelial cells) and alterations in the lipid content of the trachea, compared to controls (Shashi *et al.*, 1987, 1988, 1989). Alterations in the lipid content of the lung, thyroid, and testis (Shashi, 1988, 1992; Shashi *et al.*, 1987, 1989), muscle fibre hypertrophy and necrosis (Shashi, 1989), and reduced protein (acidic and basic) content of the thigh muscle (Shashi *et al.*, 1992) were observed in animals receiving ≥ 2.3 mg/kg bw/day fluoride, compared to controls.

In studies of the chronic toxicity of fluoride, compared to controls, bone mineralization (based on microscopic analysis) was inhibited in male and female rats administered drinking water containing 22.7 and 36.3 mg/L fluoride (as sodium fluoride) over a period of 250 days (Qiu *et al.*, 1987) [LOAEL considered = 3.2 mg/kg bw/day fluoride]. Compared to controls, the administration (orally) of 4.5 mg/kg bw/day fluoride (as sodium fluoride) to rabbits for periods ranging from 6 to 24 months produced slight alterations in ATPase (sodium and potassium) activity within erythrocytes, serum acid and alkaline phosphatase activity (Jain and Susheela, 1987a), the levels of dermatan sulphate, chondroitin-4-sulphate and chondroitin-6-sulphate in cancellous bone (Sharma and Susheela, 1988a), the number of haematopoietic cells in the blood (Susheela and Jain, 1983), and in the disaccharide content of glycosaminoglycans isolated from cancellous bone (Sharma and Susheela, 1988b). Evidence of mineralization of the aorta (Susheela and Kharb, 1990), morphological

changes within the duodenum (Susheela and Das, 1988), and alterations in skin collagen metabolism (Sharma, 1982b) have also been observed in rabbits administered 4.5 mg/kg bw/day fluoride for periods ranging from 6 to 24 months. Other effects produced following the chronic exposure of rabbits to fluoride included alterations in the proportion of erythrocytes with abnormal morphology (Susheela and Jain, 1986), the level of cortisol and corticosterone in the plasma (Das and Susheela, 1991), the level of sialic acid and glycosaminoglycans in the serum (Jha *et al.*, 1982), and a reduction in the amount of hydroxyproline present in collagen derived from tendons and cortical bone (Susheela and Sharma, 1982). Alterations in bone remodelling (based on histomorphometric analysis) have been observed in pigs (Mosekilde *et al.*, 1987; Kragstrup *et al.*, 1989) administered (orally) 2 mg/kg bw/day fluoride (as sodium fluoride) and dogs (Snow and Anderson, 1986) receiving 0.32 mg/kg bw/day fluoride (from drinking water containing sodium fluoride) over a period of 6 months.

In early carcinogenicity bioassays conducted by Kanisawa and Schroeder (1969), Taylor (1954), and Tannenbaum and Silverstone (1949), the incidence of tumours in mice administered sodium fluoride (either in their diet or drinking water) was, in general, not markedly greater than that observed in the unexposed controls. However, the documentation and protocols of these studies were inadequate. Deficiencies in design included small groups of animals of single sexes or various ages exposed to single-dose levels for short periods of time with inadequate examination of possible target tissues.

In a recent comprehensive study of the carcinogenicity of sodium fluoride in laboratory animals (NTP, 1990), groups of male and female F344/N rats and $B6C3F_1$ mice were administered drinking water containing 0, 25, 100, and 175 ppm (mg/L) sodium fluoride over a period of 2 years. There were 100 rats in each of the control and 175 ppm groups, while 70 rats/group were administered drinking water containing 25 or 100 ppm sodium fluoride. Groups of 10 rats of each sex at each level of exposure were sacrificed after 27 and 66 weeks. The estimated intakes of fluoride (from food and drinking water) by the male and female F344/N rats administered drinking water containing 0 (control), 25, 100, and 175 ppm (mg/L) sodium fluoride were approximately 0.2, 0.8, 2.5, and 4.1 mg/kg bw/day, and 0.2, 0.8, 2.7, and 4.5 mg/kg bw/day, respectively (NTP, 1990). At the end of the 2-year study (in the high-dose groups, 42 males and 54 females survived until terminal sacrifice), the levels of fluoride in the bone of the control, low-, mid-, and high-dose male and female rats were approximately 0.44, 0.98, 3.65, and 5.26 μg/mg bone ash, and 0.55, 1.34, 3.72, and 5.55 μg/mg bone ash, respectively (NTP, 1990).

In male F344/N rats receiving 0.2, 0.8, 2.5, and 4.1 mg/kg bw/day fluoride, the incidence of osteosarcomas (3 tumours in the vertebra and 1 in the humerus) was 0/80, 0/51, 1/50, and 3/80, respectively. A pairwise comparison of the incidence in the high-dose group versus control was not significant (P = 0.099) [NTP, 1990], and if an extraskeletal osteosarcoma (located in the subcutis of the flank of one high-dose male rat) was included in the total tumour incidence in this group of animals, the pairwise comparison with the control group remained not significant (P = 0.057); however, the osteosarcomas occurred with a significant (P = 0.027, by logistic regression) dose-response trend (NTP, 1990). The incidence of osteosarcoma (any site) was within the range of historical controls; however, the amount of fluoride in the diets in previous studies was approximately 3.5- to 5.9-fold higher than that in the current study (NTP, 1990). In male F344/N rats receiving 0.2, 0.8, 2.5, and 4.1 mg/kg bw/day fluoride, the incidence of neoplasms of the oral cavity (squamous papillomas or squamous cell carcinomas) and (thyroid gland) follicular cell adenomas and carcinomas was 0/80, 1/51, 2/50, and 3/80, and 1/80, 1/51, 1/50, and 4/80, respectively. There was no increase in the incidence of osteosarcomas in female F344/N rats, and the incidence of oral cavity neoplasms (squamous papillomas or squamous cell carcinomas) was 1/80, 1/50, 1/50, and 3/81 in female F344/N rats receiving 0.2, 0.8, 2.7, and 4.5 mg/kg bw/day, respectively (NTP, 1990).

In the NTP carcinogenicity bioassay in male and female F344/N rats, no significant compound-related effects upon survival, body weight, or weights of major internal organs were observed compared to controls (NTP, 1990) [no-observed-adverse-effect-level (NOAEL) = 4.1 mg/kg bw/day fluoride (male rats)]; however, the incidence of osteosclerosis in female rats administered drinking water containing 175 ppm sodium fluoride (18/81) was significantly (p = 0.04) increased, compared to controls [6/80] (NTP, 1990) [NOAEL = 2.7 mg/kg bw/day fluoride (female rats)].

In a carcinogenicity bioassay in Sprague-Dawley rats, groups of 70 animals of each sex were administered diets supplemented with various amounts of sodium fluoride over a period of 95 to 99 weeks (Maurer *et al.*, 1990). After 26 weeks on study, as many as 10 animals of each sex per group were sacrificed, and after 53 weeks, 10 animals of each sex per group were sacrificed (Maurer *et al.*, 1990). The incidence of bone tumours was 0/70, 0/58, 2/70 (1 chordoma and 1 chondroma), and 1/70 (fibroblastic sarcoma with areas of osteoid formation) in male rats, and 0/70, 2/52 (1 osteosarcoma and 1 chondroma), 0/70, and 0/70 in female rats receiving 0.1, 1.8, 4.5, and 11.3 mg/kg bw/day fluoride, respectively (Maurer *et al.*, 1990). At terminal sacrifice (i.e., after 95 and 99 weeks on study for males and females, respectively) there were 26 males and 12 females in the high-dose groups; the concentration of fluoride in the bone of the males and females receiving 0.1, 1.8, 4.5, or 11.3 mg/kg bw/day fluoride was 0.5, 5.0, 8.8, and 16.7 μg/mg bone ash, and 0.5, 4.5, 8.3, and 14.4 μg/mg bone ash, respectively. Detailed information on the incidence of tumours in tissues or organs other than the bone and stomach were not presented, and

histological examination of bone from both mid-dose groups was limited. The cranium, femur, premaxilla, maxilla, mandible, cervical vertebra, stomach, liver, kidney, incisors, adrenals, brain, heart, lungs, ovaries, uterus, pancreas, pituitary, prostate, seminal vesicles, spleen, bladder, testes, epididymides, thyroids, and parathyroids obtained at the interim and terminal sacrifices from all animals receiving 0.1 or 11.3 mg/kg bw/day fluoride were examined microscopically. The stomach, bones, and teeth from animals receiving 4.5 mg/kg bw/day fluoride and sacrificed after 26 weeks, and from animals receiving 1.8 or 4.5 mg/kg bw/day fluoride and sacrificed after 53 weeks, were also examined microscopically (Maurer *et al.*, 1990). Not all of the bones (i.e., cranium, femur, premaxilla, maxilla, mandible, cervical vertebra) from each of the remaining animals (i.e., those alive after the interim sacrifices) receiving 1.8 or 4.5 mg/kg bw/day fluoride were examined microscopically; however, tissues with gross lesions obtained from dead and moribund animals were. Sprague-Dawley rats receiving 11.3 mg/kg bw/day fluoride (administered in the diet) over a period of 95 to 99 weeks had reduced weight gain; animals receiving 4.5 and 11.3 mg/kg bw/day fluoride had an increased incidence of subperiosteal hyperostosis in the skull and hyperkeratosis and acanthosis in the stomach, compared to controls receiving 0.1 mg/kg bw/day (Maurer *et al.*, 1990) [NOAEL = 1.8 mg/kg bw/day fluoride].

For male and female B6C3F_1 mice administered drinking water containing 0, 25, 100, and 175 ppm sodium fluoride for 2 years (there were 100 animals in each of the control and 175 ppm groups, and 70 mice/group were administered drinking water containing 25 or 100 ppm sodium fluoride), the intake of fluoride from water and the diet was estimated to be approximately 0.6, 1.7, 4.9, and 8.1 mg/kg bw/day, and 0.6, 1.9, 5.7, and 9.1 mg/kg bw/day, respectively (NTP, 1990). At the end of the 2-year study (groups of 10 animals of each sex at each level of exposure were sacrificed after 24 and 66 weeks), the levels of fluoride in the bone of the control, low-, mid-, and high-dose male and female mice were approximately 0.72, 1.61, 3.58, and 5.69 μg/mg bone ash, and 0.92, 1.52, 4.37, and 6.24 μg/mg bone ash, respectively (NTP, 1990).

