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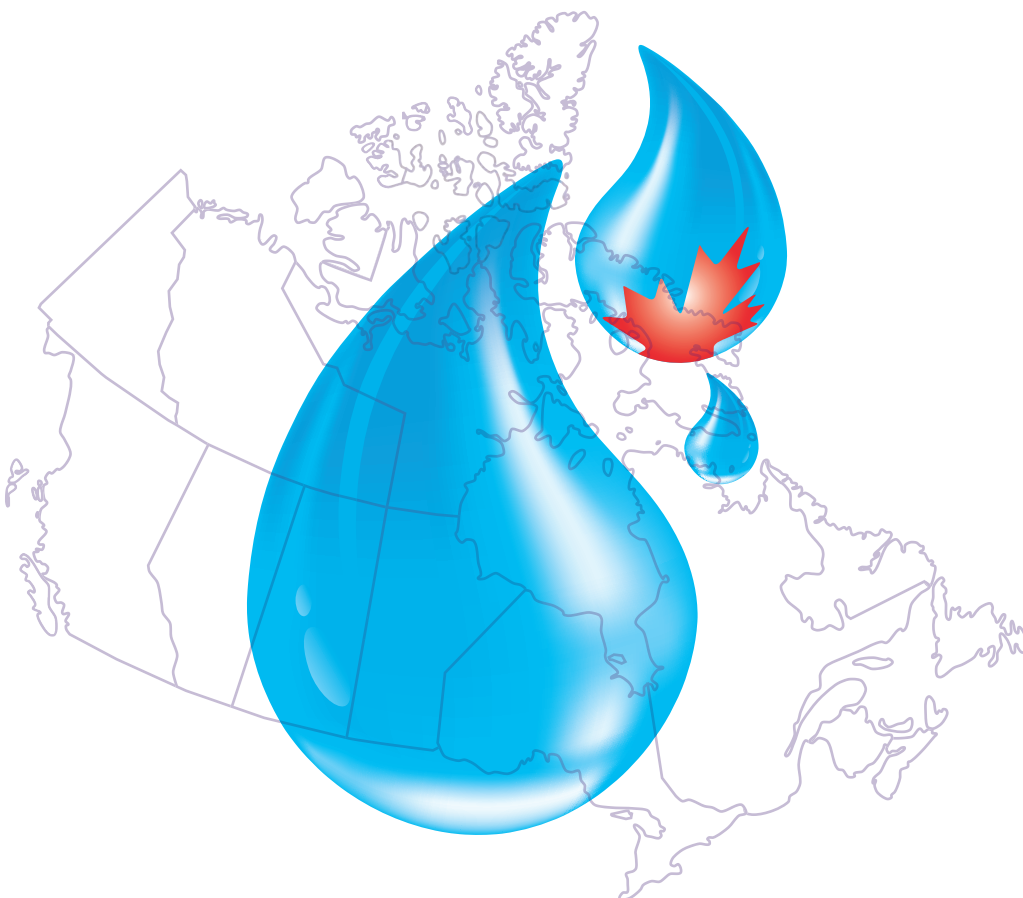
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Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Fluoride



Canada 

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Fluoride*

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Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Fluoride

**Prepared by the
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Drinking Water
of the
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Health and the Environment**

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Other Guideline Technical Documents for the Guidelines for Canadian Drinking Water Quality can be found on the following web page: www.healthcanada.gc.ca/waterquality

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Fluoride in Drinking Water

Part I. Overview and Application

1.0 Guideline

The maximum acceptable concentration (MAC) for fluoride in drinking water is 1.5 mg/L.

2.0 Executive summary

Low levels of fluoride occur naturally in most sources of drinking water in Canada. Fluoride can occur naturally in surface waters from the deposition of particulates from the atmosphere and the weathering of fluoride-containing rocks and soils, and in groundwater from leaching from rock formations. Fluoride is also introduced in the environment by a variety of human activities such as chemical manufacturing plants and waste ponds; the manufacture of aluminum, steel, glass, enamel, brick, tile, pottery, and cement; production of fluorinated chemical and phosphate fertilizer; and metal casting, welding, and brazing.

Health Canada recently completed its review of the health risks associated with fluoride in drinking water. This review assesses all identified human health risks, taking into account new studies and approaches. Based on this review, the guideline for fluoride in drinking water is a Maximum Acceptable Concentration of 1.5 mg/L.

2.1 Health effects

Dental fluorosis is the most widely and frequently studied of all adverse effects of fluoride. It is the effect occurring at the lowest level of fluoride exposure in the population. Mild and very mild dental fluorosis are not considered to be adverse effects, whereas moderate dental fluorosis is found to be an adverse effect, based on its potential cosmetic concern, and is used as the endpoint of concern in the risk assessment used to establish the Maximum Acceptable Concentration. By protecting against a cosmetic effect of moderate dental fluorosis, Canadians are also protected against the adverse health effects of severe dental fluorosis.

Skeletal fluorosis is the most serious adverse health effect clearly associated with prolonged exposure to high levels of fluoride in drinking water. Skeletal fluorosis can occur at very high exposure levels, and has rarely been documented in Canada.

The weight of evidence from all currently available studies does not support a link between exposure to fluoride in drinking water at 1.5 mg/L and any adverse health effects, including those related to cancer, immunotoxicity, reproductive/developmental toxicity, genotoxicity and/or neurotoxicity. It also does not support a link between fluoride exposure and intelligence quotient deficit, as there are significant concerns regarding the relevant studies, including quality, credibility, and methodological weaknesses.

2.2 Exposure

Major sources of exposure to fluoride are water, food and beverages, and dental products. Dental products contain high levels of fluoride and can represent a very important source of exposure, particularly in young children who are more likely to swallow toothpaste. Drinking water can be a significant source of exposure to fluoride; in 2005, community fluoridated drinking water was provided to about 43% of Canadians. To a lesser extent, fluorides are also found in Canadian soils and the atmosphere.

2.3 Treatment

Water containing fluoride levels greater than the MAC of 1.5 mg/L can be treated at both municipal and residential scales through various approaches and technologies. At the municipal level, options include blending of fluoride-rich waters with waters of low fluoride content, the selection of low-fluoride sources and the removal of excess fluoride concentration by treatment processes at public water supply or household level. A wide range of technologies, such as activated alumina, reverse osmosis, lime softening and ion exchange, are capable of reducing excess fluoride levels from drinking water.

At the residential scale, reverse osmosis systems can be used at the point of use, and must be capable of reducing the concentration of fluoride in water to a maximum of 1.5 mg/L to be certified. Distillation systems installed at the point of use are effective to remove inorganic contaminants, including fluoride, and must be capable of reducing fluoride levels to a maximum of 2.0 mg/L to be certified.

2.4 Dental health benefits

Health Canada's Chief Dental Officer has reviewed the available science on dental effects of fluoride, and sought external expert advice from the scientific dental community. Experts provided a recommendation on the optimal level, which was accepted by Health Canada's Chief Dental Officer. As a result, the optimal concentration of fluoride in drinking water for dental health has been determined to be 0.7 mg/L for communities who wish to fluoridate. This concentration provides optimal dental health benefits and is well below the MAC to protect against adverse effects. Further information can be found at:
<http://www.hc-sc.gc.ca/ewh-semt/pubs/water-eau/2008-fluoride-fluorure/index-eng.php>

3.0 Application of the guideline

Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.

The Maximum Acceptable Concentration for fluoride was established based on the segment of the population most at risk of developing dental fluorosis, children 1–4 years old. This MAC is protective of health, provided care is taken to follow Health Canada's recommendations (www.hc-sc.gc.ca/hl-vs/iyh-vsv/environ/fluor-eng.php) regarding other sources of exposure to fluoride, such as dental products.

Frequent monitoring of naturally-occurring fluoride levels is generally not required, as these levels are not expected to change rapidly. Some groundwater sources may have naturally-occurring levels of fluoride significantly above the MAC of 1.5 mg/L. In such cases, the homeowner may wish to consider residential scale treatment or an alternate source of drinking water, especially where young children are exposed on a regular basis.

Short-term exceedances slightly above the guideline value are unlikely to have an effect on health. However, in the event that monitoring data show elevated levels of naturally-occurring fluoride, it is suggested that a plan be developed and implemented to address these situations, with an emphasis on young children.

Municipalities that choose to fluoridate their drinking water supply should establish a full monitoring and reporting program for fluoride levels in drinking water to ensure that the target fluoride level is being applied at all times.

Part II. Science and Technical Considerations

4.0 Identity, use, sources and fate in the environment

In the literature, the terms “fluorine” and “fluoride” are used interchangeably as generic terms (ATSDR, 2003). The term “fluorine gas” is often used to emphasize reference to the elemental form of fluorine rather than a combined form (ATSDR, 2003). In the free state, fluorine is a pale yellow diatomic gas. However, fluorine is never found in this form in nature, because it is very chemically reactive and combines with most elements. It is the 13th most abundant element, commonly occurring in the minerals fluorspar (CaF_2), cryolite (Na_3AlF_6), and fluorapatite ($3\text{Ca}_3(\text{PO}_4)_2 \cdot \text{Ca}(\text{F},\text{Cl})_2$) (Cotton and Wilkinson, 1988; Mackay and Mackay, 1989).

Atmospheric fluorides can be removed from the air via wet and dry deposition or hydrolysis. The transport and transformation of fluoride in water are influenced by pH, water hardness, and the presence of ion-exchange materials such as clays. In soils, where fluoride is not readily leached, the transport and transformation of fluoride are influenced by pH and the formation of predominantly aluminum and calcium complexes (Environment Canada and Health Canada, 1993). Free fluoride ions predominate in aqueous solutions, but both ionic (i.e., inorganic) and non-ionic forms of fluoride can be present in plant and animal tissues. The uptake of fluoride by biota is determined by the route of exposure, the bioavailability of the fluoride, and the uptake/excretion kinetics in the organism (IPCS, 2002).

Both natural and anthropogenic sources can contribute fluoride to soil, air, water, and food. About 23,500 t of inorganic fluorides are released from anthropogenic sources in Canada each year (Environment Canada and Health Canada, 1993), whereas global volcanic sources are estimated to release 60–6000 kt annually (Symonds et al., 1988). Fluoride can occur naturally in surface waters as a result of the deposition of particulates from the atmosphere and the weathering of fluoride-containing rocks and soils. Groundwater can also contain high concentrations of fluoride owing to leaching from rocks. Chemical manufacturing plants and waste ponds can contribute fluoride to raw water sources directly through effluents or indirectly through volatilization (Canadian Public Health Association, 1979; ATSDR, 2003). Fluorine is used in aluminum, steel, glass, enamel, brick, tile, pottery, and cement manufacturing; fluorinated chemical and phosphate fertilizer production; and metal casting, welding, and brazing (Canadian Public Health Association, 1979; Environment Canada and Health Canada, 1993). Sodium fluoride (NaF) is used as a flux for deoxidizing rimmed steel, as a component of laundry soaps (removal of iron stains), in casein glues and heat-treating salts, and in the resmelting of aluminum, manufacture of vitreous enamels, pickling of stainless steel, and manufacture of coated papers (Mueller, 1994). Sodium fluoride is also used in various pesticide formulations, including insecticides and wood preservatives (Budavari, 1989).

Fluoride-containing compounds are employed in the fluoridation of drinking water for the prevention of dental caries (Reeves, 1990). Fluoride-containing dental products, including toothpaste, supplements, mouth rinses, and professionally applied gels and varnishes, are now widely available (CDA, 2005). Fluoride (primarily as NaF) has also been used in the treatment of osteoporosis (NRC, 2006).

5.0 Exposure

Fluoride is ubiquitous in the environment, but the major sources of exposure of the general population to fluoride are water, food and beverages, and dental products. To a lesser extent, fluorides are also found in Canadian soils and the atmosphere.

5.1 Water

Surveys conducted between 1984 and 1989 in several provinces found mean concentrations of fluoride¹ in non-fluoridated drinking water ranging from <50 µg/L (detection limit) in British Columbia (not detected in three locations) and Prince Edward Island (detected in four of 13 locations; <50–70 µg/L) to 210 µg/L in the Yukon (<30–650 µg/L; detection limit <30 µg/L) (Department of National Health and Welfare, 1989; Environment Canada, 1989; Greater Vancouver Regional Water District, 1990). Elevated levels of naturally occurring fluoride in drinking water are relatively infrequent in Canada, although communities in Quebec, Saskatchewan, and Alberta have recorded concentrations as high as 2520–4350 µg/L (Droste, 1987). In 1986, fluoridated drinking water was supplied to approximately 38% of the Canadian population (Droste, 1987). Between 1986 and 1989, average fluoride concentrations in fluoridated drinking water across Canada ranged from 730 µg/L (600–800 µg/L) in Newfoundland and Labrador (three locations) to 1250 µg/L (1200–1300 µg/L) in the Yukon (two locations) (Droste, 1987; Alberta Environment, 1990; Ontario Ministry of the Environment, 1990; Quebec Ministry of the Environment, 1990).

In 2007 community fluoridated drinking water was provided to about 45% of the Canadian population (Health Canada, 2009). Water fluoridation statistics for the Canadian population can be found in Appendix B (Table B-1). These statistics indicate that populations with the highest proportions of fluoridated drinking water are found in Ontario, Alberta and Manitoba, with respective percentages of 76%, 75%, and 70%. Populations with the lowest rates of fluoridated water are found in Nunavut, Yukon, Newfoundland and Labrador, British Columbia, and Quebec, with respective percentages of 0%, 0%, 1.5%, 3.7%, and 6.4%.

Provincial and territorial data provided by members of the Federal-Provincial-Territorial Committee on Drinking Water in 2005 show levels of fluoride in fluoridated drinking water systems varying from 0.46 to 1.1 mg/L on average across Canada. Furthermore, over 75% of the Canadian population on a water system are estimated to receive fluoride in their water at concentrations of less than 0.6 mg/L, and fewer than 2% of the population would receive community water at levels over 1.0 mg/L.

5.2 Food and beverages

Dabeka and McKenzie (1995) conducted a diet survey in Canada during the period 1986–1988 to assess the food supply for fluoride and other chemicals. Foods were purchased at the retail level in Winnipeg, Manitoba, and prepared for consumption, then combined into 113 composites and 39 composite subsets. The drinking water used to prepare the food came

¹ Unless otherwise specified, concentrations of fluoride refer to inorganic fluoride.

from a single source containing fluoride at 1 mg/L. The mean (range) of fluoride concentrations found in individual samples was 325 ng/g (11–4970 ng/g). Individual samples with the highest fluoride levels were cooked wheat cereal (1020 ng/g), cooked veal (1230 ng/g), shellfish (3360 ng/g), canned fish (4570 ng/g), and tea (4970 ng/g). Food categories with the highest mean fluoride levels were soups (606 ng/g), beverages (1148 ng/g), and fish (2118 ng/g). During the same diet survey, dietary intakes of fluoride were calculated for different age groups. Dietary intakes of fluoride varied from 353 µg/day for 1- to 4-year-old children to 3032 µg/day for 40- to 64-year-old males. Over all ages and sexes, the average dietary intake of fluoride was 1763 µg/day. The food category contributing most to the dietary intake of fluoride was beverages (80%).

A recently completed total diet survey estimated the dietary intakes of fluoride by Canadians using the following: food intake data from a Nutrition Canada Survey; total diet food composites prepared from foods purchased in Toronto, Ontario, in 2005; select composites prepared in Ottawa, Ontario, using water containing fluoride at 1 mg/L, as well as water with no fluoride; select commercial foods prepared and purchased in Ottawa and Gatineau, Quebec (two adjacent communities containing fluoride levels of 0.99 mg/L and 0.03 mg/L in their drinking water, respectively); and a small number of ready-to-use and powdered infant formulas. Dietary intakes of fluoride were estimated for people living in the city of Toronto, Ontario, where the average level of fluoride in drinking water was estimated to be 0.54 mg/L, as well as for communities with fluoride levels of 1 mg/L and 0 mg/L in the drinking water (Dabeka et al., 2007a). The estimated dietary intakes of fluoride for different age groups in the Canadian population over 1 year of age as a function of fluoride levels in their community drinking and food processing water can be found in Appendix B (Table B-2). The average dietary intake of fluoride in the 1- to 4-year-old group is estimated to be 0.026 mg/kg bw/day and 0.016 mg/kg bw/day in fluoridated and non-fluoridated communities, respectively. The average dietary intakes of fluoride in the Canadian population aged 20 years and older are estimated to vary between 0.024 to 0.033 mg/kg bw/day in non-fluoridated communities and between 0.038 to 0.048 mg/kg bw/day in fluoridated communities.