In male B6C3F_1 mice receiving 0.6, 1.7, 4.9, and 8.1 mg/kg bw/day fluoride, the incidence of hepatoblastomas was 0/79, 1/50, 1/51, and 3/80, respectively. The overall incidence of hepatic neoplasms (adenoma, carcinoma, hepatoblastoma) was similar among all groups, and incidence of liver tumours in all groups (control and exposed) of male mice (73% to 78%) was higher than observed (16% to 58%) in previous NTP carcinogenicity bioassays (NTP, 1990). In female B6C3F_1 mice receiving 0.6, 1.9, 5.7, and 9.1 mg/kg bw/day fluoride, the incidence of hepatoblastomas and malignant lymphomas was 0/80, 1/52, 0/50, and 2/80, and 11/80, 5/52, 11/50, and 19/80, respectively (NTP, 1990). The overall incidence of hepatic neoplasms (adenoma, carcinoma, hepatoblastoma) was similar among all groups, and the incidence of liver tumours in all groups (control and exposed) of female mice (52% to 69%) was higher than observed (3% to 20%) in previous NTP carcinogenicity bioassays (NTP, 1990). The slight increase in the incidence of malignant lymphoma (in the high-dose group)

was not statistically significant (p = 0.051), and the incidence in the control and low-dose groups was less than the lowest incidence observed in 9 other investigations conducted at the study laboratory. In addition, the incidence in the high-dose group was similar to that observed in historical controls, which ranged from 10% to 74% (NTP, 1990).

The administration of drinking water containing 25, 100, or 175 ppm sodium fluoride to male or female B6C3F_1 mice over a period of 2 years had no significant compound-related adverse effects upon survival, body weight, or weights of major internal organs compared to controls (NTP, 1990) [NOAEL = 4.9 mg/kg bw/day fluoride (male mice); NOAEL = 5.7 mg/kg bw/day fluoride (female mice)].

In a carcinogenicity bioassay in which sodium fluoride was administered in the diet to groups of 60 male and female CD-1 mice over a period of 95 and 97 weeks, respectively (10 mice of each sex per group were sacrificed after 40 weeks), the incidence of osteomas in male and female controls and mice receiving 1.8, 4.5, or 11.3 mg/kg bw/day fluoride was 1/50, 0/42, 2/44 and 13/50, and 2/50, 4/42, 2/44, and 13/50, respectively (Maurer *et al.*, 1993). The incidence of this type of tumour was increased in the high-dose groups compared to the controls; however, the animals were infected with a Type C retrovirus (Maurer *et al.*, 1993). The concentration of fluoride in the bone of male controls and mice receiving 1.8, 4.5, or 11.3 mg/kg bw/day fluoride was approximately 1.5, 4.4, 7.2, and 13.2 μg/mg bone ash, respectively; the concentration of fluoride in the bone of female controls and mice receiving 1.8, 4.5, or 11.3 mg/kg bw/day fluoride was approximately 1.0, 3.4, 6.2, and 10.6 μg/mg bone ash, respectively.

The genotoxicity of fluoride has been examined in a large number of *in vitro* and *in vivo* assays, in which a wide range of end-points has been assessed (see Supporting Documentation). Generally, fluoride is not mutagenic in microbial cells, but increases the frequency of gene-locus mutations in cultured mammalian cells and induces the "morphological transformation" of Syrian hamster embryo cells at cytotoxic concentrations *in vitro*. The available data suggest that gene-locus mutations induced by fluoride arise primarily from clastogenic events rather than point mutations, and are due to the fluoride ion *per se* and not general ionic effects. Although the results of some studies have indicated that (sodium) fluoride increases unscheduled DNA synthesis in mammalian cells, these results were not confirmed when steps were taken to eliminate potential artifacts (i.e., the formation of precipitable complexes of magnesium, fluoride and [^{3}H]thymidine).

Fluoride (as sodium fluoride) should be considered capable of inducing chromosomal aberrations, micronuclei, and sister-chromatid exchanges *in vitro* in mammalian cells, although the results from such studies have been inconsistent. The increased frequency of chromosomal aberrations in mammalian cells produced by exposure to (sodium) fluoride appears to be highly dependent upon the protocol used to quantitate the effect. The pattern of induced chromosomal aberrations (predominantly deletions and gaps, with few exchanges), increased endoreduplication, cell cycle delay, and sensitivity of cells in G_2 are all consistent with a mechanism of clastogenicity involving the inhibition of DNA synthesis and/or repair by fluoride (which has been attributed to its effects upon the synthesis of proteins involved in DNA synthesis and/or repair) rather than direct interaction between fluoride and DNA. Chromosomal aberrations have not been detected in cells exposed *in vitro* to levels of fluoride less than 10 μg/mL, which has been suggested as a threshold for the clastogenic activity of fluoride.

The results of studies on the genotoxic potential of fluoride following its *in vivo* administration to laboratory animals have varied, principally depending upon the route of administration. Sodium fluoride induces recessive lethal mutations in the germ cells of male *D. melanogaster*, and there is evidence that (sodium) fluoride induces cytogenetic damage in rodents, if the compound is administered by intraperitoneal injection. In most studies in which (sodium) fluoride was administered orally (either acutely or chronically) to laboratory animals, no effect upon the frequency of chromosomal aberrations, micronuclei, sister-chromatid exchange, DNA strand breaks, or sperm morphology was observed.

Adverse effects on reproductive function have been observed in female mice administered (orally) ≥ 5.2 mg/kg bw/day fluoride on days 6 to 15 after mating (Pillai *et al.*, 1989), and in male rabbits administered (orally) ≥ 9.1 mg/kg bw/day fluoride for 30 days (Chinoy *et al.*, 1991). Histopathological changes within the organs of the reproductive system have been observed in the testes of male rabbits administered (orally) 4.5 mg/kg bw/day fluoride for 18 to 29 months (Susheela and Kumar, 1991), in the ovaries of female rabbits injected subcutaneously with ≥ 10 mg/kg bw/day fluoride for 100 days (Shashi, 1990), and in the testes of male mice administered (orally) ≥ 4.5 mg/kg bw/day fluoride for 30 days (Chinoy and Sequeira, 1989a, 1989b). Adverse effects on the bones of developing rats have not been observed following exposure of the dams prior to breeding, and during pregnancy and lactation, to 150 ppm (mg/L) fluoride in drinking water (Ream *et al.*, 1983a), although effects on the bones of the dams were observed (Ream *et al.*, 1983b) [LOEL (dams) considered = 21.4 mg/kg bw/day].

T-Cell mitogenesis was significantly increased (84%) while B-cell activity (antibody production) was significantly reduced (10%) in female C57BL/6N mice administered (intragastrically) 13.6 mg/kg bw/day fluoride (as sodium fluoride dissolved in distilled water) for 10 weeks, compared to controls (Sein, 1988) [NOEL = 9.1 mg/kg bw/day fluoride]. Antibody production was also inhibited in female rabbits administered (orally) 4.5 mg/kg bw/day fluoride over a 6 to 9 month period (Jain and Susheela, 1987b).

2.5.2 Humans

In humans, acute (oral) exposure to fluoride may produce effects that include nausea, vomiting, abdominal pain, diarrhoea, fatigue, drowsiness, coma, convulsions, cardiac arrest, and death (ATSDR, 1991; WHO, 1984; Kaminsky *et al.*, 1990; Augenstein *et al.*, 1991; Whitford, 1990). The lethal dose (i.e., LD_{100}) of (sodium) fluoride in the average adult may be between 5 and 10 g (32 to 64 mg/kg bw fluoride) [WHO, 1984; Whitford, 1990].

Almost all epidemiological studies in which the health effects in populations exposed to fluoride in the general environment have been examined were geographic or ecologic correlational investigations. Such studies are characterized by the use of aggregate units of observation, such as counties, states, or provinces, rather than individuals, and usually involve the comparison of mortality or morbidity rates between exposed and unexposed areas or among areas with varying degrees of exposure. Generally, studies of this nature are limited, since the movement of individuals in and out of the exposed and non-exposed groups, and other variable factors (i.e., industrialization, personal habits, etc.) which have an influence on the development of adverse health effects are not taken into account, and the statistical power may be insufficient to reveal small differences in health-related effects (i.e., increases in the incidence of rare tumours). Moreover, in such ecological studies, the intake of inorganic fluoride from other sources such as food and dental care products (U.S. DHHS, 1991) was not taken into account. Notably, the total intake (i.e., total exposure) of inorganic fluoride by individuals consuming “fluoridated” or “non-fluoridated” drinking water may not be markedly different, due to the intake of significant amounts of inorganic fluoride from food and dental care products (Burt, 1992; U.S. DHHS, 1991).

The relationship between the consumption of “fluoridated” drinking water and the incidence of, or mortality due to cancer has been examined in more than 50 epidemiological studies, performed in many countries including Canada (U.S. DHHS, 1991). Based on extensive reviews of older epidemiological investigations by the International Agency for Research on Cancer (IARC, 1982, 1987), the British Working Party on the Fluoridation of Water and Cancer (Knox, 1985) and the U.S. National Academy of Sciences (cited in U.S. DHHS, 1991), there has been no consistent

evidence of an association between the consumption of “fluoridated” drinking water and increased morbidity or mortality due to cancer. Moreover, in recent ecological studies of the United States, Canada, and Europe (Hoover *et al.*, cited in U.S. DHHS, 1991; Freni and Gaylor, 1992), no consistent relationship was observed between deaths due to any type of cancer and the consumption of “fluoridated” drinking water. Thus, in virtually all of the ecological studies reported to date, there has been no reliable evidence of an association between the consumption of “fluoridated” drinking water and increased incidence of, or mortality due to cancer, although in most investigations bone cancer was not specifically assessed.

The health of workers occupationally exposed to fluorides, particularly those employed in the aluminum smelting industry, has been examined in epidemiological studies. Workers in this industrial setting are also exposed to a number of other substances (ammonia, carbon monoxide, sulphur dioxide, distillation products of tar, pitch and coal, aluminum oxide [alumina], aluminum and silicon [fluorides], cyanides, and dust and metals such as nickel, chromium, and vanadium [Hodge and Smith, 1977; Soyseth and Kongerud, 1992; Chan-Yeung *et al.*, 1983a, 1983b; IARC, 1984]). Thus, it is difficult to definitively attribute the adverse health effects observed in these occupationally exposed workers solely to their exposure to inorganic fluoride.

In a number of analytical epidemiological studies, an increased incidence of lung and bladder cancer and increased mortality due to cancer of the lung, liver, bladder, stomach and oesophagus, pancreas, lymphatic-hematopoetic system, and brain (central nervous system) was observed in workers employed in the aluminum smelting industry (using cryolite as a source of aluminum) [reviewed in Ronneberg and Langmark, 1992]; however, generally there has been no consistent pattern (bone cancer was not usually assessed). Although increases in lung cancer were observed in several studies, due to concomitant exposure to other substances it is not possible to attribute these increases to fluoride. For example, in some of these epidemiological studies the increased incidence of, or death due to cancer was attributed to the workers’ exposure to aromatic hydrocarbons (see Ronneberg and Langmark, 1992, for a review). Although Grandjean *et al.* (1992) indicated that a portion of the increase in the incidence of bladder cancer (17 observed versus 9.2 expected) in workers employed at a cryolite mill in Denmark may be attributable to occupational exposure to inorganic fluoride, the workers were exposed to other substances (e.g., quartz, siderite and small amounts of metal sulfides [Grandjean *et al.*, 1985]). The increased rate of lung cancer in fluorspar miners has been attributed to their concomitant exposure to radon gas (de Villiers and Windish, 1964, cited in WHO, 1984).

Skeletal fluorosis is a pathological condition that may arise following long-term exposure (either by inhalation or ingestion) to elevated levels of fluoride. Although the incorporation of fluoride into bone may increase the stability of the crystal lattice, and render the bone less soluble, bone mineralization is delayed or inhibited (Grynpas, 1990), and consequently the bones may become brittle and their tensile strength reduced (U.S. DHHS, 1991). Clinical signs associated with the preclinical and (3) clinical stages of skeletal fluorosis have been reviewed (U.S. DHHS, 1991), with the severity of this condition related to the amount of fluoride in the bone. In the preclinical phase, the "fluorotic" patient may be relatively asymptomatic, with only a slight increase in bone mass (detected radiographically) [however, the diagnosis of (early-stage) skeletal fluorosis may differ among health care professionals (Chan-Yeung *et al.*, 1983a)]. Sporadic pain and stiffness of the joints, chronic joint pain, osteosclerosis of cancellous bone, and calcification of ligaments are associated with the first and second clinical stages of skeletal fluorosis. Crippling skeletal fluorosis (clinical phase III) may be associated with limited movement of the joints, skeletal deformities, intense calcification of ligaments, muscle wasting, and neurological deficits (Kaminsky *et al.*, 1990; U.S. DHHS, 1991; Krishnamachari, 1987). Osteomalacia may be observed in fluorotic individuals with a reduced or suboptimal intake of calcium; secondary hyperparathyroidism may also be observed in a subset of patients (U.S. DHHS, 1991; Krishnamachari, 1987). While bone without fluoride-induced alterations contains approximately 500 to 1 000 mg fluoride/kg bone (ash weight), the concentration of fluoride in the bone of individuals with the preclinical or crippling stages of skeletal fluorosis may be between 3 500 and 5 500 or greater than 8 400 mg fluoride/kg bone, respectively (U.S. DHHS, 1991). A number of factors such as age, nutritional status, renal function, and calcium intake, in addition to the extent and duration of exposure can influence the amount of fluoride deposited in bone, and, consequently the development of skeletal fluorosis (U.S. DHHS, 1991). Individuals with impaired renal function (such as those with diabetes) may be more prone to developing fluoride-related toxicological effects (i.e., fluorosis) due to their diminished excretion of fluoride (ATSDR, 1991; U.S. DHHS, 1991; Kaminsky *et al.*, 1990; WHO, 1984). Skeletal fluorosis may be reversible (at least to some degree) in a manner that is dependent upon the extent of bone remodelling (Grandjean and Thomsen, 1983).

Twenty-three cases of osteosclerosis "due to fluoride" (based on radiographic analysis) were identified from 170 000 pelvic and spinal X-rays of individuals residing in Texas and Oklahoma, who consumed drinking water containing between 4 and 8 mg/L fluoride (Stevenson and Watson, 1960), and a greater incidence of radiographic changes in the bone was observed in individuals residing in a small town in Texas who had consumed drinking water containing approximately 8 mg/L fluoride for an average of 37 years, compared to individuals residing in another town served by drinking water containing 0.4 mg/L fluoride; however, no overt clinical symptoms of skeletal fluorosis were observed (Leone *et al.*, 1955). Felsenfeld and Roberts (1991)

recently reported the case of a 54-year old woman who, after having consumed drinking water containing approximately 8 mg/L fluoride over a period of 7 years, had osteosclerosis and stiffness in her knees and hips. Five cases of crippling skeletal fluorosis in the United States have been reported over the past 40 years; the total intake of fluoride by some of these individuals over a 20-year period was estimated to be approximately 15 to 20 mg/day (U.S. DHHS, 1991) [equivalent to a daily intake of 215 to 285 μg/kg bw/day fluoride, in an adult weighing 70 kg]. The development of (endemic) crippling skeletal fluorosis has been documented in case reports and surveys of individuals residing in areas of India, Africa, and China who consume drinking water containing fluoride (concentrations ranged from approximately 3 to more than 20 mg/L) [reviewed in Kaminsky *et al.*, 1990; WHO, 1984; U.S. DHHS, 1991; and Krishnamachari, 1987]; however, a number of factors, such as the dietary intake of calcium and protein, the extent of physical labour, climate (related to fluid intake), concomitant exposure to other substances, and the intake of fluoride from sources other than drinking water, are believed to play a significant role in the development of crippling skeletal fluorosis in persons residing in tropical areas (WHO, 1984; Krishnamachari, 1987; Singh and Jolly, 1970; Haimanot, 1990).

Epidemiological studies, in which the occurrence of skeletal fractures in relation to the consumption of "fluoridated" drinking water has been examined, have been predominantly of an ecological design, and in most of the recent and generally the largest studies, elevated rates of hip fracture have been observed in areas with drinking water containing elevated levels of fluoride (from 1 to 4 mg/L) [Cooper *et al.*, 1991; Keller, 1991, cited in Gordon and Corbin, 1992; Jacobsen *et al.*, 1992; Danielson *et al.*, 1992; Suarez-Almazor *et al.*, 1993], or where the proportion of the population consuming "fluoridated" drinking water was greater than that consuming "non-fluoridated" drinking water (May and Wilson, 1991, cited in Gordon and Corbin, 1992; Jacobsen *et al.*, 1990). There was evidence of an exposure-response relationship in 2 studies (Keller, 1991; May and Wilson, 1991, both cited in Gordon and Corbin, 1992), and the relationship was apparent in the one study of strongest design (i.e., involving analysis of time trends in comparison with that of a control population). The relative risk of hip, wrist, or spinal fracture was 2.7 (95% CI = 0.16 – 8.28) and 2.2 (95% CI = 1.07 – 4.69) in women 20 to 35 and 55 to 80 years of age, respectively, residing in an elevated-fluoride community (with drinking water containing 4 mg/L) compared to those in a control community (with drinking water containing 1 mg/L fluoride); the estimated (mean) intake of fluoride by women in the elevated-fluoride community was approximately 72 μg/kg bw/day (Sowers *et al.*, 1986, 1991).

Effects on the skeleton have been reported in a limited number of older cross-sectional epidemiological studies in which the health of populations residing in the vicinity of aluminum- or phosphate/fertilizer-production facilities was examined (Tsunoda, 1970a, 1970b; Tsiji and Tsunoda, 1970); however, there has been no consistent pattern of adverse effects in such populations exposed to often unspecified concentrations of

airborne fluorides. Skeletal effects have also been reported in some (Tourangeau, 1944; Boillat *et al.*, 1975; Schegel, 1974, all cited in Hodge and Smith, 1977; Kaltreider *et al.*, 1972; Czerwinski *et al.*, 1988), but not all studies of workers in aluminum plants who were exposed to levels of airborne inorganic fluoride considerably higher than those in the general environment. Although the occurrence of skeletal fluorosis in aluminum smelter workers was reported in other studies reviewed by Hodge and Smith (1977), the numbers of workers examined was usually small and quantitative data on exposure to airborne inorganic fluoride were not usually provided. Based on consideration of the collective data available from studies involving aluminum smelter workers, Hodge and Smith (1977) concluded that the occurrence of fluoride-induced osteosclerosis was elevated if workers were exposed to levels of airborne fluoride greater than 2.5 mg/m^3 (estimated to provide an intake of approximately 195 μg/kg bw/day fluoride, in an adult weighing 70 kg). This is consistent with the more recent observation that there were no definitive signs of skeletal fluorosis in workers exposed to approximately 0.48 mg/m^3 fluoride at an aluminum smelter in British Columbia (Chan-Yeung *et al.*, 1983a) [estimated to provide an intake of approximately 52 μg/kg bw/day fluoride, in an adult weighing 70 kg]. The development of skeletal fluorosis in cryolite workers in Copenhagen was attributed to the intake (from occupational exposure) of between 20 to 80 mg/day fluoride (estimate based on the concentration and fluoride content of dust in the factory) [Roholm, 1937, cited in Grandjean, 1982] (equivalent to a daily intake of 285 to 1 142 μg/kg bw/day fluoride, in an adult weighing 70 kg).

Sodium fluoride has been used in clinical studies for the treatment of osteoporosis. These investigations usually involve small numbers of individuals comprising only a subset of the general population (i.e., predominantly post-menopausal females) with a clinically detectable disease involving the bones, and are therefore not likely to be representative of the general population. In addition, patients undergoing therapy with (sodium) fluoride generally receive other supplements (i.e. calcium, vitamin D_2) as part of the therapeutic protocol, and the intake of inorganic fluoride from other sources (i.e., food, drinking water, dental care products) is not quantitated. Evidence of stage I fluorosis (i.e., coarsening of trabecular bone pattern) was observed in a small number of female osteoporotic patients administered 40 to 60 mg/day sodium fluoride (equivalent to a dose of 260 to 389 μg/kg bw/day fluoride, in an adult weighing 70 kg) [and calcium and vitamin D_2] over a period of 18 months (Power and Gay, 1986). Based on a review of the available data from clinical studies (details of which were not specified in the secondary account), Kleerekoper and Balena (1991) indicated that, depending upon whether the patients are receiving concurrent supplementation with calcium and vitamin D_2, a reduction in bone mineralization may be observed at doses greater than 40 mg sodium fluoride/day (equivalent to a dose of 260 μg/kg bw/day fluoride, in an adult weighing 70 kg); however, the osteomalacia may be clinically asymptomatic and not have any severe effects.