The fluoride concentration in water used to reconstitute or prepare beverages and dry concentrates can greatly influence their fluoride content (Kumpulainen and Koivistoinen, 1977; Schamschula et al., 1988; Marier, 1991). In the United States, fluoride concentrations in infant formulas were found to range from 0.127 mg/L for ready-to-use milk-based formula to 0.854 mg/L for soy-based powdered formula prepared using water containing fluoride at a concentration of 1.0 mg/L (McKnight-Hanes et al., 1988). A Canadian survey found that women consuming non-fluoridated drinking water (<0.16 mg fluoride/L) produced milk with a mean fluoride concentration of 4.4 ng/g (µg/L), whereas breast milk from women consuming fluoridated drinking water (1 mg fluoride/L) contained fluoride at a concentration of 9.8 ng/g (Dabeka et al., 1986). As a part of the total diet survey, Dabeka et al. (2007a) estimated the dietary intakes of fluoride by infants. Table B-3 (in Appendix B) shows the estimated dietary intake of fluoride by infants as a function of the fluoride level in their community drinking water and the type of infant formula fed to them. According to data shown in Table B-3, the highest estimated dietary intake of fluoride in infants is from powdered infant formula reconstituted with fluoridated drinking water. The human milk and ready-to-use infant formulas contain a low dietary intake of fluoride, even in communities with fluoridated drinking water. The category

“all formulas” takes into account average intake for consumers and non-consumers of different types of infant formula and other types of food (when applicable). Table B-3 shows that the estimated daily intake of fluoride from food and beverages of the “all formulas” group in 7–12 months old breast-fed infants varies between 0.017 and 0.021 mg/kg-bw-day in a fluoridated community and between 0.011 and 0.012 mg/kg bw/day in a non-fluoridated community. For non breast-fed infants aged 7–12 months old, daily intake is estimated to vary from 0.024 to 0.026 mg/kg bw/day in a fluoridated community and from 0.013 to 0.014 mg/kg bw/day in a non-fluoridated community.

Some ready-to-feed infant foods may also contain high levels of fluoride. For example, the mean and median fluoride concentrations of chicken-flavoured ready-to-feed infant foods were 4.04 and 4.40 µg/g, respectively, in a study by Heilman et al. (1997). Other meats, vegetables, fruits, and infant foods were consistently low in fluoride content and are not likely to be major intake sources.

The average consumption of tap water among children has declined in the United States and Canada, whereas consumption of other beverages has increased substantially (Levy et al., 1995). The fluoride content in beverages closely matches the fluoride content of water used in their processing. Owing to these differences in fluoride content of water used in processing, there is considerable variation in the fluoride content of processed beverages (Levy et al., 2006).

In areas where tea drinking is prevalent, tea is another important source of fluoride (Duckworth and Duckworth, 1978; Hargreaves, 1978; Hargreaves and Stahl, 1986; Featherstone and Schields, 1988). Raw tea leaves may contain fluoride levels as high as 400 mg/kg (Duckworth and Duckworth, 1978). The fluoride content of tea has been found to range from 0.1 to 4.2 mg/L when brewed with deionized water, with an average of about 3 mg/L (Duckworth and Duckworth, 1978; Hargreaves, 1978; Hargreaves and Stahl, 1986).

Bottled waters can show substantial variation in their fluoride contents. Most bottled waters contain less than 0.3 mg fluoride/L; however, some artesian waters and certain imported mineral waters contain higher levels of fluoride (Flaitz et al., 1989; Levy, 1994; Tate and Chan, 1994; Van Winkle et al., 1995). A 1993 study of the fluoride content of 78 bottled waters available in Iowa showed that 83% contained <0.3 mg/L, 7% contained 0.3–0.7 mg/L, 1% contained 0.71–1.00 mg/L, and 9% contained >1 mg/L (Van Winkle et al., 1995).

Sulphuryl fluoride is a pesticide that has been temporarily registered in Canada since 2006 as a fumigant for use in empty cereal grain mills, empty storage facilities, and empty food processing facilities for the control of stored product pests (PMRA, 2006a). Even if this pesticide is not registered for food use in Canada, some food items imported from other countries may contain some sulphuryl fluoride residues. The Pest Management Regulatory Agency of Health Canada has established maximum residue limits for sulphuryl fluoride in the relevant food composites (almonds, dates, field corn, prune plums, rice, figs, wheat, pistachios, walnuts, and pecans) (PMRA, 2006b).

5.3 Dental products

The most commonly used fluoride-containing dental product is toothpaste. The vast majority of toothpastes sold in North America contain fluoride as NaF (996–1222 ppm), disodium monofluorophosphate (MPF or Na₂PO₄F) (1000–1320 ppm), and/or stannous fluoride (SnF₂) (970–1455 ppm). Other fluoride-containing dental products available to the consumer

include fluoride supplements, fluoride mouth rinses and dental floss. Fluoride containing products available to dental professionals include fluoride varnishes, topical gels and topical foams (Health Canada, 2007).

Health Canada (2010a) recommends keeping fluoride intake within safe limits. For example, Health Canada recommends children under the age of three should have their teeth brushed by an adult without using any toothpaste. Health Canada also recommends children 3–6 years of age should be supervised during brushing and use only a small amount (e.g., pea-sized portion) of fluoridated toothpaste.

Considering the potential for toothpaste ingestion, a few children receive very high fluoride intake. However, this source can be very important as part of cumulative fluoride intake. This is especially true for children who are younger and more likely to swallow toothpaste. The brushing frequency, amount used, and proportions ingested are all important factors to be considered when evaluating fluoride intake (Levy et al., 2006). The Iowa Fluoride Study provides analyses of fluoride content in different beverages, such as infant formulas and bottled waters, and a longitudinal study of all fluoride exposures and ingestion among a birth cohort, with linkage to dental fluorosis and dental caries examination results in the United States. The results (see Appendix B, Table B-6) provide good quality, detailed data on estimated fluoride intake from toothpaste among children from birth to age 8 (Levy et al., 2006). As shown in Table B-6, the mean estimated dose of fluoride ingested from fluoridated dentifrice varies from 0.02 to 0.03 mg/kg bw/day for the 6–12 months old and from 0.02 to 0.04 mg/kg bw/day for the 12 months to 4 years old (48 months) children. It should be noted that children may be ingesting significantly higher doses of fluoride from toothpaste. For example, the estimated 95th percentile of fluoride ingested from fluoridated toothpaste varies from 0.06 to 0.23 mg/kg bw/day for the 6–12 months old and from 0.06 to 0.09 mg/kg bw/day for the 12 months to 4 years old children (Levy et al., 2006).

The amount of fluoride ingested by adults from toothpaste is estimated to be 1.14 µg/kg-bw per day, based on a mean concentration of inorganic fluoride in most dentifrice products of 1000 µg/g and an estimated intake of toothpaste of 0.08 g/day (Environment Canada and Health Canada, 1993).

5.4 Soil

Fluoride is a natural component of most types of soil, with concentrations ranging from 20 to 1000 µg/g in areas without natural phosphate or fluoride deposits, and up to several thousand µg/g in mineral soils with deposits of fluoride (Davison, 1983). The mean concentration of inorganic fluoride in Canada Soil Survey Committee (CSSC) reference soil samples (n=23) obtained at a depth of 0 to 130 cm was 309 µg/g (with a range of 63–1000 µg/g) (Schuppli, 1985). Children are more likely than adults to ingest soil (NRC, 2006). The estimated standard values for the daily intake of soil in the Canadian population are 35 mg/day for 0- to <6-month-olds, 50 mg/day for 6-month- to <5-year-olds, 35 mg/day for 5- to <12-year-olds, and 20 mg/day for adults (Health Canada, 1994). Hence, the estimated daily intake of fluoride from soil ingestion is estimated to be 1.19 µg/kg-bw/day and 0.09 µg/kg bw/day for the 6-month- to <5-year-olds and the 20+ years age groups, respectively.

5.5 Air

No Canadian data are available on fluoride concentrations in indoor air. Average monthly concentrations of fluoride (gaseous and particulate) in ambient air reported for a residential area in Toronto, Ontario, in 1981 ranged from 0.01 to 0.05 $\mu\text{g}/\text{m}^3$, with a mean of 0.03 $\mu\text{g}/\text{m}^3$ (McGrath, 1983). The intake of inhaled fluoride for Canadians is estimated to be about 0.01 $\mu\text{g}/\text{kg}$ bw per day (Lewis and Limeback, 1996). Since levels in ambient air are, in most cases, below detectable limits, the levels inhaled are generally very low except for in areas immediately surrounding industries that emit fluorides into the air (ATSDR, 2003). Higher levels of fluoride in ambient air were found in the vicinity of Canadian industrial sources, with mean concentrations of fluoride in samples of ambient air collected between 1980 and 1991 near emitting industries in Canada ranging up to 0.85 $\mu\text{g}/\text{m}^3$ (Environment Canada and Health Canada, 1993).

5.6 Total daily intake

According to the findings and recommendations from the Expert Panel Meeting on fluoride held in Canada in 2007, there appears to have a general decline in the overall intake of fluoride in recent years for the Canadian population (Health Canada, 2008). This decrease is probably related to the revision of the recommendations concerning the use of fluorides in the 1990s in Canada and the United States, from which significant changes were introduced. However, there are no data to evaluate the impact of these recommendations into our communities (Clark, 2006).

Until now, the best data correlating fluoride in drinking water with dental health in a population were collected in the 1940s in United States communities with varying levels of fluoride in drinking water (Dean et al., 1942). In order to use these data in a modern context, historical dietary intake of fluoride from food and beverages was calculated for the population living in the 1940s, with fluoride levels of 0, 1.0 or 1.5 mg/L in their community's drinking water. At that time, there were no confounding fluoride sources to consider, such as toothpaste, which could have influenced the prevalence of different degrees of fluorosis. This calculation uses current dietary intake data to estimate what the dietary intake of fluoride would have been in the 1940s in the above communities, but adjusts total diet study data using two methods to estimate the dietary intake (excluding tap water consumed directly) of fluoride of those living in a community with fluoride levels of 1.0 or 1.5 mg/L in drinking water. First, the calculation assumes that concentrated juices and infant formulas were absent during that period. Quite likely, evaporated milk or cow's milk were being used instead of infant formula, and thus the concentration of fluoride in evaporated milk was ascribed to infant formula. The concentrations of fluoride in cow's milk were left unchanged. Estimates of dietary fluoride intakes from food and beverages using water containing fluoride at 1.5 mg/L were linearly extrapolated from those prepared with fluoride levels at 0 and 1 mg/L (Dabeka et al., 2007b).

Tables B-4 and B-5 provide the estimated dietary intakes of infants and of children 1 year of age or older and adults, respectively, living in the 1940s in communities with differing concentrations of fluoride in their drinking water. Assuming a 1940s diet, the average dietary intake of fluoride by individuals living in a community with a fluoride level of 1.5 mg/L in drinking water is estimated to be 0.032 mg/kg bw/day. Infants up to 1 year of age living in a community with 1.5 mg fluoride/L in the drinking water, particularly those fed evaporated milk,

would have had intakes higher than those of adults, equal to 0.048 mg/kg bw/day. For children aged 1–4 years living in a community with a fluoride level of 1.5 mg/L in drinking water, the dietary intake of fluoride is estimated to be approximately 0.027 mg/kg bw/day.

The estimated total daily intakes of fluoride from drinking water, air, soil, food and beverages, and toothpaste for the 7- to 12-month, 1- to 4-year and 20+-year age groups in the Canadian population are shown in Table 1. Daily fluoride intakes from dietary supplements, mouth rinses, varnishes and gels were not estimated, as the available data on the proportion of the general population using these products or the amount of fluoride ingested from them were considered inadequate. Furthermore, their use is either not recommended or recommended only on an individual basis by dentists for children and adults at risk for dental cavities (Health Canada, 2010a).

Individual variability of fluoride intakes may be very high for each source. Infant formula is one of the dietary components that could lead to excessive fluoride intake in infants, especially that of consumption of powdered infant formula reconstituted with fluoridated water (see Table B-3). The Expert Panel on Fluoride, in its Findings and Recommendations (Health Canada, 2008), recommended that the following points should be considered:

- A few studies have found a positive association between greater use of infant formula reconstituted with fluoridated water and a greater prevalence of dental fluorosis; however, current scientific literature does not support a link between consumption of infant formula reconstituted with drinking water containing fluoride and the risk of moderate/severe dental fluorosis.
- The risk of excessive intake of fluoride is higher for infants consuming larger quantities of infant formulas. However, the bioavailability of fluoride in reconstituted infant formula is likely to be less than in drinking water.
- Extended periods (e.g., multiple years) of exposure to fluoride are associated with increased fluorosis risk, and a higher exposure in the first year of life may not be as much of a concern if it is followed by low exposure.

As part of cumulative fluoride intake, ingestion of fluoride through dental products also needs to be considered. Toothpaste can be a very important source of exposure in young children who are more likely to swallow it and hence, may increase the risk of moderate and severe forms of dental fluorosis in this population.

Table 1: Estimated daily intakes of fluoride for the 7- to 12-month, 1- to 4-year and 20+-year age groups in the Canadian general population

Daily intake of fluoride from various sources (µg/kg bw per day)									
Age groups	Type of community	Drinking water (straight) ^a	Air ^b	Soil ^c	Food and beverages ^d		Toothpaste ^e	Total (mean)	Proportion of fluoride intake from drinking water (mean)
					Food	Beverages			
7–12 months Breast-fed infants	Non-fluoridated	0.77–3.23			2.2–2.4	8.8–9.6		33.0–46.4 (39.7)	0.24–0.32 (0.28)
	Fluoridated	7.08–16.92	0.01	1.19	3.4–4.2	13.6–16.8	20.0–30.0	45.3–69.1 (57.2)	0.36–0.59 (0.48)
7–12 months Non-breast-fed infants	Non-fluoridated	0.77–3.23			2.6–2.8	10.4–11.2		35.0–48.4 (41.7)	0.27–0.35 (0.31)
	Fluoridated	7.08–16.92	0.01	1.19	4.8–5.2	19.2–20.8	20.0–30.0	52.3–74.1 (63.2)	0.42–0.60 (0.51)
1–4 years	Non-fluoridated	0.77–3.23			3.2	12.8		38.0–60.4 (49.2)	0.28–0.33 (0.31)
	Fluoridated	7.08–16.92	0.01	1.19	5.2	20.8	20.0–40.0	54.3–84.1 (69.2)	0.40–0.55 (0.48)
20+ years	Non-fluoridated	0.29–1.20			4.8–6.6	19.2–26.4		25.5–35.4 (30.5)	0.64–0.91 (0.78)
	Fluoridated	2.63–6.29	0.01	0.09	7.6–9.6	30.4–38.4	1.14	41.8–55.5 (48.7)	0.68–0.92 (0.80)

^a Drinking water: Estimated using previously reported data (1996) on levels of fluoride found in non-fluoridated areas (minimum of <50 µg/L found in British Columbia and maximum of 210 µg/L found in Prince Edward Island and Yukon) and on new fluoridation data in drinking water (2005) (minimum of 460 µg/L found in Ontario and maximum of 1100 µg/L found in Prince Edward Island), assuming that individuals from the 7 months to 4-year, and 20+-year age groups consume 0.2 L, and 0.4 L of straight tap water per day and weigh 13 kg, and 70 kg, respectively (Health Canada, 1994). The fluoride intake from the tap water used in food and beverage processing is included in the Food and Beverages category.

^b Air: Estimated inhaled fluoride intake for Canadians (Lewis and Limeback, 1996).