An increased incidence of skeletal fractures in osteoporotic patients receiving sodium fluoride has been reported in some, but not all studies, at doses equivalent to 260 μg/kg bw/day fluoride or more (Gutteridge *et al.*, 1984, cited in Inkovaara, 1991; Power and Gay, 1986; Mamelle *et al.*, 1988; Hedlund and Gallagher, 1989; Riggs *et al.*, 1990). Notably, no increase in the incidence of hip fracture was observed in a study where a large group of patients received 324 μg/kg bw/day fluoride for 2 years (Mamelle *et al.*, 1988). Interpretation of the results of these investigations is complicated by the range of treatment protocols used, the small numbers of patients examined in some studies, the small number of fractures observed, the numbers of patients that did not complete the clinical trials (due to development of adverse side effects), the wide range of ages of the patients enroled in these investigations, and the fact that these individuals have a clinically detectable disease involving the bones.

In recent case-control studies, no evidence of an association between the consumption of "fluoridated" drinking water by mothers and increased risk of spontaneous abortion (Aschengrau *et al.*, 1989), late adverse pregnancy outcome (Aschengrau *et al.*, 1993), or congenital cardiac disease in children (Zierler *et al.*, 1988), was identified. Older reports published by Rapaport between 1956 and 1963 (cited in Royal College of Physicians of London, 1976; U.S. DHHS, 1991; Kaminsky *et al.*, 1990; and WHO, 1984), in which the rates of Down's Syndrome were increased (2-fold) in areas in which the level of fluoride in the drinking water was "elevated", compared to areas where the concentrations were low (i.e., < 0.2 mg/L), have been criticized on the basis of the limited ascertainment of cases, inappropriate classification of exposure, and failure to adjust for other contributing factors (e.g., maternal age) [Royal College of Physicians of London, 1976; U.S. DHHS, 1991; Kaminsky *et al.*, 1990; WHO, 1984]. In other ecological studies by Berry (1958), Needleman *et al.* (1974), Berglund (1980) [all cited in WHO, 1984; U.S. DHHS, 1991; and Kaminsky *et al.*, 1990], Erickson *et al.* (1976), Erickson (1980), and Knox *et al.* (1980), no relationship between the rates of Down's Syndrome or congenital malformation and the consumption of "fluoridated" drinking water was identified.

Adverse effects on respiratory function and activity (e.g., reduced lung capacity, irritation of the respiratory tract, asthma, cough, bronchitis, shortness of breath, and/or emphysema) have been reported in a limited number of cross-sectional epidemiological studies in which the health of populations residing in the vicinity of aluminum-, phosphate-, or fertilizer-production facilities was examined (Osaka Prefecture, 1970; Tsunoda, 1970; and Lindberg, 1960; all cited in Hodge and Smith, 1977; Ernst *et al.*, 1986), as well as in studies of workers (predominantly those employed in aluminum smelters) occupationally exposed to airborne fluorides (Hodge and Smith, 1977; Saric *et al.*, 1979; Chan-Yeung *et al.*, 1983b; Larsson *et al.*, 1989; Soyseth and Kongerud, 1992). Owing to the exposure of the residents of these areas or

workers to other airborne contaminants and particulates, it may not be possible, however, to attribute the effects on respiratory function solely to inorganic fluoride *per se*.

Haematological effects (e.g., alterations in haemoglobin content, red, and/or white blood cell counts) have been reported in some (Balazova and Lipkova, 1974; Macuch *et al.*, 1963; both cited in Hodge and Smith, 1977), but not all (Agate *et al.*, 1949, cited in Hodge and Smith, 1977; Selikoff *et al.*, 1983) cross-sectional studies in which the health of populations residing in the vicinity of point sources of inorganic fluoride was examined; however, where haematological effects have been observed, the results were limited, owing to the small numbers examined, the absence of quantitative information on exposure to fluoride, and/or likely concomitant exposure to other substances. No evidence of significantly adverse haematological effects was reported in studies of workers exposed to 0.48 mg/m^3 fluoride (estimated to provide an intake of approximately 52 μg/kg bw/day fluoride, in an adult weighing 70 kg) at an aluminum smelter in British Columbia (Chan-Yeung *et al.*, 1983a), or osteoporotic patients administered approximately 60 mg/day sodium fluoride (equivalent to a dose of 389 μg/kg bw/day fluoride, in an adult weighing 70 kg) over a period of 5 years (Hasling *et al.*, 1987). In addition, no evidence of significantly adverse effects upon the renal or hepatic systems was observed in the clinical study conducted by Hasling *et al.* (1987).

2.5.3 Ecotoxicology

The key studies discussed in this section were selected on the basis of their scientific acceptability (e.g., proper controls, measured toxicant concentrations, acceptable protocols) and because the most sensitive biota tested were identified.

Aquatic Ecosystems

Figure 1 summarizes data on the concentrations at which adverse effects to aquatic biota (native and non-native) have been observed in selected studies. Sodium fluoride is the inorganic fluoride compound used most frequently in aquatic toxicology studies.

Inorganic fluoride toxicity to aquatic organisms appears to be negatively correlated to water hardness ($CaCO_3$) and positively correlated to temperature (Angelovic *et al.*, 1961; Pimentel and Bulkley, 1983; Smith *et al.*, 1985; Fieser *et al.*, 1986). Other important factors affecting species sensitivity to fluoride include life-stage, physiology, and exposure duration.

The fingernail clam (*Musculium transversum*) was the most sensitive freshwater species tested. Sparks *et al.* (1983) conducted an 8-week flow-through experiment in which statistically significant mortality (50%) was observed at a concentration of 2.8 mg/L fluoride. The lowest LC_{50} reported for adult rainbow trout (*Oncorhynchus mykiss*) was 3.7 mg/L fluoride in a 20-day static renewal test at 13°C in soft-water conditions (3 mg $CaCO_3$/L) [Neuhold and Sigler, 1960]. Inorganic fluoride concentrations eliciting acute and chronic effects (lethality, growth, or reproductive impairment) in other freshwater biota from 10 plant and animal taxa ranged from 15 to 340 mg/L (Figure 1). Although data on the effects of inorganic fluorides on aquatic plants are limited, the available information suggests aquatic fauna to be more sensitive.

The brine shrimp (*Artemia salina*) was the most sensitive marine species tested. In a 12-day static renewal test using brine shrimp larvae, statistically significant growth impairment (measured as body length increase relative to controls) occurred at 5.0 mg/L fluoride (Pankhurst *et al.*, 1980). In a flow-through 90-day life-cycle test, the amphipods *Grandidierella lutosa* and *G. lignorum* exposed to 6.9 mg/L fluoride had a 30% decrease in egg production compared to controls (Connell and Airey, 1982). Effect concentrations in other marine and estuarine biota (representing 6 taxa) ranged from 7.2 to 200 mg/L fluoride (Figure 1).

Terrestrial Ecosystems

Figure 2 summarizes the concentrations of inorganic fluorides at which adverse effects to terrestrial vegetation (native and non-native) have been observed in selected studies. Hydrogen fluoride is the inorganic fluoride compound used most frequently in terrestrial toxicology studies.

Hydrogen fluoride toxicity to plants has been studied extensively (Weinstein, 1977). Signs of inorganic fluoride phytotoxicity (fluorosis) such as chlorosis, necrosis, and decreased growth rates are most likely to occur in the young, expanding tissues of broadleaf plants and elongating needles of conifers (Pushnik and Miller, 1990). The induction of fluorosis has been clearly demonstrated in laboratory, greenhouse, and controlled field-plot experiments (Weinstein, 1977; Hill and Pack, 1983; Staniforth and Sidhu, 1984; Doley, 1986, 1989; McCune *et al.*, 1991).

Long-term greenhouse experiments (2 to 10 growing seasons) were conducted to determine the effects (necrosis, photosynthesis, and growth) of hydrogen fluoride on 16 varieties of flower, fruit, vegetable, and forage crops (Hill and Pack, 1983). Three identical greenhouses were used to represent a control (filtered ambient air; mean hydrogen fluoride levels were 0.03 $\mu g/m^3$ fluoride), a hydrogen fluoride treatment (filtered ambient air; mean hydrogen fluoride levels ranged from 0.3 to 1.9 $\mu g/m^3$ fluoride, depending on the exposure duration for gladioli), and an industrial treatment

(unfiltered ambient air; located 1.6 km downwind of a steel plant, mean hydrogen fluoride levels ranged from 0.2 to 1.9 μg/m^3 fluoride). The most sensitive species tested (based on measurement of necrosis over 2 growing seasons, following 117 days hydrogen fluoride exposure) was the snow princess gladiolus (*Gladiolus grandiflorus*). The lowest-observable-effect-level for leaf necrosis (65% of leaves) in this plant was 0.35 μg/m^3 fluoride. The extent of necrosis was positively correlated with increased hydrogen fluoride concentration and increased exposure duration. Less severe necrosis (2%) occurred in the industrial greenhouse chamber. The results from other test species included reduced growth or necrosis at hydrogen fluoride exposure concentrations of 0.44, 0.54, and 21.3 μg/m^3 fluoride for apples (*Malis domestica borkh*), pole beans (*Phaseolus vulgaris* Linné), and forage (red clover *Trifolium pratense* and alfalfa *Medicago sativa*).

Coniferous trees have also been identified as sensitive plant species. In field-exposure chambers, significant dose-response relationships were observed between hydrogen fluoride exposure and development of needle necrosis in 2-year-old black spruce (*Picea mariana*) and 3-year-old white spruce (*Picea glauca*) [McCune *et al.*, 1990]. Four test chambers (Boyce Thompson Institute design), one of which served as a control, were used for different hydrogen fluoride exposure regimens for each coniferous species. Measurements of tissue necrosis were recorded 10 days following hydrogen fluoride exposure (78 hours) for black spruce and 20 days following hydrogen fluoride exposure (50 hours) for white spruce. Lowest-observable-effect-concentrations for necrosis were 4.4 μg/m^3 fluoride and 13.2 μg/m^3 fluoride for black spruce and white spruce, respectively.

A number of field studies have also provided data on the effects of inorganic fluorides on different plant species. For example, the effects of fluoride emissions from a phosphorus plant in Long Harbour, Newfoundland (the plant closed in 1989), on the conifers balsam fir (*Abies balsamea*), black spruce (*Picea mariana*), and larch (*Larix laricina*), were monitored at 6 sites downwind from the plant during the summer of 1982 (Sidhu and Staniforth, 1986). Mean fluoride concentrations ranged between 11.4 μg/m^3 fluoride at a distance of 1.4 km from the source and 0.08 μg/m^3 fluoride 18.7 km from the source. At the closest site, seed production in balsam fir, black spruce, and larch was impaired by 76.4%, 87.4%, and 100%, respectively, compared to controls. At 10.3 km from the source (mean ambient air, 0.9 μg/m^3 fluoride), the effects included an observed reduction of 3 to 10% in seed size and 23 to 30% in cone size, and a decrease of 17 to 72% (varied with species) in the number of cones per tree. A significant negative correlation was observed between atmospheric fluoride levels and seed production for all 3 species. A significant negative correlation was also observed between foliar injury in the 3 species (chlorosis and necrosis) and mean atmospheric fluoride levels.

Investigations of the effects of fluoride on wildlife have focused on impacts on the structural integrity of teeth and bone. Most observations have involved large herbivores. For example, several lesions were found in mule deer (*Odocoileus hemionus),* elk (*Cervus canadensis),* and American bison (*Bison bison)* exposed to elevated levels (no specific anthropogenic sources identified) of fluoride in Utah, Idaho, Montana, and Wyoming (Shupe *et al.*, 1984). Black-tailed deer (*Odocoileus hemionus columbianus)* near an aluminum smelter in Washington were found to have dental disfigurement, with the premolars of one individual being worn down to the gumline. Fluoride levels in ribs ranged from 2 800 to 6 800 mg/kg on a fat-free basis, compared to control deer, which had 160 to 460 mg/kg (Newman and Yu, 1976). Lameness of deer adjacent to an aluminum smelter in Montana was noted by Kay *et al.* (1975). They speculated that fluorosis was the cause of a change in age structure of the mule deer population. Levels in mandibles of the mule deer and white tail deer (*Odocoileus virginianus)* ranged from 1 800 to 5 600 and 3 400 to 9 800 mg/kg, respectively, on a fat-free basis, whereas those of control deer contained less than 200 mg/kg. White-tailed deer inhabiting an area adjacent to an aluminum smelter in South Carolina had fluoride-induced mottling of the teeth, but no osteofluorosis (Suttie *et al.*, 1987). Mean levels in mandibles of deer older than 2.5 years were 286 mg/kg ash weight before opening of the smelter and 1 275 mg/kg 3 years after start-up (measurements on a fat-free basis are about 70% of what they would be as ash weight). The only identified Canadian report is by Karstad (1967), who reported dental disfigurement and jaw fracturing in white-tailed deer drinking water from a contaminated pond on an industrial facility (site unspecified). Mandibular bone fluoride content ranged from 4 300 to 7 125 mg/kg fat-free basis, while levels in control deer ranged from 167 to 560 mg/kg.

Differences seen in various species may be dependent upon the availability of fluoride in their food. In animals, fluoride accumulates primarily in the bone in vertebrates and in the chitinous exoskeleton of insects and arthropods. For example, Thomson (1987) reported that levels in livers of the short-tailed vole inhabiting a contaminated area were only 1.5% that of the bone. There is thus little or no accumulation in soft, edible tissues. Exposure of predatory wildlife is therefore often minimal, as fluoride is largely unavailable to those mammalian and avian predators that do not digest bone. For example, barn owls regurgitate pellets that contain virtually intact skeletons of their prey (Thomson, 1987).

The lowest dietary level observed to cause an effect on wild ungulates was in a controlled captive study, where white-tailed deer were exposed to 10 (control feed), 35, and 60 mg/kg wet weight fluoride (as sodium fluoride) in their diet for 2 years (Suttie *et al.*, 1985). A general mottling of the incisors characteristic of dental fluorosis was noted in the animals at the 35 mg/kg diet dose; those on the higher dose also experienced minor increased wear of the molars, as well as mild hyperostoses of the long bones of the leg. No gross abnormalities of the mandible were observed. Mean

fluoride content of the mandibles was approximately 1 700 mg/kg ash weight for the control, 4 550 for the low-dose, and 6 600 for the high-dose group, the latter 2 levels being similar to those observed in affected wild deer near sources of industrial pollution (Karstad, 1967; Kay *et al.*, 1975; Newman and Yu, 1976). Studies demonstrating effects on other mammals and wild birds are scarce. Deer mice (*Peromyscus maniculatus*) fed diets of 38 (control), 1 065, 1 355, and 1 936 mg/kg diet dry weight (as sodium fluoride) for 8 weeks exhibited, at all concentrations above the control, marked weight loss, mortality, changes in femur size, and dental disfigurement (Newman and Markey, 1976). Bank voles (*Clethrionomys glareolus*) showed a reduction in the number of litters per female, an increase in the number of days from mating to producing the first litter, increased mortality of offspring, and a changed sex ratio (greater number of males) in offspring of animals fed 97 mg/kg diet (wet or dry basis not specified) [Krasowska, 1989]. Animals fed 47 mg/kg diet also showed these effects, but the differences were not significant from the control. Fluoride was suggested as the cause of reduced milk production with subsequent mortality of kits in farm-raised foxes (*Vulpes vulpes*) fed a diet containing 97.6 to 136.8 mg/kg diet dry weight fluoride (Eckerling *et al.*, 1986). Lower reproductive success of screen owls (*Otus asio*) was noted when birds were fed 200 mg/kg diet wet weight (as sodium fluoride), but not when fed 40 mg/kg diet (Pattee *et al.*, 1988; Hoffman *et al.*, 1985).

3.0 Assessment of "Toxic" under CEPA

3.1 CEPA 11(*a*): Environment

Inorganic fluorides are produced in Canada and emitted into the Canadian environment both from anthropogenic (estimated at 23 500 tonnes/year) and from natural sources (amounts not known). Gaseous inorganic fluoride compounds (e.g., hydrogen fluoride and sulphur hexafluoride) are primarily released into the atmosphere whereas particulate compounds (e.g., sodium fluoride and calcium fluoride) are released into aquatic and terrestrial environments.

For the purpose of assessing "toxic" under paragraph 11(*a*) of CEPA, this assessment focuses on the environmental compartments that have the highest concentrations and the biota considered to be at greatest risk from fluoride exposure and effects in Canada (e.g., phytotoxicity of atmospheric levels, impact on aquatic biota from water exposure, and wildlife exposure through plant consumption).

Hydrogen fluoride is believed to be the most important inorganic fluoride species affecting terrestrial plants, and its phytotoxicity has been studied extensively (Weinstein, 1977). The most sensitive plant species tested (gladioli, *Gladiolus grandiflorus*) elicited significant tissue necrosis at fluoride levels as low as 0.35 $\mu g/m^3$ fluoride. In addition, other controlled greenhouse and field studies have reported similar effect thresholds for a variety of species, including 0.44 $\mu g/m^3$ fluoride for apples (*Malis domestica borkh*), 0.54 $\mu g/m^3$ fluoride for pole beans (*Phaseolus vulgaris* Linné), and 0.9 $\mu g/m^3$ fluoride for balsam fir (*Abies balsamea*), black spruce (*Picea mariana*), and larch (*Larix laricina*). In all cases the extent of fluoride phytotoxicity was positively correlated with increased concentration and increased exposure duration. Mean inorganic fluoride levels (principally hydrogen fluoride) measured in air at various locations in Canada range from 0.01 to 1.0 $\mu g/m^3$ fluoride, with the higher values occurring near known industrial sources. Much of the available concentration data from the vicinity (within a few km) of industrial sources in Canada are within the same range of effects thresholds for several sensitive terrestrial plants.

The clam (*Musculium transversum*) and rainbow trout (*Oncorhynchus mykiss*) are among the freshwater aquatic species most sensitive to the effects of inorganic fluorides, based on an 8-week LC_{50} of 2.8 mg/L fluoride and 20-day LC_{50} of 3.7 mg/L fluoride (13°C, 3 mg $CaCO_3$/L), respectively. The brine shrimp (*Artemia salina*) and the amphipods *Grandidierella lutosa* and *G. lignorum* were among the most sensitive marine species tested with lowest-observed-effect-concentrations of 5.0 mg/L fluoride and 6.9 mg/L fluoride (based on growth impairment over 12 days and decrease in egg production over 90 days, respectively). Dividing the lowest-observed-effect-levels by a

factor of 10 to account for differences in inter-species sensitivity and to extrapolate laboratory findings to the field yields estimated effects thresholds of 0.28 mg/L fluoride for freshwater species and 0.5 mg/L fluoride for marine aquatic species. Most of the available data on inorganic fluoride levels in surface waters of aquatic ecosystems in Canada were identified in relation to known anthropogenic sources. Available data on mean inorganic fluoride levels in freshwater in Canada indicate a range between 0.1 and 3.8 mg/L. Mean inorganic fluoride levels in marine surface waters in Canada range between 1.0 and 3.0 mg/L. Therefore, the majority of freshwaters and virtually all of the marine waters sampled for inorganic fluorides in Canada in the vicinity of known anthropogenic sources have mean concentrations that are equal to, or exceed the lowest-estimated-effects-threshold-concentrations for freshwater and marine species.

In order to determine the potential impact of fluoride exposure on wildlife in Canada, estimates were made of the uptake of fluoride by white-tailed deer (*Odocoileus virginianus*) as a result of consumption of contaminated browse. Deer were chosen as the model species, as field data demonstrating effects in the wild suggest that they are a sensitive indicator. As well, a controlled feeding study is available to help interpret exposure estimates in the field. Cornwall Island, Ontario, was chosen as an exposure site as it is adjacent to an aluminum smelter, a known source of fluoride emission. For many years cattle in the area ingesting fluoride-contaminated forage have suffered from a number of fluorotic lesions, and studies suggest that deer are as sensitive as or more sensitive than cattle to fluoride exposure (Suttie *et al*., 1985). From available data on levels of fluoride in air and plants, this site is representative of several of the more contaminated areas in Canada.

Data on fluoride levels in native plants were used to estimate seasonal rates of uptake in white-tailed deer. Since plant tissues were not collected during winter, concentrations of fluoride in winter twigs were calculated from air and green leaf levels (Sidhu, 1992). The diet composition of deer in Eastern Canada was estimated from Crawford (1982), Brown and Doucet (1991) and Hiebsch and Boersma (1990). The mean fluoride content of deer browse calculated on an annual basis for the Cornwall Island area is 38 mg/kg dry weight (Table 2). In a captive study, white-tailed deer exposed to 35 and 60 mg/kg fluoride (wet weight) in their diet for 2 years demonstrated lesions of the incisors at both doses; as well, at the higher dose, a mild increase in wear of the molars and mild hyperostoses of the long bones of the leg were observed. Levels in the mandibles were equivalent to levels observed in some wild deer obtained near sources of industrial pollution, where effects have been seen. Assuming equal bioavailability of the fluoride in the browse as in the controlled study, levels of fluoride in browse are at a level where fluorosis would occur in deer populations. Exposure to predatory mammals and birds capable of digesting bone would be higher, although data to quantitatively estimate this are unavailable.