Fluoride (December 2010)

- ^c Soil: Calculated from the mean fluoride concentration of soil of 309 µg/g (Schuppli, 1985), assuming an ingestion rate of 50 mg/day in 6-month- to 4-year-old children, and 20 mg/day in adults (Health Canada, 1994). Body weights were assumed to be 13 kg and 70 kg for individuals from the 7-month to 4-year and 20+-year age groups, respectively (Health Canada, 1994).
- ^d Food and beverages: Ranges of mean intake data from the food basket survey for the 7- to 12-months, 1- to 4-year, and 20+-year age groups (Dabeka et al., 2007a). Data for the 7- to 12-month age groups are estimated as an average consumption for all the different types of formulas and food. They refer to the “All Formulas” category in Table B-3. These data do not present the worst-case scenario of exposure in infants, which is considered to be the exclusive consumption of powdered infant formula reconstituted with fluoridated drinking water.
- ^e Toothpaste: Ranges of mean values of toothpaste ingestion in the 7- to 12-month and 1- to 4-year age groups are derived from the Iowa Fluoride Study (Levy et al., 2006). Toothpaste ingestion in the adult group is calculated assuming 80 mg/day of toothpaste ingestion at a fluoride concentration of 1000 µg/g (Environment Canada and Health Canada, 1993). For the 7- to 12-month-old group, the mean toothpaste ingestion ranges from 20 to 30 µg fluoride/kg-bw per day. For 1- to 4-year-old children, the mean intake varies between 20 and 40 µg fluoride/kg-bw per day. Mean values are used in the range of fluoride intake from toothpaste, as recommended by the Expert Panel on Fluoride (Health Canada, 2008).

6.0 Analytical methods

The United States Environmental Protection Agency (EPA) currently has one approved analytical method (Method 300.0 Revision 2.1) for the analysis of fluoride in drinking water (U.S. EPA, 1993). EPA also approves the following methods, developed by voluntary consensus standard organizations (U.S. EPA, 2003a):

- Ion chromatography method – SM 4110B (APHA et al., 1998); D4327-97 (ASTM, 1997)
- Manual electrode method – SM 4500F-C (APHA et al., 1998); D1179-93B (ASTM, 1993)
- SPADNS colorimetric method – SM 4500F-D alone or in combination with SM 4500F-B as a preliminary distillation step (APHA et. al., 1998)
- Automated Complexone method – SM 4500F-E (APHA et al., 1998)

EPA method 300.0 Revision 2.1 is based on ion chromatography, and has a method detection limit (MDL) of 0.01 mg F⁻/L. The ion chromatograph separates the anions of interest, which are measured using a system comprised of a guard column, an analytical column, a suppressor device and a conductivity detector (U.S. EPA, 1993).

Methods SM 4110B (APHA et al., 1998) and D4327-97 (ASTM, 1997) are equivalent to EPA method 300.0. An MDL is not stated for method SM 4110B, but is identified as 0.002 mg F⁻/L in the most recent version of APHA et al. (2005). Data from a single EPA laboratory provides an MDL of 0.01 mg/L for method D4327-97. Limitations of ion chromatography methods are: (1) the difficulty to quantify samples with low fluoride concentration because of the negative effect of the elution of water (“water dip”); and (2) possible interference from the simple organic acids (formic, carbonic, etc.) which elute close to the fluoride peak.

Method SM 4500F-C and method D1179-93B determine the fluoride concentration potentiometrically using an ion selective electrode in conjunction with a standard sleeve-type reference electrode. A potential is developed across the lanthanum fluoride crystal electrode by the sample solution at one side, and an internal reference solution at the other. These methods are suitable for fluoride concentrations ranging from 0.1 mg/L to more than 10 mg/L (APHA et al., 1998) and from 0.1 mg/L to 1000 mg/L (ASTM, 1993), respectively. A common problem using the ion selective electrode is the interference of S⁺⁴, Fe⁺³, and Al⁺³ cations and formation of complexes with the fluoride. This is resolved by the addition of a buffer, which reacts with the interfering cations and releases the fluoride anions.

The SPADNS 4500F-D colorimetric method is based on the reaction between fluoride and a zirconium-dye lake, where the colour of the sample becomes lighter as the fluoride concentration increases. The concentration of fluoride is measured using a photometer at 550 nm to 580 nm, or a spectrophotometer at 570 nm. This method has a linear analytical range of 0 to 1.4 mg/L. When using this method, the preliminary distillation method 4500F-B should be used to prepare sample when these contain interfering ions or are coloured or turbid.

In the Automated Complexone method SM 4500F-E, the sample is distilled, and the distillate reacts with alizarine fluorine blue-lanthanum reagent to form a blue complex. The fluoride concentration is derived by colorimetry at 620 nm. The method is suitable for fluoride concentrations ranging from 0.1 mg/L to 2 mg/L.

The Centre d'expertise en analyse environnementale du Québec (CEAEQ, 2007) reported a method (MA.303 – Anions 1.0) for measuring fluoride in drinking water with a detection limit of 0.03 mg/L. The method is based on ion chromatography equipped with a conductivity detector and used in accredited laboratories in Quebec.

The United States EPA's six-year review of the analysis of Water Supply data (U.S. EPA, 2003a) indicates that manual electrode methods SM 4500F-C and D1179-93B were the predominant methods used by the accredited laboratories participating in the studies. A small percentage of the laboratories participating in the Water Supply study employed two of the EPA's other approved analytical methods: 380-75WE (automated electrode) and 129-71W (automated alizarin) (U.S. EPA, 2003a) but no supporting information on these methods is available.

The current U.S. EPA practical quantitation limit (PQL) (based on the ability of laboratories to measure the concentration of an analyte within reasonable limits of precision and accuracy) for fluoride is 0.5 mg/L (U.S. EPA, 1986). Analysis of Water Supply data, based on methods comparison and methods usage, suggested that the PQL for fluoride could possibly be lowered, however, further analysis would be required (U.S. EPA, 2003a).

7.0 Treatment technology

7.1 Municipal scale

Control options for excess fluoride levels in the drinking water include blending of fluoride-rich waters with waters of low fluoride content, the selection of low-fluoride sources and the removal of excess fluoride concentration by treatment processes at public water supply or household level. A wide range of technologies such as activated alumina (AA), reverse osmosis (RO), lime softening, and ion exchange, are capable of reducing of excess fluoride levels from drinking water. Coagulation has been shown to reduce fluoride, however, it is less effective since it requires large amounts of coagulant.

Generally, conventional water treatment processes (coagulation, flocculation, and clarification) have only a small effect in reducing the excess levels of fluoride in drinking water (NAS, 1977; Department of National Health and Welfare, 1993a; NHMRC, 2004; WHO, 2004). The selection of an appropriate treatment process for a specific water supply will depend on the characteristics of the raw water supply and the operational condition of the specific treatment method. The raw water pH and the presence of competing ions such as arsenic, selenium, silica, chloride, sulfate, nitrate, and hardness ions can greatly affect the efficiency of fluoride removal.

The EPA has identified adsorption on AA and RO as the best technologies generally available for excess fluoride reduction (U.S. EPA, 1986). Removal efficiencies in the range of 85% to 95% are achievable, depending on treatment system design (U.S. EPA, 2003b). For water systems that required only the removal of excess fluoride from raw water, the AA treatment method is preferred. RO treatment is the recommended process for water systems that need to reduce the total dissolved solids (TDS) and other contaminants in addition to fluoride (U.S. EPA, 1986). Studies have shown that the two treatment processes described above are effective, but relatively expensive to build and maintain on a municipal scale. Costs

and issues related to the handling of hazardous substances may make AA unsuitable for small water treatment utilities (Fox and Sorg, 1987; U.S. EPA, 1998).

7.1.1 *Coagulation techniques*

Although not highly effective, inorganic coagulants such as aluminum sulfate (alum) or a ferric salt, may be able to reduce fluoride in drinking water, however, the processes would require very large amounts of coagulant (Sorg, 1978; Singh and Clifford, 1981; Crittenden et al., 2005). During the coagulation/flocculation processes, the fluoride ions are removed by adsorption and co-precipitation.

Fluoride removal by alum coagulation is affected by factors such as a coagulant dose and pH. Experimental data illustrated that the optimum pH range for removal of fluoride is between 6.2 and 7.0 (U.S. EPA, 1984, 2002; Potgieter, 1990). The cations associated with the fluoride ions in the water, affect the rate of fluoride removal (J.E. Serrine Co and Aware Inc, 1977). Sodium fluoride salts demonstrated a higher degree of defluoridation, while magnesium and aluminum fluoride salts have a modest removal rate. Another consideration pertaining to the use of alum coagulation is the ability of fluoride to form inorganic complexes with aluminum. Since the complexes remain soluble in the water, they increase the aluminum residual in the finished water and reduce the removal rate for fluoride ions (Cushing et al., 2000; Field et al., 2000; Pommerenk and Schafran, 2002).

Full-scale data showed a reduction of an influent fluoride concentration in the range of 2.0–2.6 mg/L to an effluent level of less than 1.8 mg/L, using a total alum coagulant (alum and sodium aluminate) dose in the range 23–30 mg/L, at a pH ranged from 7.0 to 7.3 (Cushing et al., 2000).

In laboratory studies, Mathu et al. (2003) reported that polyaluminum chloride (PACl) reduced influent fluoride concentrations of 4, 3 and 2 mg/L to 1.95, 0.80 and 0.85 mg/L, respectively, using a coagulant dose of 500 mg/L, at a pH value of 7.93. Results from this study indicate that the pH value, the coagulant dose, and the initial fluoride concentration are critical control parameters with regard to decreasing fluoride levels. Parallel experiments conducted with an alum coagulant at the same pH, the same influent concentrations and coagulant doses showed fluoride effluent concentrations of 1.50, 1.40 and 1.30 mg/L, respectively.

The high quantity of coagulant required and the cost of the chemicals limit this technology from some specific applications, especially in small treatment systems. This quantity would result in generation of a large volume of sludge, which requires pretreatment and disposal (U.S. EPA, 2002).

7.1.2 *Activated alumina*

The most practical municipal-scale technology for the reduction of excess fluoride concentrations in drinking water is adsorption with AA (γ -aluminum trioxide), which shows a high affinity and selectivity towards fluoride ions (Sorg, 1978; Wu and Nitya, 1979; U.S. EPA, 1980; Barbier and Mazounie, 1984; Schoeman and Leach, 1987; Clifford, 1999; Ghorai and Pant, 2004; Chauhan et al., 2006). Full-scale and pilot-scale studies have demonstrated that effluent concentrations of fluoride below 1.0 mg/L are achievable using this treatment process (Barbier and Mazounie, 1984; U.S. EPA, 1984; Schoeman and Leach, 1987; Guo-Xun, 1994).

As the raw water is continuously passed through the AA packed beds, (in series or parallel), the fluoride ions are exchanged with the hydroxides on the surface of the alumina. Factors such as a pH, influent fluoride concentration, media particle size, and competing ions (arsenic, selenium, silica, hardness ions) have a significant impact on fluoride removal. In addition, the effectiveness of the process is also a function of the flow rate, the empty bed contact time (EBCT), and media regeneration.

Due to the amphoteric nature of AA, this process is influenced by pH. Below pH 8.2 (a typical zero point charge for AA), the AA surface has a net positive charge, and it will adsorb anions found in the water. A number of studies have shown that optimum fluoride removal by AA is achieved at pH between 5.5 and 6.0 (Rubel and Woosley, 1978; Choi and Chen, 1979; Barbier and Mazounie, 1984; Schoeman and Leach, 1987; OME, 1992, U.S. EPA, 1998, 2002; Clifford, 1999; Meenakshi and Maheshwari, 2006). At this pH, the attraction of the fluoride ions to the AA surface is most favourable and interference by competing cations and silicate is minimal. In order to optimize the removal efficiency of the process, an adjustment of a pH of the water may be required, prior to and after the treatment process.

At a pH greater than 6.0, silicate, hardness cations (Ca^{2+} and Mg^{2+}) compete with fluoride ions for exchange sites of the adsorption media (Potgieter, 1990; U.S. EPA, 2002). If the source water contains an excess fluoride level and is contaminated with arsenic cations, arsenic is preferentially adsorbed on AA at the same optimal pH, resulting in reduced efficiency for fluoride removal (U.S. EPA, 1980, 2002). The fluoride removal process is not affected by chloride (U.S. EPA, 1984, 2002; Potgieter, 1990; Meenakshi and Maheshwari, 2006) or sulfate (Sorg, 1978; Potgieter, 1990; U.S. EPA, 2002) anions in the water. In contrast, one laboratory study (Singh and Clifford, 1981) showed that sulfate anions caused a significant reduction in the efficiency of the process at the optimum pH for fluoride removal.

In addition, some studies demonstrated that, if the alkalinity of the raw water is increased, the fluoride adsorption is decreased (Savinelli and Black, 1958; Bishop and Sansoucy, 1978; Barbier and Mazounie, 1984; U.S. EPA, 1984). However, the pH was not specified for these studies. In contrast, one study (Singh and Clifford, 1981) found no significant influence of bicarbonate (alkalinity) on fluoride removal at pH 6.0.

The capacity of AA to remove fluoride is reduced with a decreased influent fluoride concentration (Barbier and Mazounie, 1984; U.S. EPA, 1984). Fluoride removal capacity was decreased from of 700 grains/ft³ (1601 g/m³) to 450 grains/ft³ (1030 g/m³) when the influent fluoride concentration was reduced from 8 mg/L to 3 mg/L (U.S. EPA, 1984).

A survey of treatment plants using AA in the United States, showed greater than 95% fluoride reduction under a variety of operating conditions, with influent concentrations ranging from 4.5 to 7.5 mg/L (U.S. EPA, 1984). A plant facility using two columns in series, containing 3 m³ AA each, operating at a feed flow rate of 108 L/m²/min, retention time of 16 min, and feed water pH of 5.6, was able to reduce an influent concentration of 7.2 mg/L fluoride to below 1 mg/L in the finished water (Schoeman and Leach, 1987). A full-scale study demonstrated that a single AA bed achieved an average effluent fluoride level to below 1 mg/L (range from 0.56 to 0.80 mg/L) from an influent concentration of 3 mg/L, and a retention time of 13.3 min. The pH of the raw water was maintained at a range of 6.5–7.0 using carbon dioxide gas. Under these operating conditions an adsorption capacity of 3–4 mg F⁻/g AA may be achieved (Guo-Xun 1994). Pilot scale results obtained using regenerated AA, showed the reduction of an influent

fluoride concentration from 11.5 mg/L to an effluent concentration of below 1 mg/L. Adsorption capacity in the range of 3.8–4.5 mg F⁻/g AA, was achieved using a bed depth of 1.5 metres, and a flow rate of 13.3 bed volumes/hours (Barbier and Mazounie, 1984).

When employing AA technology, operational issues that must be considered include AA from “cemented alumina beds” which tends to dissolve as a result of the regeneration process; the fouling of the AA bed with particulates resulting in an increase in headloss across the media bed (U.S. EPA, 1984, 2002); and metal hydroxides, suspended solids, carbonates and adsorbed silicates which can reduce the adsorption capacity of AA (Schoeman and Leach, 1987; U.S. EPA, 2002). As well, in order to prevent fouling of the AA column, there needs to be sufficient oxidation of iron and manganese ions followed by filtration of the raw water, before the AA beds.

Activated alumina treatment also has the potential for “chromatographic peaking”. At pH>8 predominant hydroxyl ions are preferred over any other ions for adsorption onto AA, thus releasing fluoride ions into the finished water. Choi and Chen (1979) and Hao and Huang (1986) documented the formation of alumino-fluoro soluble inorganic complexes, which are derived from the reaction between aluminium (formed through dissolution of acid-treated alumina) and fluoride.

Additional considerations include the chemical handling requirements, pH adjustments, and regeneration of exhausted AA beds, all of which can make the AA technology dangerous and complex for small systems.

Several authors have reported a wide range of adsorbents such as bone char, coal-based sorbents, burnt clay, zeolites, flyash, and brick for the removal of excess fluoride levels in drinking water (Schoeman and Botha, 1985; Potgieter 1990; Bregnhøj, 1995; Karthikeyan et al., 1999; Mehrotra et al., 1999; Sivasamy et al., 2001).

7.1.3 Reverse osmosis and nanofiltration processes

Reverse osmosis and nanofiltration (NF) technologies have been shown to be effective methods for the reduction of fluoride concentrations below 1 mg/L in drinking water (U.S. EPA, 1988; Durand-Bourlier and Laine, 1991; Pontie et al., 1996; Cohen and Conrad, 1998; Lhassani et al., 2001; U.S. EPA, 2002).