Table 2
Estimated Diet of White-tailed Deer Living on Cornwall Island, Ontario by Season

Diet Component	Inorganic Fluoride Concentration mg/kg (dry weight)	Seasonal Variation of Inorganic Fluoride content of White-tailed Deer Diet (% of diet)[a] mg/kg (dry weight)			
		Spring	Summer	Fall	Winter
Leaves	68[b]	(65) 44	(65) 44	(35) 24	(0) 0
Twigs	20[c]	(10) 2	(0) 0	(10) 2	(65) 13
Other	14.5[d]	(25) 4	(35) 5	(55) 8	(35) 5
Mean diet by season (mg/kg [dry weight])		50	49	34	18
Mean Annual Inorganic Fluoride Content of Deer Diet: 38 mg/kg (dry weight)					

a. Proportion of diet items by season (Hiebsch and Boersma, 1990).
b. Mean level of inorganic fluorides in red maple leaves (*Acer rubrum*) collected in summer, 1988 from Cornwall Island (Ontario Ministry of the Environment, 1990b).
c. Based on a 1:1 diet of red maple twigs (*Acer rubrum*) and balsam fir (*Abies balsamea*). Inorganic fluoride levels in maples leaves were converted to twig levels by multiplying by 0.2 (Sidhu, 1992). Balsam fir levels were calculated from average ambient air levels on Cornwall Island during summer, 1991 (Environment Canada, 1991) and the regression equation $Y = 4.12 + 0.982X + 0.00175X^2$, where X is the air concentration in µg fluoride/dm^2/7 days and Y is the Balsam fir current year foliar concentration in mg/kg (dry weight) [Sidhu, 1992].
d. Mean 1988 fluoride levels in foliage plants for cattle at Cornwall Island (Ontario Ministry of the Environment, 1990b).

On the basis of available information, inorganic fluorides are entering the Canadian environment from anthropogenic sources in quantities resulting in concentrations in some Canadian waters, plants, and air, that may cause long-term harmful effects to biota in aquatic and terrestrial ecosystems. It has been concluded that inorganic fluorides have the potential to cause harm to the environment.

3.2 CEPA 11(*b*): Environment on Which Human Health Depends

Inorganic fluoride compounds (except sulphur hexafluoride) are not expected to remain in the troposphere very long or migrate to the stratosphere. Even though sulphur hexafluoride is long-lived enough to migrate into the stratosphere, its contribution to stratospheric ozone depletion is considered minimal, because fluorine is much less efficient and less available than chlorine in the catalytic destruction of ozone in the stratosphere (Chu, 1991).

The global atmospheric concentration of sulphur hexafluoride is estimated to range from 0.006 to 0.3 μg/m^3 (average approximately 0.0091 μg/m^3). This is about 300 to 3 000 times less than the combined CFCs and about 10^8 times less than carbon dioxide global concentrations. Due to the long tropospheric residence time of sulphur hexafluoride and its strong absorption potential in the infrared region, the estimated Global Warming Potential of sulphur hexafluoride is 6 800 to 12 000 times higher than for carbon dioxide, and 2 to 8 times higher than CFC-11, the standard example of the CFCs known to contribute to global climate change (Environment Canada, 1993). Furthermore, there is considerable uncertainty regarding global and Canadian release rates of sulphur hexafluoride, its Global Warming Potential, and its potential contribution to global climate change. Chu (1991) estimates the potential contribution of sulphur hexafluoride to the global climate change as less than 0.01%, based on estimated air concentrations of sulphur hexafluoride (0.01 μg/m^3) and CFCs (10 μg/m^3), assuming a comparable infrared absorption efficiency between these 2 compounds, and attributing 10% to 12% of the global climate change effect to CFCs. Using the same equation, but assuming air concentrations ranging from 0.006 to 0.3 μg/m^3 for sulphur hexafluoride and from 2.8 to 23.9 μg/m^3 for CFCs (Ramanathan *et al.*, 1985), infrared absorption efficiencies for sulphur hexafluoride of 2 to 8 based on the Global Warming Potential, and attributing 10% of the global climate change effect to CFCs, results in potential contributions of 0.02% to 1% by sulphur hexafluoride. These two estimates differ by two orders of magnitude.

The levels of sulphur hexafluoride in the Canadian atmosphere are unknown. Furthermore, the detailed relationship between environmental levels, Global Warming Potential, and contribution to global climate change are not known. Thus, it is not possible to determine the contribution of inorganic fluorides to global climate change.

Therefore, based upon the available data, there is insufficient information to conclude whether sulphur hexafluoride is entering the environment in quantities or under conditions that may constitute a danger to the environment on which human life depends.

3.3 CEPA 11(*c*): Human Life or Health

Population Exposure

The average daily intake of inorganic fluoride has been estimated based on the levels in air, drinking water, soil, and food and the amounts consumed by various age groups of the population of Canada (Table 3) [Environmental Health Directorate, 1992]. The total average daily intake of inorganic fluoride via ingestion by exclusively breast-fed infants was estimated to range from approximately 0.5 to 2.6 μg/kg bw/day, while the intake in exclusively formula-fed infants was estimated to range from 13.6 to 93.0 μg/kg bw/day. The total average daily intake of inorganic fluoride via ingestion

for individuals consuming “non-fluoridated” drinking water was estimated to range from approximately 17.2 to 96.4 μg/kg bw/day. The total daily intake of inorganic fluoride via ingestion for individuals consuming “fluoridated” drinking water was estimated to range from 32.8 to 160.4 μg/kg bw/day. On the basis of available data, it is evident that for individuals consuming “non-fluoridated” drinking water, the greatest source of exposure to inorganic fluoride occurs via the ingestion of food; for individuals consuming “fluoridated” drinking water, the greatest contribution to the total intake of inorganic fluoride comes from the water itself, as well as food. Generally, exposure to airborne fluoride makes only a minor contribution to the total intake of inorganic fluoride; the average daily intake via inhalation was approximately 0.01 μg/kg bw/day. Dental products that contain fluoride, such as toothpaste, have been identified as significant sources of inorganic fluoride for children and adolescents (Drummond *et al.*, 1990).

The intake of inorganic fluoride could possibly be higher in communities near point sources such as aluminum smelters, and brick and phosphate plants; however, the estimated daily intake of inorganic fluoride by individuals residing near point sources was not substantially greater than that observed for the general population (estimated intakes of inorganic fluoride via ingestion by individuals consuming “non-fluoridated” and “fluoridated” drinking water ranged up to 102 and 166 μg/kg bw/day, respectively). The estimated intakes of inorganic fluoride via inhalation ranged from 0.02 to 0.38 μg/kg bw/day. These estimates were based on monitoring data from various locations, and represent a “worst case scenario,” in which an individual is assumed to be exposed to contaminated air and soil. Based on comparisons of data (Kumpulainen and Koivistoinen, 1977; Selikoff *et al.*, 1983; Jones *et al.*, 1971; Muramoto *et al.*, 1991; Sakurai *et al.*, 1983) on the concentrations of (total) fluoride in a limited number of foodstuffs obtained in close proximity to point sources with those obtained elsewhere, it is likely that intake in food may be elevated for populations residing in the vicinity of industrial sources; however, available data were considered insufficient to quantitatively estimate the intake of inorganic fluoride in food for populations in Canada under such conditions and it was considered, therefore, to be similar to that for the general population.

Table 3
Estimated Daily Intake of Inorganic Fluoride by the General Population of Canada

	Estimated Intake of Inorganic Fluoride by Various Age Groups (μg/kg bw/day)				
Route of Exposure	0 – 6 mo[a]	7 mo – 4 yr[b]	5 – 11 yr[c]	12 – 19 yr[d]	20+ yr[e]
Ambient Air[f]	0.01	0.01	0.01	0.01	0.01
Food[g]	13.6 – 91.5	22.30	16.44	13.64	30.08
Breast Milk[h]	0.47 – 1.05	–	–	–	–
Soil[i]	0.03 – 1.55	0.02 – 1.19	0.01 – 0.40	0.002 – 0.11	0.002 – 0.09
"Fluoridated" Drinking Water[j]	–	44.92 – 76.92	24.33 – 41.67	16.65 – 28.51	15.64 – 26.79
"Non-Fluoridated" Drinking Water[k]	–	3.08 – 12.92	1.67 – 7.00	1.14 – 4.79	1.07 – 4.50
Household Products[l]	–	20.00 – 60.00	8.15 – 20.00	2.46	1.14
Total Intake[m] Breast-Fed Infants	0.51 – 2.61	–	–	–	–
Total Intake[n] Formula-Fed Infants	13.64 – 93.06	–	–	–	–
Total Intake "Fluoridated" Water[o]	–	87.25 – 160.42	48.94 – 78.52	32.76 – 44.73	46.87 – 58.11
Total Intake "Non-Fluoridated" Water[p]	–	45.41 – 96.42	26.28 – 43.85	17.25 – 21.01	32.30 – 35.82

a. Assumed to weigh 7 kg, breathe 2 m^3 air, drink 750 mL of breast milk or infant formula (as food), and consume 35 mg soil per day (Environmental Health Directorate, 1992).
b. Assumed to weigh 13 kg, breathe 5 m^3 air, drink 0.8 litres of water, and consume 50 mg soil per day (Environmental Health Directorate, 1992).
c. Assumed to weigh 27 kg, breathe 12 m^3 air, drink 0.9 litres of water, and consume 35 mg soil per day (Environmental Health Directorate, 1992).
d. Assumed to weigh 57 kg, breathe 21 m^3 air, drink 1.3 litres of water, and consume 20 mg soil per day (Environmental Health Directorate, 1992).
e. Assumed to weigh 70 kg, breathe 23 m^3 air, drink 1.5 litres of water, and consume 20 mg soil per day (Environmental Health Directorate, 1992).
f. Based on the mean concentration of inorganic (gaseous and particulate) fluoride in ambient air of 0.03 $\mu g/m^3$, reported for Toronto, Ontario (McGrath, 1983), and assuming the concentration in indoor air is identical to (outdoor) ambient air (Environmental Health Directorate, 1992).
g. Formula-fed infants (0 - 6 months): based on the mean concentrations of inorganic fluoride in infant formulas purchased in the United States of 0.127 and 0.854 mg/L reported for ready-to-use, milk-based formula and soy-based powdered formula (prepared with drinking water containing 1 ppm fluoride), respectively (McKnight-Hanes *et al.*, 1988), and assuming infants are exclusively formula-fed and consume 750 mL formula per day (Environmental Health Directorate, 1992). General Population (7 months and older): based on levels of inorganic fluoride detected (Dabeka and