The performance of the membrane systems depends on a variety of factors, including the quality of the raw water, the type of the membrane, molecular weight cutoff, and recovery of the system (Jacangelo et al., 1997). The presence of iron, manganese, silica, scale-producing compounds, and turbidity could negatively affect the system performance. A pretreatment of the feed water is required to prevent scaling and fouling of the RO membranes. The RO product water typically requires post-treatment, consisting of pH and alkalinity adjustments (U.S. EPA, 1984, 2002).

In a study of a full-scale system using a thin-film composite RO membrane, a fluoride influent concentration of 5.5 mg/L was reduced to 0.4 mg/L, achieving a fluoride removal of over 90% at a system recovery greater than 73%. Results from this study also indicated that water quality and pilot-scale membrane units should be used when selecting membranes for full scale applications (Cohen and Conrad, 1998). Pilot-scale RO data demonstrated an average fluoride reduction up to 94%. An average effluent fluoride level below 1 mg/L was calculated based on the stated influent concentration range from 5.3–14.5 mg/L, under a variety of

operating conditions. Results of this study indicate that the variation of the percentage removal was dependent on the raw water quality and membrane material (U.S. EPA, 1988). Laboratory experiments studied the impact of different operational parameters on the performance efficiency of a thin-film polyamide membrane with spiral-wound configuration. The calculated results have demonstrated an average fluoride reduction of 88% from an influent concentration in the range of 1.4–6.6 mg/L to an average concentration below 0.5 mg/L for tested groundwater (Arora et al., 2004).

Full-scale NF results showed a reduction of an influent fluoride concentration in brackish water from 13.5 mg/L to 0.7 mg/L (Pontie et al., 1996). A pilot-scale unit constructed with two pressure vessels with NF membranes demonstrated that a fluoride influent concentration of 2.8 mg/L was reduced to 0.6 mg/L and achieved an overall system recovery of 85% at a flux rate of 22.6 L/m²/h. Prefiltration of the raw water and addition of a scale inhibitor were required prior to the NF process (Durand-Bourlier and Laine, 1997).

7.1.4 Lime softening

Lime softening (LS) is a precipitative process for the removal of calcium and magnesium ions of hard water, and can also be used to reduce fluoride levels from potable water. In the softening process, calcium and magnesium ions precipitate as calcium carbonate (CaCO₃) and magnesium hydroxide Mg(OH)₂. The fluoride ions are adsorbed by the gelatinous Mg(OH)₂ precipitate and co-precipitate with it (U.S. EPA, 1984, Leung and Hrudehy, 1985). This technology is more applicable for a source water with a higher level of magnesium. If the raw water has a low magnesium content, magnesium salt may be added. It has been stated that influent concentrations of 3.2 mg/L have been reduced to below 1 mg/L when an additional quantity of magnesium was added to the lime softening (U.S. EPA, 1984a). As the magnesium hydroxide precipitates at a pH greater than 10.5, adjustment of the pH is necessary. Fluoride may also precipitate as calcium fluoride (CaF₂), when using a lime softening process, particularly with high fluoride concentrations in the feed water (U.S. EPA, 1984, 2002).

Lime softening is an expensive process and is not recommended unless there is also a need to reduce hardness in the raw water (Singh and Clifford, 1981; U.S. EPA, 1984, 2002). The large quantity of chemicals and their high cost preclude this process for the removal of fluoride, unless hardness reduction is a concurrent treatment goal. These systems also create significant quantities of sludge, which require pretreatment and disposal, and add to the cost of the process (U.S. EPA, 2002).

7.1.5 Anion exchange

Anion exchange (AX) is a physical/chemical process which employs exchange of negatively charged ions in the raw water with ions sorbed at the solid phase of the synthetic resins. The raw water continuously passes through a bed of ion exchange resin in a downflow or an upflow mode until the resin is exhausted. Factors affecting the fluoride removal by anion exchange technology include the influent fluoride concentration, the concentration of competing ions, and media regeneration. A study reviewed by J.E. Serrine Co and Aware Inc. (1977) and the United States EPA (1984a) indicated that strong-base anionic resins are not effective for fluoride removal when chloride, sulfate, and nitrate concentrations are greater than the fluoride concentration. This study demonstrated that strong-base anionic resins in the chloride form

had a capacity of 100–400 grains F/ft³ (228–915 g F/m³), which is not considered economically feasible. This process is highly subject to chromatographic peaking if the beds are not monitored adequately, since fluoride is the least preferred anion by resins (Clifford, 1999, U.S. EPA, 2002).

7.1.6 *Emerging treatment technologies*

Electrodialysis (ED) is an electrochemical separation process in which ions are transported through semi-permeable membranes under the influence of an electric potential. In electrodialysis reversal (EDR) the polarity of the electrodes is changed periodically across the ion exchange membranes. Tahaik et al., (2006) studied the optimization of the recovery rate of the water in a pilot scale electrodialysis process and reported a reduction of an influent fluoride concentration of 1.8 mg/L to 0.5 mg/L. A laboratory study by Amor et al. (1998), indicated that an ED unit, fitted with 10 pairs of anion and cation exchange membranes, could achieve an effluent fluoride concentration of 0.21 ppm and 0.67 ppm from brackish water containing 3 mg/L fluoride and 3000 mg/L total dissolved solids (TDS), at applied voltages of 15 V and 10 V, respectively. Results from this study showed that the performance of the system is increased with increased voltage, water temperature and flow rate.

A full scale EDR system with a capacity of 3.8 MGD (14.3 MLD) reported a 75% fluoride removal efficiency, reducing the influent concentration from 4.8 mg/L to an effluent level of 1.2 mg/L. A pretreatment, as a prefiltration of the raw water was required prior to the process (Thompson and Robinson, 1991).

The Donnan Dialysis (DD) process is similar to ED/EDR, but the driving force of the process is a difference in the chemical potential rather than an electrical potential. A pilot-scale experiment using synthetic water achieved reductions from 9.5 mg/L and 6.1 mg/L of influent fluoride levels to effluent concentrations of 0.95 mg/L and 0.15 mg/L, respectively (Hichour et al., 2000).

Bone char, a blackish, porous, granular material with a specific affinity for fluoride, can be used in water with high alkalinity and high total dissolved solids (TDS), but imparts an undesirable taste to the water. Bone char is soluble in acid and the recommended pH to prevent loss of the media is approximately 7.0. The presence of arsenic ions could reduce fluoride removal efficiency (J.E. Serrine Co and Aware Inc., 1977). Full scale data indicates that two defluoridation units operated in parallel with an influent concentration in the range of 9–12 mg/L were capable of reducing fluoride levels to 0.6 mg/L (U.S. EPA, 1984).

Tricalcium phosphate (powder and granular form) has been successfully used for fluoride removal. Experimental data shows that fluoride influent concentration and raw water pH had no significant effect on the exchange capacity of tricalcium phosphate. The powder form removes the fluoride ions through the precipitation of apatites and has been shown to have greater capacity for fluoride removal (J.E. Serrine Co and Aware Inc., 1977; U.S. EPA, 1984).

Lounici et al. (1997) studied a new technology, based on the combination of the AA column and an electrochemical system, which creates an electric field in the column and increases the fluoride sorption of the media. Parameters such as pH, temperature, influent fluoride concentration and hardness of water have a major effect on the efficiency of the process. This electrosorption process, applied in the defluoridation of groundwater, achieved an effluent concentration of less than 0.4 mg/L from an average influent concentration of 3 mg/L.

7.2 Residential scale

Generally, it is not recommended that drinking water treatment devices be used to provide additional treatment to municipally treated drinking water. In cases where an individual household obtains its drinking water from a private well, a private residential drinking water treatment device may be an option for reducing excess fluoride concentrations in drinking water.

Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF International/American National Standards Institute (ANSI) drinking water treatment unit standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Certified devices for the reduction of fluoride from drinking water rely on reverse osmosis and distillation treatment processes.

Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 2007):

- Canadian Standards Association International (www.csa-international.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- Underwriters Laboratories Inc. (www.ul.com);
- Quality Auditing Institute (www.qai.org);
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained from the SCC (www.scc.ca).

RO systems certified to NSF/ANSI Standard 58 (Reverse Osmosis Drinking Water Treatment Systems) are intended for point-of-use installation only. RO requires larger quantities of influent water to obtain the required volume of drinking water, because these systems reject part of the influent water. A consumer may need to pretreat the influent water to reduce fouling and extend the service life of the membrane. For a drinking water treatment device to be certified to NSF/ANSI Standards 58, the device must be capable of reducing the concentration of fluoride in water from an influent (challenge) concentration of 8.0 mg/L to a maximum of 1.5 mg/L (NSF/ANSI, 2005).

Distillation systems certified to NSF/ANSI Standard 62 (Drinking Water Distillation Systems) are intended for point-of-use installation only. The distillation process is effective for the reduction of inorganic contaminants, but requires an electrical energy input. For a drinking water treatment device to be certified to NSF/ANSI Standard 62, the device must be capable of reducing the concentration of fluoride in water from an influent (challenge) concentration of 8.0 mg/L to maximum of 2.0 mg/L (NSF/ANSI, 2004).

NSF/ANSI Standard 53 (Drinking Water Treatment Units – Health Effects) is also applicable for the reduction of fluoride in drinking water (NSF/ANSI, 2006). However, there are currently no certified products under this standard for the removal of fluoride.

Preliminary data shows that AA treatment devices are effective for fluoride removal, but the technology is still under investigation. As point-of-use AA devices are not equipped to adjust the pH of the incoming water, removal efficiency may not be optimal. Point-of-entry AA technologies can remove fluoride, but these devices may not be economically feasible (U.S. EPA, 2006).

Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the water it produces to verify that the treatment device is effective. Devices can lose removal capacity through usage and time, and need to be maintained and/or replaced. Consumers should verify the expected longevity of the components in their treatment device as per the manufacturer's recommendations.

8.0 Kinetics and metabolism

Rao et al. (1995) developed a sex-specific physiologically-based pharmacokinetic (PBPK) model to describe the absorption, distribution, metabolism, and elimination of fluorides in rats and humans. This model is useful for predicting long-term metabolic features and tissue concentrations of fluoride that may reflect positive or negative effects of fluoride on human health. It also provides a basis for interspecies extrapolation of the effective fluoride doses at the target tissue (bone), in the assessment of risk from different exposure conditions.

8.1 Absorption

About 75–90% of ingested fluoride is absorbed by the gastrointestinal tract (Whitford, 1999). In both adults and children, peak plasma levels were reached 30–60 minutes after the ingestion of fluoride doses ranging from 0.5 to 10 mg (as sodium fluoride) (Carlson et al., 1960; Ekstrand et al., 1977, 1983). The absorption of fluoride in infants, children, and adults appears to be similar. The half-time for absorption is approximately 30 minutes (Whitford, 1999). The absorptive process occurs by passive diffusion, and the mechanism and rate of gastric absorption of fluoride are related to gastric acidity. The ingestion of fluoride with food delays its absorption and reduces its bioavailability (IPCS, 2002). Ekstrand and Ehrnebo (1979) performed an investigation on the influence of milk products on sodium fluoride bioavailability in man. According to their findings from combined plasma and urine data, the 100% bioavailability of sodium fluoride tablets during fasting was greatly decreased by coadministration of milk (50–79%) and of milk with white bread, cheese and yoghurt (50–71%). In a later investigation performed in humans, Trautner and Einwag (1989) have also found reduced peak plasma levels of fluoride when administered with food. Intake of milk reduced F bioavailability by 30% compared with the fasting stomach exposure. In a paper published in the same year, Trautner (1989) suggested that the lower peak levels may well reduce the risk of enamel mottling, while the prolonged serum F levels may produce sustained F concentrations in the oral cavity by salivary F retention, which would prevent caries. Shulman and Vallejo (1990) performed an other study in order to determine the effect of milk and solid foods on fluoride absorption in humans. Milk was found to reduce fluoride absorption by 13%, while the presence of food reduced the absorption by 47%. In a review article, Rao (1984) mentioned that several explanations have been offered for the decreased bioavailability of fluoride from dietary sources: a) binding of F to the food constituents through physical sequestration or chemical bond; b) food acting as a

physical barrier preventing F access to the mucosal surface of the oral cavity and the gastrointestinal tract; c) the modulating effect of stomach contents under strong acidic conditions. In a recent study, Yadav et al. (2007) reported that in humans, bioavailability of fluoride from various food items varies from 2 to 79%.

The water solubility of fluoride compounds can influence their absorption; sodium fluoride is more readily absorbed than the less soluble calcium fluoride (CaF_2) and disodium monofluorophosphate (McIvor, 1990; IPCS, 2002). Fluoride compounds that occur naturally or are added to drinking water yield fluoride ions which are almost completely absorbed by the gastrointestinal tract. Thus, fluoride in drinking water is generally bioavailable (IPCS, 2002). A study was done to compare the bioavailability of fluoride in naturally fluoridated water with that in artificially fluoridated water and to investigate the effect of water hardness on the bioavailability of fluoride in drinking water. This study found no evidence for any differences between the absorption of fluoride ingested from artificially fluoridated drinking water and that from drinking water in which fluoride is present naturally or between the absorption of fluoride from hard and soft waters, at fluoride concentrations close to 1 mg/L (Maguire et al., 2004).

8.2 Distribution and metabolism

Once absorbed, fluoride is rapidly distributed throughout the body via the blood (ATSDR, 2003). Two metabolic pathways are recognized as the main factors that determine plasma fluoride clearance: namely, calcified tissue fluoride retention and urinary fluoride excretion (Whitford, 1990). Up to 75% of absorbed fluoride may be deposited in calcified tissues, with the highest deposition found in children with active bone growth or individuals consuming non-fluoridated drinking water (Hodge and Smith, 1965). Approximately 99% of total body fluoride is localized in calcified tissues (i.e., bones and teeth), where it is substituted for hydroxyl ions (OH^-) in hydroxyapatite, forming fluorapatite (Grandjean and Thomsen, 1983; Grynepas, 1990; Kaminsky et al., 1990; Hamilton, 1992). The dose, duration of exposure, and turnover rate of skeletal components all affect calcified tissue fluoride concentrations (Caraccio et al., 1983; U.S. EPA, 1985). Although bone fluoride concentrations increase with age, the amount retained on a daily basis is inversely related to age; this is due to the greater surface area for fluoride uptake in hydrated young bone and the increased rate of resorption over formation in the elderly (Whitford, 1990). Fluoride can be mobilized from bone through a relatively rapid interstitial ion-exchange mechanism or a much slower bone remodelling process (Hodge and Smith, 1970). The rates at which fluoride is cleared from plasma by calcified tissues and the kidneys in adults are approximately equal (Whitford, 1999).

Many of the factors affecting the uptake and retention of fluoride in bone also affect fluoride concentrations in teeth, with the exception that tooth enamel and dentin do not undergo continuous remodelling (IPCS, 2002). Enamel fluoride concentrations decrease with distance from the tooth surface and also vary with location, surface wear, age, and degree of exposure to systemic and topical fluorides (Weatherell et al., 1977; Schamschula et al., 1982). In children, clearance from plasma by calcified tissue is higher than clearance by kidneys. The balance of fluoride (total intake minus total excretion) is higher in children than in adults (Whitford, 1999). The fractional fluoride retention in children aged 3–5 years residing in an area with a fluoride concentration of 0.5–0.6 mg/L in their drinking water was estimated to be 54.5% (Villa et al., 2000). Mean iliac bone fluoride concentrations recorded for adults (60 years of age) consuming

non-fluoridated (<0.1 mg/L) and fluoridated (0.97 mg/L) drinking water were 351 mg/kg (106–790 mg/kg) and 1090 mg/kg (347–2360 mg/kg), respectively (Alhava et al., 1980). Surface enamel fluoride concentrations were reported to be 740–1400 mg/kg and 1351–2100 mg/kg for adults 20 years of age or older from communities with drinking water fluoride concentrations of 0.1 and 1 mg/L, respectively (Berndt and Stearns, 1979). The concentration of fluoride in dentin is generally 2–3 times higher than that in enamel (NAS, 1971).

The plasma half-life of fluoride in humans and rabbits ranges from 2 to 11 hours following single or multiple oral doses of sodium fluoride (3.0–40 mg fluoride) (Ekstrand et al., 1977; Nedeljkovic et al., 1989). The mean plasma level in 127 subjects with 5.03 mg fluoride/L in drinking water was $106 \mu\text{g/L} \pm 76$ (SD) (Y. Li et al., 1995). In Catalonia (Spain), where public drinking water contains 0.12 mg fluoride/L, the mean serum fluoride concentration in 250 healthy individuals was $17.5 \mu\text{g/L}$, ranging from 1 to $47 \mu\text{g/L}$ (Torra et al., 1998).

Fluoride is readily transferred from mother to fetus across the placenta (IPCS, 2002). The significantly low cord serum levels of fluoride compared with neonatal and maternal serum levels may be explained by placental sequestration of fluoride, which suggests that cord serum levels do not reflect fetal fluoride status (Shimonovitz et al., 1995).

Recent animal studies on the distribution of fluoride in the body have been published. Buzalaf et al. (2004) investigated whether the fluoride concentrations in nails and the periosteal surface of the femur were elevated after an acute dose of fluoride in rats. The mean nail and bone concentrations were significantly higher than those of the control group at 4 hours and thereafter. Thus, the proximal portion of nails and bone surface are suitable biomarkers for acute fluoride exposure in rats. A study by Bezerra de Menezes et al. (2003) confirmed that bone is a good biomarker for chronic and acute exposure to fluoride in rats. However, the fluoride concentration on the femur surface (periosteal) was more closely correlated with mortality than that in the whole bone, showing that the ratio $[\text{F}^-]_{\text{periosteal bone}}/[\text{F}^-]_{\text{whole bone}}$ is a biomarker for acute fluoride toxicity. The results of a study from Rodrigues et al. (2004) suggest that fingernails and toenails may be suitable biomarkers of subchronic exposure to fluoride from fluoride dentifrice in small children. Tsunoda et al. (2002) exposed groups of mice to 0, 1, 5, 25, or 125 mg sodium fluoride/L of drinking water for one month to determine fluoride levels in liver, kidney, and brain. In the liver and the kidney, the 125 mg/L group had a significantly higher mean fluoride concentration compared with other groups. There were no significant differences in fluoride concentration in the cerebrum among the different groups. A study conducted in rats by Borke and Whitford (1999) indicated that chronic fluoride ingestion (10, 50 or 150 mg F/L in drinking water) producing high plasma fluoride levels may affect calcium homeostasis by increasing the turnover/breakdown or decrease the expression of plasma membrane and endoplasmic reticulum calcium-pump proteins (Borke and Whitford, 1999). In a study conducted by Luke (2001), the fluoride content of the pineal gland, muscle and bone was measured in cadavers of 11 older individuals (aged 70–100). On average, the pineal gland and muscle contained 297 ± 257 and 0.5 ± 0.4 mg F/kg wet weight, respectively. The bone content of fluoride was 2037 ± 1095 mg F/kg ash weight. Since no correlation was found between pineal fluoride and bone fluoride content, the authors stated that pineal fluoride concentrations are not indicators of long-term fluoride exposure and body burden.

8.3 Excretion

Fluoride is excreted primarily via the urine, with perspiration, saliva, breast milk, and faeces making smaller contributions to daily body clearance (Van Rensburg, 1979; Ekstrand et al., 1984a, 1984b; Whitford, 1990). In adult humans, approximately 50–75% of an oral dose of fluoride appears in the urine within 24 hours after ingestion (Spencer et al., 1970, 1981; Ekstrand et al., 1977). The average 24-hour fractional urinary fluoride excretion relative to customary daily fluoride ingestion in adolescents and adults aged 11–75 years has been established at 0.35 and 0.75, respectively (Villa et al., 2004). Fluoride urinary excretion has also been measured in children. The proportion of fluoride excreted in urine in preschool children (3–6 years old) was also investigated (Haftenberger et al., 2001); on average, 51.5% of the fluoride ingested was excreted in urine. The fraction of the total daily fluoride intake excreted in the urine of children aged 3–5 years was measured to be 35.5% on average (Villa et al., 2000). In 4-year-old children, a much higher value was found, with 80% excretion of ingested fluoride 24 hours after ingestion (Zohouri and Rugg-Gunn, 2000). The mean total fluoride intake for these children was 0.030 mg/kg bw/day. A mean value of 39% of fractional fluoride excretion has been calculated in children aged 5–6 years both under customary conditions of fluoride intake and during a 4-day study period (Ketley and Lennon, 2001).

The renal clearance of fluoride in the adult typically ranges from 30 to 50 mL/min (IPCS, 2002). The percentage of the filtered fluoride reabsorbed from the renal tubules varies widely from about 10% to 90%. The degree of reabsorption depends largely on the pH of the tubular fluid, urinary flow, and renal function (Ekstrand et al., 1980, 1982; Whitford, 1996). Whitford (1999) compared the results of many studies in infants and children with those in adults and concluded that there are no apparent age-related differences in renal clearance rates (adjusted for body weight or surface area) between children and adults. However, in older adults (>65 years), a significant decline in renal clearance of fluoride has been reported (Jeandel et al., 1992). This is consistent with the declines in glomerular filtration rate and renal clearance of many substances that are also observed in the elderly (Whitford, 1999). Under conditions of relatively constant exposure, urinary excretion correlates well with drinking water fluoride levels and is often used as an indicator of exposure (Heintze et al., 1998; Al-Saleh and Al-Doush, 2000; IPCS, 2002).

9.0 Health effects

9.1 Effects in humans

9.1.1 Essentiality

Although Health Canada has classified fluoride as an essential element in the past (Department of National Health and Welfare, 1983), it now recommends that fluoride requirements should “only be based on the beneficial effect on dental caries” and notes that “attempts to demonstrate its essentiality for growth and reproduction in experimental animals have not been successful” (Department of National Health and Welfare, 1990). Similarly, the United States National Research Council considers fluoride to be a “beneficial element for humans” (NRC, 1989). An expert consultation of the World Health Organization categorized fluoride among “potentially toxic elements, some of which may nevertheless have some essential

functions at low levels.” Fluoride was regarded as “essential,” since the consultation “considered resistance to dental caries to be a physiologically important function” (WHO, 1996). The Institute of Medicine (IOM) in United States established an adequate intake (AI) for fluoride based on maximal dental caries reduction without unwanted side effects. By definition, an AI is an average nutrient intake that appears to be sufficient to sustain a defined nutritional state in a specified population (IOM, 1997).

9.1.2 *Acute effects*

In humans, acute ingestion of fluoride can result in nausea, vomiting, abdominal pain, diarrhoea, fatigue, drowsiness, coma, convulsions, cardiac arrest, and death (Kaminsky et al., 1990; Whitford, 1990; Augenstein et al., 1991; ATSDR, 2003). Effects are most severe following ingestion of the more soluble fluoride salts (e.g., sodium fluoride) (WHO, 1984). Nausea and vomiting were reported in a group of seven students who ingested drinking water at a fluoride concentration of 92 mg/L during an incident at an elementary school (Sidhu and Kimmer, 2002). The LD₁₀₀ for fluoride in the average adult has been estimated to be 32–64 mg/kg bw (as sodium fluoride). An acute dose of 5 mg fluoride/kg bw has been considered to be the minimum that might lead to adverse health effects (Whitford, 1996).

One fatality was reported after an acute fluoride poisoning resulted from improper control of drinking water fluoridation. The fluoride concentration of a water sample from the responsible well was 150 mg/L, and the individual was estimated to have ingested approximately 17.9 mg fluoride/kg-bw (Gessner et al., 1994).

9.1.3 *Musculoskeletal effects*

Most of the available studies of potential non-neoplastic human health effects from chronic fluoride ingestion have focused on adverse effects on the skeleton, principally skeletal fluorosis and fractures. The data consist primarily of case reports of individuals exposed to drinking water containing naturally occurring elevated concentrations of fluoride, clinical studies of osteoporosis patients treated with sodium fluoride, and epidemiological studies of populations exposed to various concentrations of fluoride in drinking water.

Skeletal fluorosis is an excessive accumulation of fluoride in bone associated with increased bone density and outgrowths (exostoses) (ATSDR, 2003). Fluoride incorporated into bone (i.e., as fluorapatite) produces a crystal lattice that undergoes less resorption (i.e., is less soluble and more stable) and has an increased compression strength, but is more brittle and has a decreased tensile strength (Grynopas, 1990; Ad Hoc Subcommittee on Fluoride, 1991). Characteristic signs and symptoms of skeletal fluorosis have been defined by four stages, including a preclinical stage (NRC, 2006). The preclinical stage and clinical stage I do not present significant clinical symptoms and are composed of two grades of increased skeletal density. Symptoms are observed in the clinical stage II, characterized by sporadic pain, stiffness of joints, and osteosclerosis of the pelvis and spine. In the clinical stage III, chronic joint pain, arthritic symptoms, calcification of ligaments, and osteosclerosis of cancellous bones can be observed (NRC, 2006). Clinical stage III has been termed “crippling” skeletal fluorosis because mobility is affected as a result of excessive calcifications in joints, ligaments, and vertebral bodies (NRC, 2006). The more severe symptoms tend to be associated with the vertebral column in the lower, weight-bearing parts of the body (Gruber and Baylink, 1991).

Ashed bone fluoride concentrations may range from 3500 to 5500 mg/kg in clinical stage I skeletal fluorosis to >8400 mg/kg in clinical stage III (Ad Hoc Subcommittee on Fluoride, 1991). Age, nutritional deficiencies, renal insufficiency, bone remodelling, and the dose and duration of fluoride exposure can all influence the occurrence of the disease (Grandjean and Thomsen, 1983; Kaminsky et al., 1990; Ad Hoc Subcommittee on Fluoride, 1991; IPCS, 2002; ATSDR, 2003).

9.1.3.1 Case reports

Extremely high concentrations of fluoride in the groundwater near the Gaspé peninsula of Quebec resulted in acute symptoms of skeletal fluorosis in a 58-year-old male farmer and his 57-year-old wife. It is estimated that the husband consumed approximately 50 mg fluoride/day (25 mg fluoride/L in drinking water) over a 6-year period before he suffered from severe pain and stiffness in his joints and difficulty breathing. His wife's consumption was less (about 30–40 mg fluoride/day), and she experienced only mild pain in her hands and wrists (Boyle and Chagnon, 1995). Another North American case report of stage I skeletal fluorosis involved a 54-year-old woman from Oklahoma who consumed drinking water containing fluoride at a concentration of 7–8 mg/L for 7 years (Felsenfeld and Roberts, 1991). Crippling skeletal fluorosis has been described in only five North American case reports over the past 40 years, all from the southwestern United States: three were associated with long-term consumption (40–60+ years) of drinking water containing elevated concentrations of fluoride (2.4–7.8 mg/L) (Sauerbrunn et al., 1965; Goldman et al., 1971; Fisher et al., 1989), one involved a history of geophagia (eating soil) (Fisher et al., 1981), and one gave no details on fluid or food consumption (Bruns and Tytle, 1988). Although a review estimated the total fluoride intake for some of these patients to be 15–20 mg/day for 20 years (Ad Hoc Subcommittee on Fluoride, 1991) (estimated fluoride intake: 215–285 µg/kg bw per day; Department of National Health and Welfare, 1993b), only one case report, that of a 40-year-old woman with a history of geophagia, gave an estimate of daily fluoride intake (1.4 mg/day from drinking water, 4.2 mg/day from tea, and 10.0 mg/day from soil consumption) (Fisher et al., 1981). Several of the cases were complicated by pre-existing or associated renal disease, polydipsia, and the daily consumption of large quantities of tea (Sauerbrunn et al., 1965; Goldman et al., 1971; Fisher et al., 1981, 1989). A recent report of instant tea being related to skeletal fluorosis has been published (Whyte et al., 2005); routine drinking of approximately 4–8 L of double-strength instant tea was reported to be related to skeletal fluorosis of a 52-year-old woman.

9.1.3.2 Clinical studies

The incidence of skeletal fractures has been examined in several clinical case studies of osteoporosis patients undergoing treatment with sodium fluoride for extended periods of time. Inkovaara (1991) found a 7.5% incidence of hip fracture in male and female geriatric patients (n = 146) administered sodium fluoride at 25 mg/day (estimated fluoride intake: 162 µg/kg bw per day; Department of National Health and Welfare, 1993b) for five months or 25 mg sodium fluoride twice weekly for three months, compared with a 3.0% incidence in controls (n = 169; p < 0.1). Inkovaara (1991) also commented on an additional study that reported an incidence of hip fracture of 5/16 in osteoporosis patients (mean age 70) receiving sodium fluoride at 40–80 mg/day (estimated fluoride intake: 260–520 µg/kg bw per day;

Department of National Health and Welfare, 1993b) supplemented with calcium and vitamin D for four years, compared with an incidence of 0/8 for controls. Mamelle et al. (1988) found no significant difference in the occurrence of hip fractures between a group of 257 osteoporosis patients of both sexes (mean age 70.1 years) treated with sodium fluoride at 50 mg/day (estimated fluoride intake: 324 µg/kg bw per day; Department of National Health and Welfare, 1993b) supplemented with calcium and vitamin D for two years and a group of 209 control patients treated with a variety of non-fluoride regimes during the same period. The administration of 50 mg sodium fluoride/day combined with calcium or calcitriol to 35 women (68 years of age) for 12 or 13 months resulted in a hip fracture incidence of 5/35 compared with an incidence of 0/43 in patients administered only calcitriol or a placebo ($p = 0.015$) (Hedlund and Gallagher, 1989). In another study, women of median age 68 years who were administered sodium fluoride at 75 mg/day (estimated fluoride intake: 486 µg/kg bw per day; Department of National Health and Welfare, 1993b) supplemented with calcium for 4 years experienced significantly ($p < 0.01$) more non-vertebral fractures than controls treated with calcium alone. However, the difference in hip fracture incidence between the two groups was not significant (Riggs et al., 1990).

Post-menopausal women (mean age 67 years) treated with sodium fluoride at 40–60 mg/day (estimated fluoride intake: 260–389 µg/kg bw per day; Department of National Health and Welfare, 1993b) supplemented with calcium and vitamin D for 18 months were observed to have an increased incidence of hip fracture compared with patients receiving only calcium and vitamin D (6/25 vs. 1/24; $p > 0.05$). Radiographic signs of stage I skeletal fluorosis were observed for 8/25 of these post-menopausal women, whereas patients treated only with calcium and vitamin D showed no evidence of skeletal fluorosis (Power and Gay, 1986). Kleerekoper and Balena (1991) reported that, depending on whether there is concurrent supplementation with calcium and vitamin D, mild, asymptomatic osteomalacia may occur in osteoporotic patients administered sodium fluoride doses above 40 mg/day (estimated fluoride intake: 260 µg/kg bw per day; Department of National Health and Welfare, 1993b).

A meta-analysis was performed by Haguenaer et al. (2000) to examine the effects of fluoride in the treatment and prevention of postmenopausal osteoporosis in women. Results from this meta-analysis of 11 randomized controlled trials, including 1429 patients, suggest that fluoride significantly increases bone mineral density (BMD) at the lumbar spine after 2 and 4 years of treatment. The relative risk (RR) for patients with a new vertebral fracture was not significant at 2 or 4 years of treatment with fluoride. The RR for new non-vertebral fractures was not significant at 2 years (RR 1.2; 95% confidence interval [CI] = 0.68–2.10), but was increased at 4 years in the treated group (RR 1.85; 95% CI = 1.36–2.50). According to the authors, although fluoride has an ability to increase BMD at the lumbar spine, it does not result in a reduction in vertebral fractures (Haguenaer et al., 2000).