McKenzie, 1993; Taves, 1983) in 109 individual foods from Canada (and the United States), in the following food groups (Environmental Health Directorate, 1992): 0.01 - 0.80 μg/g in dairy products; 0.12 - 1.02 μg/g in cereal products; 0.01 - 0.58 μg/g in fruit; 0.01 - 0.68 μg/g in vegetables; 0.04 - 4.57 μg/g in meat/fish/eggs; 0.05 - 0.13 μg/g in fats; 0.11 - 0.35 μg/g in nuts/legumes; 0.02 - 0.86 μg/g in foods containing primarily sugar; 0.41 - 0.84 μg/g in soup; 4.97 μg/g in tea; and the daily intake of each food item by the various age groups of the general population of Canada (Environmental Health Directorate, 1992).

h. Based on the mean concentrations of inorganic fluoride of 4.4 and 9.8 ng/g reported for samples of breast milk from mothers living in communities served by "non-fluoridated" and "fluoridated" drinking water, respectively (Dabeka *et al.*, 1986), assuming the density of breast milk is equal to 1.0 g/mL.
i. Based on a range of concentrations of total inorganic fluoride of 6 ppm (μg/g) reported by Sidhu (1982) for soil collected in Newfoundland, to 309 ppm (μg/g) [mean concentration in Canadian surface soil (0 - 130 cm depth)] (Schuppli, 1985).
j. Based on a range of mean concentrations of inorganic fluoride in "fluoridated" drinking water of 0.73 mg/L, determined from fluoride levels in 3 communities in Newfoundland and Labrador, to 1.25 mg/L, determined from 2 communities in the Yukon (Droste, 1987).
k. Based on a range of mean concentrations of inorganic fluoride in "non-fluoridated" drinking water of (at least) 0.05 mg/L (reported for 3 communities in British Columbia) [Greater Vancouver Water District, 1990], to 0.21 mg/L (reported for an unspecified number of communities in the Yukon) [Health and Welfare Canada, Yukon Territory, 1989, cited in Hill and Hill, 1991].
l. Based on a mean concentration of inorganic fluoride in most dentifrice products of 1 000 ppm (μg/g) (Beltran and Szpunar, 1988; Whitford, 1987) and an estimated intake of dentifrice of 0.26 - 0.78 g/day for children 7 months to 4 years of age, 0.22 - 0.54 g/day for children 5 to 11 years of age, 0.14 g/day for adolescents 12 to 19 years of age, and 0.08 g/day for adults 20+ years of age (Levy, 1993), assuming an average of 2 brushings per day (Bruun and Thylstrup, 1988).
m. Estimated total daily intake of inorganic fluoride by exclusively breast-fed infants in Canada.
n. Estimated total daily intake of inorganic fluoride by exclusively formula-fed infants in Canada.
o. Estimated total daily intake of inorganic fluoride by individuals consuming "fluoridated" drinking water in Canada.
p. Estimated total daily intake of inorganic fluoride by individuals in Canada consuming drinking water that is not "fluoridated".

Effects

There has been no consistent evidence of an association between the consumption of "fluoridated" drinking water and the incidence of, or mortality due to cancer in a large number of ecological studies performed in many countries. Although these results do not support the hypothesis of an association, their considerable limitations preclude firm conclusions regarding the carcinogenicity of fluoride in humans. For example, cancer of the bone was not assessed in the majority of these studies. The incidence of, or death due to cancer has also been investigated in a number of historic cohort studies of workers exposed to fluoride predominantly in the aluminum smelting industry. While excesses of cancers of different types have been reported in various studies, the only site for which there was excess risk in several investigations is lung cancer, for which the weight of evidence is considered moderate. Due to possible confounding by concomitant exposure to other substances in analytical studies of

occupationally exposed workers, however, the observed excesses cannot confidently be attributed to fluoride. Moreover, bone cancer was not assessed in the majority of these studies. Available information is considered inadequate, therefore, to assess the carcinogenicity of inorganic fluoride in humans.

In early carcinogenicity bioassays conducted by Kanisawa and Schroeder (1969), Taylor (1954), and Tannenbaum and Silverstone (1949), the incidence of tumours in mice administered sodium fluoride (in either the diet or drinking water) was, in general, not markedly greater than that observed in controls. Owing to inadequate documentation and to numerous methodological shortcomings, however, the results of these investigations do not contribute meaningfully to an assessment of the weight of evidence of the carcinogenicity of (sodium) fluoride.

The administration of drinking water containing sodium fluoride (in amounts estimated to provide intakes ranging from 0.6 to 9.1 mg/kg bw/day fluoride) to male and female B6C3F_1 mice over a period of 2 years produced a marginal (statistically insignificant) increase in the incidence of hepatoblastoma, compared to the incidence in groups of "controls" administered drinking water without added fluoride; however, this minor increase was not considered "biologically significant," since the overall incidence of hepatic tumours (adenoma, carcinoma, hepatoblastoma) was not increased in animals receiving sodium fluoride, and the incidence of all hepatic tumours in these groups of mice was higher than that in previous NTP carcinogenicity bioassays (NTP, 1990). The marginal increase in the incidence of malignant lymphoma in female B6C3F_1 mice administered drinking water containing sodium fluoride was considered not to be compound-related, since the incidence in the high-dose group was similar to that observed in historical controls (NTP, 1990). No other increases in tumour incidence were observed; however, failure to attain the maximum tolerated dose may have reduced somewhat the sensitivity of this study in mice. In a less extensive carcinogenicity bioassay in which the incidence of osteomas in male and female CD-1 mice receiving 25 mg/kg bw/day sodium fluoride in the diet was increased compared to controls (Maurer *et al.*, 1993), the specific role of fluoride in the etiology of the tumours cannot be determined with certainty, owing to the infection of these animals with Type C retrovirus (U.S. DHHS, 1991; U.S. NRC, 1993; Maurer *et al.*, 1993).

The administration of drinking water containing sodium fluoride (in amounts estimated to provide intakes ranging from 0.2 to 4.5 mg/kg bw/day fluoride) to F344/N rats produced a marginal increase in the incidence of oral cavity neoplasms (in males and females) and tumours in the thyroid gland (in males) [NTP, 1990]. The squamous cell tumours of the oral cavity were not considered to be compound-related, since the incidence of tumours in the high-dose group was not significantly different from the controls, the incidence of these neoplasms was within the range observed in historical controls, and there was no supporting evidence of focal hyperplasia of the

oral mucosa (NTP, 1990). The marginal increase in thyroid (follicular cell) tumours was also considered not to be compound-related, since the incidence of these tumours in the high-dose group was not significantly different from the controls, the incidence of these neoplasms was within the range observed in historical controls, and the incidence of follicular cell hyperplasia was not increased in fluoride-exposed animals (NTP, 1990). The incidence of osteosarcoma in groups of male and female F344/N rats administered drinking water containing sodium fluoride (in amounts estimated to provide intakes ranging from 0.8 to 4.5 mg/kg bw/day fluoride) over a period of 2 years was not significantly increased, compared to controls receiving approximately 0.2 mg/kg bw/day fluoride (NTP, 1990); however, for the male F344/N rats, it was reported that "the osteosarcomas occurred with a significant dose response trend ($P = 0.027$, by logistic regression)" [NTP, 1990]. In a more limited carcinogenicity bioassay conducted by Maurer *et al.* (1990), the administration of diets containing sodium fluoride (in amounts estimated to provide intakes ranging from 1.8 to 11.3 mg/kg bw/day fluoride) to male and female Sprague-Dawley rats over a period of 95 to 99 weeks produced no significant increase in the incidence of any types of tumours, compared to groups of controls receiving approximately 0.1 mg/kg bw/day fluoride, although a small number of malignant tumours of the bone was observed.

In assessing the evidence for the carcinogenicity of fluoride, some significance has been attributed to the observation of a dose-response trend in the occurrence of osteosarcomas in male F344/N rats administered sodium fluoride in drinking water (NTP, 1990). Such a trend associated with the occurrence of a rare tumour in the tissue in animals and humans in which fluoride is known to accumulate cannot be easily dismissed. Moreover, the level of fluoride in the bones of the high-dose group of male rats in the NTP carcinogenicity bioassay, in which a non-significant increase in osteosarcomas was observed, is similar to that measured in humans with skeletal fluorosis. However, the biological significance of this dose-respond trend is tempered somewhat by the lack of statistical significance of the observed excess in the high-dose males in comparison with controls, as well as by the absence of a comparable statistically significant trend in the incidence of osteosarcomas in female F344/N rats or male and female $B6C3F_1$ mice receiving comparable amounts of inorganic fluoride (NTP, 1990). Indeed, the levels of fluoride in the bone of (male and female) F344/N rats and $B6C3F_1$ mice administered sodium fluoride in drinking water were similar (NTP, 1990). No dose-response trend in the incidence of osteosarcomas was observed in groups of male and female Sprague-Dawley rats administered diets containing sodium fluoride (Maurer *et al.*, 1990), even though the levels of fluoride in the bone in the high-dose animals were greater than those in the male F344/N rats in which there was an increase in osteosarcomas in the NTP (1990) carcinogenicity bioassay; however, there may be variations in sensitivity of the two strains to the effects of fluoride. Moreover, there were more animals in the high-dose group in the NTP bioassay (n = 100, 42 males at termination) compared to that in the study by Maurer *et al.* (1990) [n = 70, 26 males at termination], and in the latter study, detailed

information on the incidence of tumours in tissues or organs other than the bone and stomach were not presented, and histological examination of bone from the 2 mid-dose groups at terminal sacrifice was limited. Furthermore, a small number of osteosarcomas was observed in the fluoride-exposed Sprague-Dawley rats, compared to none in the controls (Maurer *et al.*, 1990). There is controversy concerning whether or not the osteomas in male and female CD-1 mice observed in the carcinogenicity bioassay conducted by Maurer *et al.* (1993) should be classified as neoplasms, and a retrovirus (in addition to fluoride) has been implicated in their etiology; however, the significant increase in (the highest dose) fluoride-exposed versus control groups (in animals infected with retrovirus), in a tissue in which fluoride is known to accumulate, adds some weight, albeit weak, to the evidence of carcinogenicity.