9.1.3.3 *Epidemiological studies – skeletal fluorosis*

Studies from the United States showed no evidence of skeletal fluorosis in people who had consumed drinking water containing fluoride at concentrations of 1.2 and 3.3–6.2 mg/L for 10 years and a lifetime, respectively (McCauley and McClure, 1954; Schlesinger et al., 1956; Hodge and Smith, 1981; Sowers et al., 1986). In an early study conducted in Texas, radiographic evidence of osteosclerosis but not clinical signs of skeletal fluorosis were reported for 18% of

people from a small town who had consumed drinking water containing 8 mg/L fluoride for an average of 37 years, whereas the incidence was only 4% for the population of a town where the drinking water contained 0.4 mg/L fluoride (Leone et al., 1955). X-rays of residents of Texas and Oklahoma who had consumed drinking water containing fluoride at concentrations of 4–8 mg/L indicated 23 cases of osteosclerosis “due to fluoride” but no cases of skeletal fluorosis (Stevenson and Watson, 1957). In a review of available radiographic studies, Kaminsky et al. (1990) concluded that for individuals in the United States who had consumed drinking water containing fluoride at levels of 4.0 mg/L, there was no evidence of the skeletal changes associated with skeletal fluorosis. Endemic crippling skeletal fluorosis has been reported in adults and children from areas of India, Africa, and China where the fluoride concentrations in drinking water have ranged from 3 to >20 mg/L (Royal College of Physicians of London, 1976; Krishnamachari, 1987; Kaminsky et al., 1990; Ad Hoc Subcommittee on Fluoride, 1991; Wang et al., 1999; Shivashankara et al., 2000; IPCS, 2002). As not all residents of these areas show signs of the disease, other factors, such as dietary deficiencies (e.g., protein, calcium, etc.) and other sources of daily fluoride intake, may be contributing to the development of the disease (Singh and Jolly, 1970; Royal College of Physicians of London, 1976; IPCS, 2002).

9.1.3.4 Epidemiological studies – skeletal fractures

Possible associations between the occurrence of skeletal fractures (predominantly hip fractures in elderly persons) and the exposure of populations to fluoridated drinking water have been examined in a number of epidemiological studies of the ecological or geographical correlation type. Studies of this type can suffer from a number of weaknesses, such as a lack of information on individual fluoride intake (i.e., intake from other sources, such as food, dental products, etc.) within the fluoridated and control communities; population differences in various factors (e.g., smoking, lifestyles, environmental and occupational exposures, genetics, etc.) that could affect the occurrence of fractures; uncontrolled migration between fluoridated and control areas; and geographical variations in the quality of disease diagnosis and reporting (IARC, 1982; Ad Hoc Subcommittee on Fluoride, 1991; Department of National Health and Welfare, 1993b). Results are contradictory regarding the potential link between fluoride in drinking water and the risk of skeletal fractures. Main results from various types of epidemiological studies (cross-sectional, cohort and case-control) are presented here for hip fractures and overall or other fractures:

A) Hip fracture:

Keller et al. (1991) found an increased risk of hip fractures in men and women aged 65 years and older living in fluoridated (1.3–2.0, 2.1–3.9 or >4.0 mg/L) versus non-fluoridated (<0.4 mg/L) communities. May and Wilson (1991) found an increased hip fracture rate in men and women older than 65 years receiving fluoridated drinking water (up to 1.0 mg fluoride/L) compared to non-fluoridated drinking water. Jacobsen et al. (1992) reported a slightly but significantly higher relative risk of hip fracture for white men and white women older than 65 who resided in fluoridated (1.0 mg/L) versus non-fluoridated (<0.3 mg/L) counties. Increased age-adjusted risk ratios were found for hip fractures in 65-year-olds in the fluoridated (1.0 mg/L) versus non-fluoridated (<0.3 mg/L) communities (Danielson et al., 1992). In a study of hip fracture hospitalization rates in Alberta between

1981 and 1987 in adults greater than 45 years of age from Edmonton, where fluoridation (up to 1 mg/L) was initiated in 1967, and Calgary, where the drinking water contained 0.3 mg/L fluoride, men from Edmonton in the age groups 45 or 65 years of age had significantly higher hip fracture rates than the corresponding age groups from Calgary. However, there were no significant differences between the two cities when all age groups of women were considered or when both sexes were combined (Suarez-Almazor et al., 1993). Li et al. (2001) have found an increased risk of hip fractures in 50 year olds exposed to high natural levels of fluoride (4.32 mg/L) in drinking water compared to low levels (0.34 mg/L). Kurtzio et al. (1999) found an increased risk of hip fractures in women aged 50–64 years when exposure to fluoride in drinking water at levels higher than 1.5 mg/L was compared with women having exposure to low levels (0.1 mg/L). When all age groups were analysed together, there was no significant association. No link was found for fractures of the hip among either men or women 65–89 years of age exposed to natural and adjusted fluoridated drinking water at 0.7 mg/L compared to lower natural levels of fluoride at 0.3 mg/L in drinking water (Karagas et al., 1996). No association was found between hip fracture and an estimated average lifetime exposure to fluoride in drinking water at 0.9 mg/L (Hillier et al., 2000). In a study that compared hip fracture rates in Rochester, Minnesota, 10 years prior to the initiation of drinking water fluoridation in 1960 and 10 years after, fluoridation was not associated with a risk of hip fracture in men and women 50 years of age or older (Jacobsen et al., 1993). Furthermore, a protective association was observed in women drinking fluoridated water (Jacobsen et al., 1993). Cauley et al. (1995) found fewer hip fractures in non-black women aged 65 years and exposed for 20 years to fluoridated drinking water (1.0 mg/L) compared with lower natural levels of fluoride in drinking water (0.15 mg/L). Lehmann et al. (1998) also found fewer hip fractures in fluoridated communities (0.77–1.20 mg/L) in both men and women \geq 35 years of age, compared to lower levels of exposure (0.08–0.36 mg/L). A decreased risk of hip fracture was observed in women with high toenail fluoride levels (>5.50 ppm) compared to those having lower toenail fluoride levels (<2.0 ppm) (Feskanich et al., 1999). The risk of hip fracture was slightly reduced in older women (>65 years) who drank fluoridated drinking water compared to those drinking non-fluoridated water during the past 20 years (Phipps et al., 2000).

B) Overall and other types of fractures:

A significantly higher incidence of skeletal fractures was found in post-menopausal women (age 55–80 years) who lived in an elevated-fluoride community (4 mg/L) for at least 10 years compared with those who lived in an “optimally” fluoridated (1.0 mg/L) community. No such association was found for pre-menopausal women (age 20–35 years) (Sowers et al., 1986). Five years later (1988–1989), an increased risk for any fracture in the post-menopausal group was found in the elevated-fluoride community compared to the fluoridated community. Karagas et al. (1996) reported modestly higher rates of fracture of the distal forearm and proximal humerus in elderly men (aged 65–89 years) living in an area with natural and artificial fluoridated drinking water (0.7 mg/L) compared to areas with lower levels of fluoride (0.3 mg/L). Feskanich et al. (1999) found an increased risk of forearm fractures in women with higher levels of fluoride measured in toenail (>5.50 ppm

vs <2.0 ppm). An increased risk of overall fractures was observed in men and women 50 years of age exposed to high natural levels of fluoride (4.32 mg/L) in drinking water compared to lower levels of exposure to fluoride in drinking water (1.00–1.06 mg/L) (Li et al., 2001). However, a protective effect of fluoride in drinking water for overall fractures was observed when levels of 1.00–1.06 mg/L were compared with low levels of fluoride in drinking water (0.34 mg/L). Fewer osteoporotic and non-spine fractures were observed in non-black women aged 65 years exposed to fluoridated (1.0 mg/L) compared to non-fluoridated (0.15 mg/L) drinking water for 20 years (Cauley et al., 1995). Results from the same study did not show any association with fluoridated drinking water and wrist or spinal fractures (Cauley et al., 1995). Fabiani et al. (1999) found a lower rate of femur fractures in residents living in a community with fluoride in drinking water at 1.45 mg/L than a low-fluoride exposed county (0.05 mg/L). Phipps et al. (2000) also found a reduced risk of vertebral fracture in older women (>65 years) exposed to fluoridated versus non-fluoridated drinking water for 20 years. This protective effect was not significant for humerus fractures (Phipps et al., 2000).

9.1.3.5 Epidemiological studies – bone mineral density

Cauley et al. (1991) reported no association between exposure duration and BMD in white women (65–93 years of age) exposed to fluoridated (1.0 mg/L) versus non-fluoridated drinking water for an average of 6 years (duration range 0–38 years). A later study by the same group also found no evidence of any impact of the exposure of non-black women aged 65 years to fluoridated (1.0 mg/L) versus non-fluoridated (0.15 mg/L) drinking water for 20 years (Cauley et al., 1995). Comparison of women aged 46–65 years living in areas with fluoride levels below 0.6 mg/L (mean 0.18 mg/L) with women living in areas with levels of 1.0 mg/L found significantly lower bone densities for pre-menopausal women, but no association was found for post-menopausal women (Lan et al., 1995). In a study in Saskatchewan, BMD was measured in 24 healthy women from Regina (fluoride 0.1 mg/L) and 33 women from Saskatoon (fluoride 1.0 mg/L). Women exposed to fluoridated water had significantly higher mean BMD for total anterior-posterior lumbar spine and estimated volumetric L3 (3rd lumbar vertebra), with no difference in BMD for total body or proximal femur (Arnold et al., 1997). Men and women (aged 60 years) with high levels of fluoride in their community water system (2.5 mg/L) had significantly higher lumbar spine BMD than those living in the low-fluoride community (0.03 mg/L), whereas only women in the high-fluoride community had significantly higher proximal femur BMD than those living in the low-fluoride community. No significant impact on the BMD of older adults was found at levels of exposure considered “optimal” for the prevention of dental caries (0.7–1.2 mg/L) (Phipps et al., 1998). In a study performed later by the same group of researchers, an increase in BMD at the femoral neck and at the lumbar spine was found in older women (65 years) who lived in a fluoridated versus non-fluoridated drinking water community for the last 20 years. However, a decrease in the BMD at the distal radius was found in women of the fluoridated versus non-fluoridated community (Phipps et al., 2000). Lehmann et al. (1998) found no correlation between fluoride exposure and age-adjusted BMD in males and females aged 20–60 years of age who drink water naturally fluoridated at 0.77–1.20 mg/L compared to exposure at lower levels of fluoride in dinking water (0.08–0.36 mg/L). Sowers et al. (2005) found that the mean distal radius BMD was

significantly higher in women living in communities with a high concentration of fluoride in drinking water (4.0 mg/L) compared to those living in communities with “optimal” fluoride levels (1.0 mg/L) in drinking water.

Overall, these studies show that, whereas exposure to fluoride concentrations at 1.0–1.5 mg/L was occasionally associated with a positive effect on BMD, it did not significantly increase the risk of fractures (Tardif, 2006). Studies that do not control for confounding factors, such as intake of calcium, fluoride or vitamin D supplements, intake of other medication, or consider traumatic fractures, should be interpreted cautiously (Health Canada, 2008). Some reviews or meta-analyses were performed in order to gain insight on the impact of water fluoridation on health, including bone health effects. A review completed by Raheb (1995) concluded that there was inconsistent evidence for an association between increased risk of hip fracture and water fluoridation, primarily because the number of reported hip fractures in several studies was too small to enable conclusions to be drawn about hip fracture risk. According to a review on the effect of fluoride on the skeleton by Kleerekoper (1996), epidemiological studies suggest that communities with fluoride in drinking water (1–4 mg/L) may have lower prevalence of vertebral fractures, but at the expense of an increased incidence of osteoporotic hip fractures. An extensive literature review called the “York review” (McDonagh et al., 2000) was produced by the National Health Service Centre for Reviews and Dissemination, University of York; The Dental Public Health Unit, University of Wales, Cardiff; and the Department of Epidemiology and Public Health, University of Leicester. According to the York review report (McDonagh et al., 2000), bone effects were the most studied potential adverse effect of fluoride after fluorosis. All but one study were noted to be of “lowest quality of evidence, high risk of bias.” Using a qualitative method of analysis, they did not find a clear association between hip fracture and water fluoridation, and the evidence for other fractures was similar. The authors of the York review mentioned that the overall findings of the studies on bone fracture showed small variations around the “no effect” mark. A meta-regression of bone fracture studies also found no association with water fluoridation (McDonagh et al., 2000). A few years later, the Australian National Health and Medical Research Council concluded that “epidemiological data currently available do not allow a useful estimate of the potential impact of fluoridation on bone disorders other than fracture, although the few studies that have been carried out to date do not suggest a problem” (NHMRC, 2007).

The United States National Research Council recently convened the Committee on Fluoride in Drinking Water to review the health effects of ingested fluoride, in response to the United States Environmental Protection Agency’s (EPA) request for an independent evaluation of the scientific basis of EPA’s Maximum Contaminant Level Goal of 4 mg/L and Secondary Maximum Contaminant Level of 2 mg/L in drinking water, and the adequacy of those guidelines to protect children and others from adverse health effects (NRC, 2006). The Committee focussed its attention on studies that examined long-term exposure to fluoride in the range of 2–4 mg/L or above in drinking water. After their review of the relationship between fluoride and bone fracture risk, there was consensus among Committee members that under certain conditions, fluoride might weaken bone and increase the risk of fractures: lifetime exposure to fluoride at drinking water concentrations of 4 mg/L or higher is likely to increase fracture rates in the population, compared with exposure to 1 mg/L, particularly in some demographic subgroups that are prone to accumulate fluoride in their bones (e.g., people with renal disease) (NRC, 2006).

Furthermore, they indicated that there were few studies to adequately assess fracture risk in populations exposed to fluoride at 2 mg/L in drinking water; thus, no conclusions could be drawn about the fracture risk or safety of fluoride in drinking water at that level of exposure.

9.1.4 *Cancer epidemiology*

Since the introduction of water fluoridation to North America in the 1950's, more than 50 epidemiological studies have been conducted to examine possible associations between the ingestion of fluoridated drinking water and the occurrence of cancer (Ad Hoc Subcommittee on Fluoride, 1991). A time trend analysis by Freni and Gaylor (1992) examined the change in cumulative risk of bone cancer for persons 10–29 or 0–74 years of age in 1958–1987 in fluoridated (i.e., fluoride in drinking water serving at least 50% of the population increased to 1 mg/L during or before 1960) versus non-fluoridated areas of the United States, Canada, and Europe. The mean change with time in the cumulative bone cancer risk was not significantly different for fluoridated versus non-fluoridated areas (Freni and Gaylor, 1992). Hoover et al. (1991a) compared fluoridated counties (i.e., the percentage of the population receiving fluoridated water increased from <10% to >60% within a 3-year period) with control counties (i.e., <10% of population exposed to fluoridated water) from two National Cancer Institute Surveillance, Epidemiology and End Results (NCI SEER) Program registries (Iowa and Seattle, Washington), for the occurrence of cancer and cancer mortality in Caucasians. The observed incidences of osteosarcoma (91 cases), generalized bone and joint cancer (290 cases), cancer of the oral cavity (2693 cases), and renal cancer (2583 cases) in the fluoridated counties were compared with the expected incidences in the control counties. No consistent differences in the observed versus expected cases were noted for any of the cancer types. There was a significant trend ($p = 0.04$) towards increased risk of renal cancer for both sexes combined as the duration of water fluoridation increased from <5 to 15–19 years in the Seattle area (i.e., the relative risk increased from 0.9 [95% CI = 0.7–1.1] to 1.0 [95% CI = 0.9–1.2]). However, no significant trends were observed when males and females were analysed separately or when the data were broken down according to diagnoses made from 1973 to 1980 and from 1981 to 1987 (Hoover et al., 1991a, 1991b).

An examination of the entire NCI SEER incidence database showed that for all ages combined, the incidence of osteosarcoma increased by 18% in males and decreased by 11% in females between the above two periods. For males <20 years of age in fluoridated communities, the incidence rate of osteosarcoma increased by 53% between 1973 and 1980 (88 cases) and between 1980 and 1987 (100 cases), but further analyses showed that the increase was not related to the duration of water fluoridation (Hoover et al., 1991a, 1991b). Hoover et al. (1991a, 1991b) also analysed information on more than 2.3 million United States cancer deaths occurring between 1950 and 1985 and found no consistent association between exposure to fluoridated drinking water (i.e., counties >50% urbanized in 1980 where the proportion of the population receiving water containing >0.3 mg fluoride/L increased from <10% to >66% within a 3-year period) and deaths due to any type of cancer.

The aforementioned epidemiological studies are of the ecological or cross-sectional correlation type, which suffer from a number of weaknesses, including variations in fluoride intake, geographical differences in variable factors affecting the occurrence of cancer, migration between areas, and variations in the quality of mortality and morbidity data (IARC, 1982;

Ad Hoc Subcommittee on Fluoride, 1991; Department of National Health and Welfare, 1993b). Some stronger methodological studies such as case-control studies have been undertaken, which avoid some weaknesses associated with the ecological or geographical types.