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 *D. melanogaster*, and cytogenetic damage after intraperitoneal injection 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), it 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 result from its inhibition of enzymes involved in DNA synthesis and/or repair.

Therefore, although there is some evidence for the carcinogenicity of inorganic fluoride, available data are inconclusive. For such compounds, the assessment of "toxic" under paragraph 11(*c*) of CEPA is based on a comparison of concentrations in environmental media or estimated daily intakes with those to which it is believed that a person can be exposed daily over a lifetime without developing deleterious non-neoplastic effects. Based on the available data, it is evident that (with the exception of dental fluorosis) following long-term exposure, skeletal effects in humans occur at doses or 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.

Skeletal changes have been observed in a number of animal species (i.e., cattle, sheep, rodents) exposed to inorganic fluoride. Dose-response relationships concerning exposure to inorganic fluoride and effects on the skeleton in rats have been reported in well-designed and adequately conducted long-term toxicological studies (NTP, 1990; Maurer *et al.*, 1990). No adverse effects on the skeleton have been observed in F344/N and Sprague-Dawley rats receiving 2.7 and 1.8 mg/kg bw/day

fluoride, respectively (NTP, 1990; Maurer *et al.*, 1990); however, rats are generally regarded as less sensitive to the toxicological effects (on the skeleton) of fluoride than are humans or larger animals (Franke, 1989; Turner *et al.*, 1992). Compared to humans, the lower sensitivity of rats to the toxicological effects of fluoride on the skeleton has been attributed to differences in toxicokinetics (i.e., absorption and elimination) and skeletal development (i.e., in contrast to humans there is little or no bone remodelling in rats) [O'Flaherty, 1991a, 1991b; Chavassieux, 1990; Turner *et al.*, 1992; Franke, 1989; Grynpas, 1990], although Whitford *et al.* (1991) reported that the ratio of the renal and extra-renal clearance to plasma clearance of fluoride in rats was similar to that in humans. In studies in which effects on the skeleton were observed in dogs (Snow and Anderson, 1986) and pigs (Mosekilde *et al.*, 1987) receiving approximately 0.32 and 2 mg/kg bw/day fluoride, respectively, no overtly pathological effects on the bone or on the general health of the animals were observed, although the animals were exposed for a relatively short duration (i.e., 6 months). Notably, dogs and pigs are considered to be more appropriate models for examination of the potential effects of various agents on the skeleton in humans (Snow and Anderson, 1986; Mosekilde *et al.*, 1987; Chavassieux, 1990). Bone matrix formation (based on histomorphometric analysis) in male C57BL/6 mice receiving 0.8 mg/kg bw/day fluoride in drinking water over a period of 4 weeks was increased 20%, compared to controls; however, no pathological effects were observed (Marie and Mott, 1986). 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 have been emphasized in the derivation of an effect level for inorganic fluoride.

Case reports or descriptive ecological studies of skeletal fluorosis or osteosclerosis in the United States (Stevenson and Watson, 1960; Leone *et al.*, 1955; Felsenfeld and Roberts, 1991; U.S. DHHS, 1991) or studies on the occurrence of endemic (crippling) skeletal fluorosis in areas in other countries in which the levels of fluoride are naturally very high, provide little quantitative information useful in establishing an effect level for fluoride, since nutritional intake, the intake of fluoride (and additional minerals) from other sources, potentially confounding concomitant exposures, and the extent of physical labour, all of which have been suggested to play a role in the etiology of this disease (see WHO, 1984, and Singh and Jolly, 1970, cited in U.S. EPA, 1985, for a review), were not adequately documented. There is also limited quantitative information on exposure to inorganic fluoride and the development of skeletal effects (osteosclerosis or fluorosis) in occupationally exposed workers (Kaltreider *et al.*, 1972; Tourangeau, 1944, Boillat *et al.*, 1975, and Schegel, 1974, all cited in Hodge and Smith, 1977; Grandjean, 1982; Chan-Yeung *et al.*, 1983a; Czerwinski *et al.*, 1988; Roholm, 1937, cited in Grandjean, 1982). Inconsistent results of inherently limited cross-sectional studies of small populations exposed to often unspecified concentrations of fluoride in the vicinity of industrial sources (Tsunoda, 1970; Tsiji and Tsunoda, 1970, cited in Hodge and Smith, 1977), contribute little to an

assessment of exposure-response 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, is inadequate, owing to the limitations of the protocols and characteristics of the patients in these studies. Moreover, these clinical studies were undertaken to assess the considered beneficial effect of fluoride (i.e., its capacity to increase bone mass), rather than its potential to produce adverse effects after long-term exposure.

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 (Chan-Yeung *et al.*, 1983a), as well as by the multiplicity of factors that may influence the amount of fluoride deposited in the bone, and hence the severity of the disease. When the results are evaluated collectively, however, the available data indicate that potentially adverse effects associated with skeletal fluorosis are likely to be observed at intakes greater than approximately 200 μg/kg bw/day fluoride. In case accounts, the development of crippling skeletal fluorosis was attributed to an intake of approximately 215 to 285 μg/kg bw/day fluoride (in adults) [U.S. DHHS, 1991]. Skeletal fluorosis has been observed in cryolite workers having estimated (occupational) intakes of approximately 285 to 1 142 μg/kg bw/day fluoride (Roholm, 1937, cited in Grandjean, 1982), and in patients receiving approximately 260 to 389 μg/kg bw/day fluoride for the treatment of osteoporosis (Power and Gay, 1986). In clinical studies, minor increases in the incidence of hip fracture have been observed in groups of osteoporotic patients administered (sodium) fluoride at doses equivalent to 260 μg/kg bw/day fluoride or more (Gutteridge *et al.*, 1984, cited in Inkovaara, 1991; Power and Gay, 1986; Mamelle *et al.*, 1988; Hedlund and Gallagher, 1989; Riggs *et al.*, 1990); however, the incidence of hip fracture in these studies, which generally involved small numbers of elderly patients with a clinically detectable disease of the bone, was low. The weight of evidence in ecological studies (Jacobsen *et al.*, 1990, 1992; Cooper *et al.*, 1991; Danielson *et al.*, 1992; Keller, 1991, and May and Wilson, 1991, both cited in Gordon and Corbin, 1992; Suarez-Almazor *et al.*, 1993) indicates that there may be an association between the consumption of "fluoridated" drinking water and an increased incidence of hip fracture (based on hospitalization rates) particularly among the elderly. These results should be interpreted with caution, however, in view of the limitations of epidemiological investigations of this experimental design. Moreover, owing to the lack of data on individual exposure in such studies, it is difficult to derive meaningful conclusions concerning the exposure-response relationship for possible skeletal effects associated with exposure to fluoride. Although the relative risk of hip, wrist, or spinal fracture was increased in some groups of women residing in an elevated-fluoride community (with drinking water containing 4 mg/L, and having an estimated (mean) intake of approximately 72 μg/kg bw/day fluoride) compared to those in a control community (with drinking water containing 1 mg/L fluoride) [Sowers *et al.*, 1986, 1991], the

estimated intake of fluoride by women in the elevated-fluoride community was likely underestimated (since it was derived solely on the amount of water-based beverages consumed), and the level of calcium in the drinking water from the elevated-fluoride community was approximately 25% of the level in the control community.

It is concluded, therefore, on the basis of data from several different types of studies, that potentially adverse effects associated with skeletal fluorosis are likely to be observed at intakes of greater than approximately 200 μg/kg bw/day fluoride. Moreover, predicted concentrations of fluoride in bone resulting from a daily intake of 200 μg/kg bw/day are within the range of those reported to be associated with effects on the skeleton (Turner *et al.*, 1993). Confidence in this value is limited, however, due to the limitations of identified case reports, and individual epidemiological and clinical studies in which the relationship between exposure to inorganic fluoride and effects on the skeleton have been examined, as well as those factors which can influence the development of skeletal fluorosis. Based on the limited available data, adverse effects upon haematopoietic, hepatic, or renal function are not expected to occur at such levels of intake, since adverse effects upon the bone marrow, liver, or kidney were not observed following the administration of approximately 389 μg/kg bw/day fluoride to osteoporotic patients over a period of 5 years (Hasling *et al.*, 1987). There are insufficient quantitative data available from studies in humans to conclude unequivocally that exposure to this level of inorganic fluoride would have no adverse effect upon human reproduction and development, or the central nervous and immune systems.

Based on available information, the estimated average daily intakes of inorganic fluoride, which range from approximately 0.5 to 160 μg/kg bw/day by various age groups in the general population (or up to 167 μg/kg bw/day by those residing in the vicinity of point sources of inorganic fluoride) are less than the level at which adverse effects upon the skeleton (the end-point considered most sensitive on the basis of available data) are anticipated (i.e., ≥ 200 μg/kg bw/day fluoride).

Therefore, based upon the available data, it has been concluded that inorganic fluorides[6] are not entering the environment in quantities or under conditions that may constitute a danger to human life or health.

6. The assessment of whether inorganic fluorides are entering the environment in quantities or under conditions that may constitute a danger to human life or health is based on the effects of the fluoride ion derived from inorganic substances.

3.4 Conclusion

It has been concluded that inorganic fluorides are entering the environment in quantities or under conditions that may be harmful to the environment. There is insufficient information to conclude whether sulphur hexafluoride is entering the environment in quantities or under conditions that may constitute a danger to the environment on which human life depends. It has been concluded that inorganic fluorides (i.e., the fluoride ion derived from such inorganic substances) are not entering the environment in quantities or under conditions that may constitute a danger to human life or health.

4.0 Recommendations

In view of the small difference between the estimated daily intake of inorganic fluorides and the level at which adverse effects on the skeleton are anticipated, it is recommended that exposure of the population of Canada to inorganic fluorides continue to be closely monitored. Acquisition and evaluation of additional data in the following areas would also permit a more complete assessment:

(i) data from an epidemiological case-control study in the United States, in which the occurrence of osteosarcoma in relation to exposure to fluoride and the levels of this substance in bone is currently being assessed;

(ii) additional information from analytical epidemiological studies in which effects upon reproduction and development, skeletal fracture, and the development of skeletal fluorosis is assessed in relation to total exposure to inorganic fluoride;

(iii) the extent of inorganic fluoride releases into aquatic environments from the fluoridation of municipal drinking water and the effects on aquatic life;

(iv) the relationship between the levels of fluoride in sediment and toxicity to benthic organisms (in areas of Canada where high levels of inorganic fluorides in sediments are known or expected to occur); and

(v) the relationship between levels of gaseous inorganic fluorides (especially sulphur hexafluoride) and global climate change potential.

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