A population-based case-control (retrospective) study was conducted among residents of New York State, excluding New York City. Cases (n = 130) were diagnosed with paediatric osteosarcoma between 1978 and 1988, at age 24 years or younger. The lifetime exposure to each source of fluoride was assessed according to a total lifetime exposure index. The fluoride level was assumed to be 1.0 mg/L for fluoridated areas and 0 mg/L for non-fluoridated areas. Based on the parents' responses, total lifetime fluoride exposure was not significantly associated with osteosarcoma among all subjects combined or among females. However, a significant protective trend was observed among males. The protective trend was associated with fluoridated toothpaste, fluoride tablets, and dental fluoride treatments among all subjects, including males. Based on the subjects' responses, no significant associations between fluoride exposure and osteosarcoma were observed. According to the authors, the results showed that fluoride exposure did not increase the risk of osteosarcoma and, rather, might be protective in males (Gelberg et al., 1995).

A case-control study was undertaken to compare 167 osteosarcoma cases with 989 frequency-matched cancer referents reported during 1979–1989, using proxy exposure measures and readily available data from the Wisconsin Cancer Reporting System. Differences in potential exposure to waterborne radiation and fluoridated drinking water, population size for the listed place of residence, and seasonality were assessed. No association was found between potential exposure to fluoridated drinking water and osteosarcoma (OR 1.0, 95% CI = 0.6–1.5) (Moss et al., 1995).

Recently, Bassin et al. (2006) explored age-specific and sex-specific effects of fluoride in drinking water and the incidence of osteosarcoma based on data from a matched case-control study conducted throughout 11 hospitals in the United States. Data acquired included a complete residential history for each patient and type of drinking water (public, private well, bottled) used at each address. Analysis was limited to cases less than 20 years old, and standardized fluoride exposure estimates were based on the Centres for Disease Control and Prevention-recommended target levels that take climate into account. Exposure was categorized into three groups (<30%, 30–99%, >99% of target²) and used conditional logistic regression to estimate odds ratios. The analysis, based on 103 cases under the age of 20 and 215 matched controls, disclosed that for males, the unadjusted odds ratios for higher exposures were greater than 1.0 at each exposure age, reaching a peak of 4.07 (95% CI = 1.43–11.56) at age 7 years for the highest exposure. The adjustment for potential confounders produced similar results, with an adjusted odds ratio for males of 5.46 (95% CI = 1.50–19.90) at age 7 years. This exploratory analysis found an association between fluoride exposure in drinking water during childhood and the incidence of osteosarcoma among males but not consistently among females.

² Target concentration of fluoride in drinking water, according to climate. This level can vary from 0.7 to 1.2 mg fluoride/L, assuming that the drinking water consumption rate varies in different areas of the United States. The target level of fluoride in drinking water is considered to be 0.7 mg/L for locations in warmer climates (higher ingestion rate) and 1.2 mg/L for locations in colder climates (lower ingestion rate) (Bassin et al., 2006).

A letter to the editor was published by Douglass (Bassin's thesis director) and Joshipura (2006) to warn readers not to generalize or overinterpret the results of the Bassin et al. (2006) paper. According to the authors, Bassin et al. (2006) presented only the first of two sets of cases with their own control group. Douglass and Joshipura's (2006) research group also found some positive associations between fluoride and osteosarcoma in the analysis of the first set of cases; however, their preliminary findings from the analysis of the second set of cases (1993–2000) did not appear to replicate the overall findings from the first part of the study. The authors state that their findings do not suggest an overall association between fluoride exposure and osteosarcoma (Douglass and Joshipura, 2006).

In a review of the epidemiological evidence on the relationship between contaminants in drinking water and cancer, Cantor (1997) indicated that additional data gathered since 1990 do not suggest an association between osteosarcoma (or other cancer) risk and fluoride in drinking water. More recent reviews by various scientific organizations also suggest that there is no clear association between water fluoridation and overall cancer incidence, including osteosarcoma and bone/joint cancers, and mortality (McDonagh et al., 2000; IPCS, 2002; ATSDR, 2003; American Dental Association, 2005; NHMRC, 2007). The Committee on Fluoride in Drinking Water convened by NRC (2006) mentioned that the combined literature of epidemiological studies does not clearly indicate whether fluoride at higher concentrations is carcinogenic in humans and recognizes the following challenges in assessing whether fluoride exposure constitutes a risk factor for osteosarcoma. Firstly, because the disease is so uncommon, there are not many studies that are able to capture new cases in the population. Secondly, it is difficult to know precisely the amount of fluoride to which each individual is exposed because not only is fluoride found commonly in a number of sources, but the method of measuring it in the human body (bone samples) is too invasive (NRC, 2006). According to the findings and recommendations from the Expert Panel Meeting on fluoride held recently in Canada (Health Canada, 2008), the weight of scientific evidence does not support a link between fluoride and cancer. The experts agreed that it is important to avoid generalization and overinterpretation of the results of the Bassin et al. (2006) paper and to await the publication of the full study before drawing conclusions and influencing any related policy decisions (Health Canada, 2008).

9.1.5 Reproductive/developmental epidemiology

Human studies on the reproductive and developmental effects of ingested fluoride have included a number of case–control and ecological studies examining possible associations between exposure to fluoridated drinking water or fluoride supplements during pregnancy and adverse effects on reproductive function or fetal development. In three case–control studies, no associations were found between fluoride intake and increases in spontaneous abortions (Aschengrau et al., 1989), congenital cardiac disease (Zierler et al., 1988), or late adverse pregnancy outcomes, including congenital anomalies, stillbirths, and deaths (Aschengrau et al., 1993). An ecological study that examined total annual fertility rate in women aged 10–49 years from 30 regions of the United States reported that twice as many regions containing counties with at least 3 mg fluoride/L in their drinking water showed significant negative associations between total annual fertility rate and fluoride exposure compared with positive associations. Although meta-analysis of the region-specific results gave a combined negative total annual fertility rate/exposure association, the authors cautioned that the measures of exposure

and outcome may differ between individual women and that the occurrence of significant positive total annual fertility rate/exposure associations in some regions indicates the possibility of confounding by unknown factors (Freni, 1994). In a clinical study, children from mothers who had been exposed to fluoridated drinking water and who had received a fluoride supplement (1 mg/day) during pregnancy (n = 117) were found to be slightly but significantly heavier and longer at birth and suffered from fewer birth defects than those whose mothers had consumed fluoridated water but had received no supplement (n = 375) (Glenn et al., 1982).

In a case-control study with fluoride in drinking water (1.5–14.5 mg/L), serum testosterone levels were compared for 30 patients with skeletal fluorosis and healthy males consuming water containing fluoride levels below 1 mg/L (control group 1, n = 26). A second category of controls was used (control group 2, n = 16), composed of individuals living in the same house and thus consuming the same water as the patients but not exhibiting clinical manifestations of skeletal fluorosis. To establish the clinical diagnosis of fluorosis, each patient met the following criteria: a) had lived in an endemic area for more than five years, b) had an increased serum and urine fluoride concentration, c) had typical symptoms and findings on physical examination (i.e. low back pain, leg pain, constipation/diarrhea, etc.), and, d) had no evidence of other metabolic bone disorders. X rays of the lumbar spine, forearm and pelvis featured increased bone density of the spine/pelvic bones and calcification of the interosseous membrane or other ligaments in 85% of the patients. Serum testosterone levels in skeletal fluorosis patients were significantly lower than those of control group 1 ($p < 0.01$). Testosterone levels of control group 2 were also significantly lower than those of control group 1 but higher than those in the patient group. Results of this study suggest that fluoride toxicity could cause adverse effects on the reproductive hormonal environment (Susheela and Jethanandani, 1996). Investigators from another study conducted in men occupationally exposed to fluoride (exposure estimated to range from 3 to 27 mg/day) found alterations in serum hormone concentrations but found normal semen parameters (Ortiz-Perez et al., 2003).

A few epidemiological studies have examined the link between fluoride exposure and human developmental outcomes. Gupta et al. (1995) compared children (5–12 years, weighing 15–30 kg) consuming fluoride-rich drinking water at 4.5 and 8.5 mg/L (group A) and manifesting clinical, dental, and/or skeletal fluorosis with age- and weight-matched children consuming drinking water containing fluoride at ≤ 1.5 mg/L (group B). A total of 22 of the 50 children (44%) in group A and 6 of the 50 children (12%) in group B revealed spina bifida occulta in the lumbosacral region. According to the authors, since this defect occurs during the antenatal period, the observations indicate that an association may exist between spina bifida occulta and high fluoride intake during the antenatal period. Dick et al. (1999) reported that infants exposed to fluoridated water supplies *in utero* were not at increased risk for sudden infant death syndrome (SIDS) (adjusted OR = 1.19, 95% CI = 0.82–1.74). For breast-fed infants at the time of death/nominated sleep, the association between fluoridated water exposure and an increased risk for SIDS was not statistically significant. Similarly, fluoridated formula feeding, when compared with non-fluoridated formula feeding, showed no statistically significant increased risk of SIDS. The authors concluded that exposure to fluoridated water supplies prenatally or postnatally did not affect the relative risk for SIDS at the time of death (Dick et al., 1999). Whiting et al. (2001) performed a systematic review of research studies that investigated

the incidence of Down's syndrome in areas with differing levels of fluoride in their water supplies. According to the authors, all the studies were of the ecological type and scored poorly on the validity assessment. The estimates of the crude relative risk ranged from 0.84 to 3.0. Four studies showed no significant associations between the incidence of Down's syndrome and water fluoride level, and two studies by the same author found a significant ($p < 0.05$) positive association (increased Down's syndrome incidence with increased water fluoride level). Only two of the studies controlled for confounding factors, and only one of these presented summary outcome measures. The evidence of an association between water fluoride level and Down's syndrome incidence is inconclusive (Whiting et al., 2001).

According to the NRC Committee on Fluoride in Drinking Water (NRC, 2006), the number of available studies on the link between human developmental/reproductive effects and fluoride in drinking water are few and have some significant shortcomings in design and power, limiting their impact.

9.1.6 *Mutagenicity/genotoxicity*

A few epidemiological studies were conducted to evaluate the possible link between exposure to fluoride in drinking water and genotoxicity. Y. Li et al. (1995) investigated the genotoxic risks of long-term ingestion of drinking water containing fluoride (0.2, 1.0, or 4.8 mg/L) in humans from a Chinese population with normal or inadequate nutrition. Blood lymphocytes were examined to determine the frequency of sister chromatid exchange (SCE). The average daily fluoride intake as well as urine and plasma fluoride levels increased as the fluoride content of the drinking water increased. The authors observed that while the numerical differences were small, subjects with low fluoride in the water (0.11 and 0.23 mg/L) had significantly higher SCE frequencies than those with higher fluoride exposures, indicating greater genotoxic potential in populations exposed to low fluoride concentrations. A study completed by Jackson et al. (1997) provided evidence that the long-term ingestion of drinking water containing fluoride at 4.0 mg/L (vs. 0.2 and 1.0 mg/L) did not have any clinically important physiological or genotoxic effects in healthy adults. Increased SCE frequency and/or chromosomal aberrations were observed in fluorosis-endemic areas of Inner Mongolia, China, and in North Gujarat, India (Sheth et al., 1994; Wu and Wu, 1995; Joseph and Gadhia, 2000). However, the interpretation of these studies is complicated by the limited details provided on subject selection and by possible confounding variables (IPCS, 2002).

In a clinical study in India, Ramesh et al. (2001) analysed *p53* mutations in various exons in tissue of osteosarcomas and correlated the findings with bone fluoride levels in patients. Tissue samples from 20 osteosarcoma patients were examined for possible genetic alterations, including mutations, as pertaining to the extent of fluoride accumulation in bone. Mutation observed in two cases (10% incidence) was associated with very high levels of fluoride in bone (64 000 and 89 000 $\mu\text{g/g}$). According to the authors, the high fluoride bone content and the similarity of the mechanisms of action between fluoride-induced DNA damage and chemically induced *p53* mutations suggest that high fluoride bone content may have been one of the major factors causing osteosarcoma in subjects with *p53* mutations (Ramesh et al., 2001). Since this study have significant uncertainties, such as the small amount of subjects, the absence of a control group and the lack of control for other causes of *p53* mutations, these results must be interpreted with caution.

9.1.7 Neurobehavioural effects

The impact of fluoride exposure on children's intelligence quotient (IQ) was measured in several studies in China (X.S. Li et al., 1995; Zhao et al., 1996; Lu et al., 2000; Xiang et al., 2003; Wang et al., 2007). As discussed later in this section, these studies are controversial and therefore need to be interpreted cautiously. The first study involved 907 children aged 8–13 years living in areas that differed in the amount of fluoride present in the environment. The average IQ of children living in areas with a medium or severe prevalence of fluorosis was lower than that of children living in areas with only slight dental fluorosis or no fluorosis (80.3 vs. 89.9) (X.S. Li et al., 1995). Zhao et al. (1996) compared the IQs of 160 children (ages 7–14) living in a village with naturally occurring fluoride (4.12 mg/L in drinking water) with those of children living in a non-endemic fluoride village (0.91 mg/L in drinking water). The authors found that the average IQ of children living in a high-fluoride area was significantly lower than those in the low-fluoride area (97.69 vs. 105.21). Another study measured the IQs of 118 children aged 10–12 years who were lifelong residents of two villages of similar population size and social, educational, and economic background, but differed in the level of fluoride in their drinking water (3.15 vs. 0.37 mg/L). The IQ of the children was significantly lower in the high-fluoride area than in the low-fluoride area (92.27 vs. 103.05). An inverse relationship was also present between IQ and urinary fluoride concentrations (Lu et al., 2000). IQ was also measured in a study undertaken in 512 children, aged 8–13 years, living in two villages. The mean IQ was significantly lower (92.02) in the high-fluoride village (mean water fluoride: 2.47 mg/L) than in the low-fluoride village (mean water fluoride: 0.36 mg/L; mean IQ 100.41). Higher drinking water fluoride levels were significantly associated with higher rates of mental retardation (IQ <70) and borderline intelligence (IQ 70–79) (Xiang et al., 2003).

In a recent cross-sectional study, Wang et al. (2007) investigated the influences of arsenic and fluoride exposure on children's intelligence and growth. They studied 720 children aged 8–12 years in rural China exposed to arsenic at 2, 142, or 190 µg/L in drinking water and a group exposed to both fluoride at 8.3 mg/L and arsenic at 3 µg/L. An IQ test was used to investigate the influences of these exposures on children's intelligence. The mean IQ score decreased from 105 for the control group to 101 for the medium-arsenic group and to 95 for the high-arsenic group. The mean IQ score was 101 for the high-fluoride group, significantly lower than the control. Children in the control group were taller than those from the high-fluoride group, weighed more than those from the high-arsenic group, and had higher lung capacity than those from the medium-arsenic group. The authors concluded that children's intelligence and growth can be affected by high arsenic or high fluoride concentration. Caution should be taken in the interpretation of this study done in a rural China context.

These studies were included in the review conducted by the Expert Panel on fluoride convened by Health Canada in 2007. Despite the consistency in the results from these studies, the panel agreed that the weight of evidence does not support a link between fluoride and IQ deficit. There are significant concerns regarding the available studies, including quality, credibility, and methodological weaknesses, such as the lack of control for confounding factors, the small number of subjects, and the dose of exposure (Health Canada, 2008). Most of these studies performed in China were also included in the reviews conducted by other organizations and/or committees, which also mentioned that the significance of these studies is uncertain (IPCS, 2002; ATSDR, 2003; NRC, 2006).

9.1.8 Other health effects

Several studies have investigated a spectrum of health effects on humans associated with exposure to fluoride in drinking water. The studies presented below assessed the link between fluoride in drinking water and gastrointestinal symptoms, otosclerosis, urolithiasis, and parathyroid hormone levels.

Dasarathy et al. (1996) compared 10 patients with documented osteofluorosis (high endemic fluoride level = 4.9 mg/L) with 10 age- and sex-matched healthy volunteers (fluoride level = 0.34 mg/L). All patients with osteofluorosis had gastrointestinal symptoms, the most common being abdominal pain. None of the control subjects had any clinical symptoms or mucosal abnormalities. It was concluded that gastrointestinal symptoms as well as mucosal abnormalities are common in patients with osteofluorosis. Results from a meta-analysis completed by Haguenaer et al. (2000) showed that the relative risk for gastrointestinal side effects of a fluoride treatment for post-menopausal osteoporotic fractures was increased after 4 years of treatment (RR = 2.18, 95% CI = 1.69–4.57), especially if fluoride was used at high doses and in a non-slow-release form.

Vartiainen and Vartiainen (1996) conducted a study in Finland to assess the effect of drinking water fluoridation on the course of hearing of otosclerotic ears. The study population comprised 150 patients with surgically proven otosclerosis with an average follow-up of about 9 years. Of these, 41 patients were living in the town of Kuopio and drinking fluoridated tap water (1 mg/L) and 109 patients lived in surrounding communities with fluoride-poor water (average of 0.1 mg/L). The results show that, at the end of the follow-up period, patients living in Kuopio showed better air conduction thresholds than other patients at two different frequencies tested. According to the authors, sodium fluoride intake of 1 to 3 mg daily in a low-fluoride area would have a beneficial effect on cochlear otosclerosis.

Using a retrospective chart review and a residential history questionnaire, Vartiainen and Vartiainen (1997) compared the prevalence of clinical otosclerosis (formation of spongy bone in the ear) in subjects born between 1948 and 1962 and living either in a low-fluoride area (average fluoride level 0.1 mg/L in drinking water) or in an area with fluoridated tap water (1 mg/L). The prevalence of clinical otosclerosis was found to be 0.35% of persons exposed to fluoridated tap water and 0.32% of those consuming fluoride-poor water. The study did not show any effect of drinking water fluoridation on the prevalence of otosclerosis.

The prevalence of urolithiasis (kidney stones) was found to be 4.6 times higher in a fluoride-endemic area than in a non-endemic area. The prevalence was almost double that in subjects with fluorosis than without fluorosis in the endemic area. No relationship was observed between urolithiasis and the duration of fluorosis. The fluoride levels in drinking water ranged from 3.5 to 4.9 mg/L in the endemic area. Urinary stones from endemic patients had higher fluoride, oxalate, and calcium levels than those from non-endemic patients. According to the authors, the data suggest that fluoride *in vivo* may behave as a mild promoter of urinary stone formation by (a) excretion of insoluble calcium fluoride, (b) increasing oxalate excretion, and (c) mildly increasing the oxidative burden (Singh et al., 2001).

A review of the scientific literature on fluoride and immune function was performed by Challacombe (1996). This author mentioned that fluoride at high concentrations can be an adjuvant for specific immunity, but there is no evidence of any deleterious effect of fluoride on specific immunity and no confirmed reports of allergic reactions (Challacombe, 1996).

In a cross-sectional clinical study, Gupta et al. (2001) evaluated the effect of ingestion of drinking water containing high fluoride on serum parathyroid hormone. Two hundred children (aged 6–12 years) were selected from four areas (50 from each area) with water containing fluoride at 2.4, 4.6, 5.6, and 13.5 mg/L. Serum calcium levels were well within the normal range for patients of all areas, but an increase in serum parathyroid levels was noted. The increased serum parathyroid levels were well correlated with increased fluoride ingestion. The severity of skeletal fluorosis was observed to increase with increasing concentration of serum parathyroid.

Although there is no evidence that fluoride is an endocrine disruptor, there are some data to suggest that fluoride does adversely affect some endocrine glands (ATSDR, 2003), such as the thyroid (NRC, 2006). However, available studies on the effects of fluoride exposure on endocrine function have several design limitations which prevents their use in a risk assessment context. For example, many studies failed to measure actual hormone concentrations, did not report nutritional status (iodine, calcium or selenium intake) or general dietary status, or did not control for individual variability (age, sex, genetic background or other factors) (NRC, 2006). The effects of fluoride on thyroid function, for instance, might depend on whether iodine intake is low, adequate, or high, or whether dietary selenium is adequate. More severe effects on thyroid function were seen in populations with low-iodine intake (NRC, 2006). In Canada, iodized salt is mandatory and the iodine intakes for Canadians were estimated to be in excess of 1 mg/day (IOM, 2001), which is above the adequate intake recommended by the Institute of Medicine (2001) to avoid iodine deficiency. Hence, low-iodine situations are unlikely to occur in the Canadian population.

Overall, the results from these various studies show that adverse health effects are usually associated with high levels of fluoride in drinking water. The NRC Expert Committee on Fluoride in Drinking Water (NRC, 2006) did not find any human studies on drinking water containing fluoride at 4 mg/L where gastrointestinal, hepatic, or immune effects were carefully documented. Based on Health Canada's review of available science, as supported by the Expert Panel Meeting on fluoride, the weight of evidence does not support a link between exposure to fluoride in drinking water at 1.5 mg/L and any adverse health effects including cancer, immunotoxicity, reproductive and/or developmental toxicity, genotoxicity, and/or neurotoxicity (Health Canada, 2008).

9.2 Effects on experimental animals and *in vitro*

9.2.1 Acute toxicity

Oral fluoride LD₅₀s in rats and mice range from 25.5 to 45.7 mg/kg bw for stannous fluoride (SnF₂) (Segreto et al., 1960; Lim et al., 1975, 1978), from 31 to 101 mg/kg bw for sodium fluoride (DeLopez et al., 1976; Lim et al., 1978; Skare et al., 1986a; Whitford et al., 1987; Gruninger et al., 1988), and from 54 to 102 mg/kg bw for disodium monofluorophosphate (Shourie et al., 1950; DeLopez et al., 1976; Lim et al., 1978; Whitford et al., 1987).

9.2.2 Musculoskeletal effects

In a comprehensive National Toxicology Program (NTP) chronic toxicity/carcinogenicity bioassay, groups of male and female F344/N rats and B6C3F1 mice (70–100 per sex per dose) were exposed to drinking water containing 0, 25, 100, or 175 mg sodium fluoride/L for 2 years

(estimated fluoride intakes 0.2, 0.8, 2.5, and 4.1 mg/kg bw/day for male rats, 0.2, 0.8, 2.7, and 4.7 mg/kg bw/day for female rats; 0.6, 1.7, 4.9, and 8.1 mg/kg bw/day for male mice, 0.6, 1.9, 5.7, and 9.1 mg/kg bw/day for female mice). Bone ash fluoride content increased in both species during the course of the study, with terminal concentrations ranging from 0.44 µg/mg (controls) to 5.26 µg/mg (high-dose group) in male rats, from 0.55 to 5.55 µg/mg in female rats, from 0.72 to 5.69 µg/mg in male mice, and from 0.92 to 6.24 µg/mg in female mice. The high-dose female rats had a significantly higher incidence of osteosclerosis and a slight but significant increase in brain to body weight ratio compared with controls. Serum alkaline phosphatase activity was increased in high-dose male mice after 66 weeks and in high-dose female mice after 27 and 66 weeks (NTP, 1990). Estimated no-observed-adverse-effect levels (NOAELs) were 2.7 and 4.1 mg/kg bw/day for the female and male rats, respectively, and 5.7 and 4.9 mg/kg bw/day for the female and male mice, respectively (Department of National Health and Welfare, 1993b).

In another chronic toxicity/carcinogenicity bioassay, sodium fluoride was administered via the diet to groups of male and female Sprague-Dawley albino rats (70 per sex per dose) and CD-1 mice (60 per sex per dose) for 95 weeks (male rats and mice), 99 weeks (female rats), or 97 weeks (female mice). Estimated fluoride intakes for both rats and mice were 0.1 (low-fluoride diet control), 1.8, 4.5, and 11.3 mg/kg bw/day. At the end of the study, bone ash fluoride content ranged from 0.5 µg/mg (controls) to 16.7 µg/mg (high-dose group) in male rats, from 0.5 to 14.4 µg/mg in female rats, from 1.5 to 13.2 µg/mg in male mice, and from 1.0 to 10.6 µg/mg in female mice. Increased subperiosteal hyperostosis in the medium- and high-dose rats was the most notable non-neoplastic skeletal effect observed in the study. Other effects included reduced weight gain in the high-dose rats and hyperkeratosis and acanthosis in the stomachs of medium- and high-dose rats (Maurer et al., 1990, 1993). For the rats, a NOAEL was estimated at 1.8 mg/kg bw/day (Department of National Health and Welfare, 1993b).

The influence of fluoride intake on bone strength was investigated in four groups of Sprague-Dawley rats fed chronically with a low-fluoride diet *ad libitum* and receiving fluoride at 0, 5, 15, or 50 mg/L in their drinking water. Mechanical strength of the right femur was measured by three-point bending after 3, 6, 12, or 18 months of treatment. Femoral failure load was not significantly decreased in rats treated for 3 and 6 months, but was decreased by 23% in rats treated for 12 or 18 months at 50 mg/L. The decreased strength resulting from fluoride intake was significant in older rats only and was not associated with a decrease in bone density or mineralization defects. Fluoride intake at high levels resulted in slight increases in trabecular bone volume and trabecular thickness, but these effects could not be demonstrated consistently (Turner et al., 1995). In another chronic study from the same group (Turner et al., 1996), skeletal fragility and mineralization were evaluated in controls and in rats with renal deficiency chronically exposed to fluoridated water at concentrations of 0, 5, 15, or 50 mg/L for a period of 6 months. Plasma fluoride levels were equivalent to those in humans consuming fluoridated water levels of 0, 1, 3, and 10 mg/L, respectively, and were greatly increased by renal deficiency in all animals consuming fluoridated water. Notably, rats with renal deficiency drank more (approximately 60% greater) and excreted more water (approximately 85% greater). There was a strong positive, non-linear relationship between plasma fluoride and bone fluoride levels, suggesting non-linear binding characteristics of fluoride to bone. The amount of unmineralized osteoid in the vertebral bone was related to the plasma fluoride levels. Vertebral osteoid volume was increased over 20-fold only in animals with renal deficiency that had received fluoride

levels of 15 or 50 mg/L, suggesting osteomalacia. A fluoride concentration of 50 mg/L reduced femoral bone strength by 11% in control rats and by 31% in renal-deficient rats. Vertebral strength also was decreased significantly in renal-deficient rats given fluoride at 50 mg/L (Turner et al., 1996).

Two chronic studies investigated whether changes in fluoride metabolism in nutritionally deficient rats resulted in manifestation of any extraskeletal toxicity. Whereas the first study monitored the effect of calcium deficiency on the effects of chronic fluoride exposure, the second study observed fluoride effects in rats that were deficient either in protein or in energy and total nutrient intake. Control and experimental rats received drinking water containing fluoride at 0, 5, 15, or 50 mg/L for 16 or 48 weeks. Control rats were fed optimal diets, and experimental rats were fed diets deficient in calcium (study 1) or protein (study 2). An additional group of experimental rats (study 2) was provided with a restricted diet (deficient in energy and total nutrient intake). There were differences among fluoride treatment groups in fluoride excretion and retention that resulted in significantly greater fluoride levels in tissues of the experimental rats. However, fluoride treatment did not result in any harmful, extraskeletal biochemical, physiological, or genetic effects in the nutritionally deficient rats (Dunipace et al., 1998a).

9.2.3 Carcinogenicity

In 1990, the NTP completed a comprehensive study on the carcinogenicity of sodium fluoride administered in drinking water (0, 25, 100, or 175 mg/L) to male and female F344/N rats and B6C3F1 mice. Osteosarcomas were not induced in the female F344/N rats; in male rats, the incidence was 0/80, 0/51, 1/50, and 3/80 for the four respective dose groups. The incidence in the high-dose male rats was not significantly different from the control group incidence ($p = 0.099$), although a significant dose–response trend was observed ($p = 0.027$). One high-dose male had a subcutaneous osteosarcoma, but no primary bone tumour; although this tumour increased the significance of the trend test ($p = 0.010$), the pairwise comparison with controls remained non-significant ($p = 0.057$). Although the incidence in the high-dose male rats was significantly higher than the average rate for male control rats in the NTP historical database, the investigators concluded that it was more appropriate to use concurrent controls for comparison purposes because more extensive gross and histopathological examinations of bone and other tissues were made in the current study and because the fluoride content of the standard diet used in the older studies (28–47 mg/kg) was equivalent to a total fluoride intake between the low- and medium-dose groups in the current study. No other observed tumours (squamous cell neoplasms of the oral mucosa, thyroid gland follicular cell neoplasms, hepatoblastoma, malignant lymphoma) in mice or rats were considered to be significant by the NTP investigators. Based on the study results, the NTP concluded that there was “equivocal evidence of carcinogenic activity” (defined as a marginal increase in neoplasms that may be related to chemical administration) of sodium fluoride in male F344/N rats, but no evidence of carcinogenic activity in female F344/N rats or male or female B6C3F1 mice (NTP, 1990).

In another carcinogenicity bioassay, Sprague-Dawley rats and CD-1 mice received sodium fluoride at doses of 0, 4, 10, or 25 mg/kg bw/day in the diet for 95–99 weeks (Maurer et al., 1990, 1993). The incidences of bone tumours (chordoma, chondroma, fibroblastic sarcoma, and osteosarcoma) in rats (0/70, 0/58, 2/70, and 1/70 for the males and 0/70, 2/52, 0/70, and

0/70 for the females) were not statistically different compared with controls. Osteomas were found to occur with a statistically significant dose–response trend in both the male and female mice (2/50, 0/42, 5/44, and 26/50 for males and 4/50, 10/42, 5/44, and 26/50 for females), and statistically significant increases were observed for high-dose males and females compared with controls. However, after reviewing the osteoma data, the United States Armed Forces Institute of Pathology commented that none of these tumours advanced beyond the benign state or showed pre-cancerous morphology, many were multicentric (i.e., most primary bone cancers are unicentric), and a human counterpart to this type of tumour is not known (NRC, 1993). The United States Food and Drug Administration examined the results of the study, noted a number of problems affecting the interpretation of the results (e.g., high levels of minerals, ions, and vitamins in the diet and water; inappropriate dose determination in the preliminary studies; low survival rate for experimental animals; and infection of the mice with a retrovirus) and concluded that “under the conditions of the studies, malignant tumours related to dietary fluoride exposure in rodents were not observed” (Ad Hoc Subcommittee on Fluoride, 1991).

In order to examine the potential impact of long-term exposure to sodium fluoride on the induction of bone tumours by external beam irradiation, the NTP recently completed a supplemental 2-year study. The femoral-tibial joint of the left hind limb of 100 male F344 rats was irradiated from a ^{137}Cs source. The animals were divided into two groups of 50; one was administered drinking water containing 250 mg sodium fluoride/L for two years, while the other group received plain deionized water. Two additional groups of 50 male F344 rats (not exposed to radiation) received drinking water containing either 250 mg sodium fluoride/L (113 mg fluoride/L) or plain deionized water for two years. Bone fluoride analysis conducted at the end of the study revealed significant accumulation of fluoride in the bones of groups of rats exposed to sodium fluoride. Exposure to irradiation, sodium fluoride, or both was not associated with an increase in bone tumours or other neoplastic lesions (NTP, 2006).

9.2.4 *Reproductive/developmental toxicity*

In the last 20 years, many good quality reproductive and developmental animal studies have been published. These laboratory studies have tested the effects of a range of fluoride concentrations in drinking water and indicate that the adverse effects on the reproductive and/or developmental function(s) occur only at very high concentrations (at much higher exposure levels than those at which dental and/or skeletal fluorosis are expected to occur).

Several researchers have examined the effects of relatively high doses of sodium fluoride administered either in drinking water or in the diet on reproductive function in experimental animals. In a study in which weanling Swiss-Webster female mice were fed a low-fluoride diet (0.1–0.3 mg/kg) and administered drinking water containing fluoride concentrations up to 200 mg/L (approximately 40 mg/kg bw/day from drinking water) for 5 weeks prior to and during breeding, it was observed that maternal growth, survival, and litter production were reduced or inhibited (Messer et al., 1973). A multigeneration mouse study showed no significant difference in reproductive function for females fed a diet containing <0.5, 2, or 100 mg fluoride/kg (Tao and Suttie, 1976). No pregnancies or embryo implantations were reported in groups of Swiss albino mice orally dosed with fluoride at either 5.2 or 17.3 mg/kg bw/day on days 6–15 after mating (Pillai et al., 1989).

Al-Hiyasat et al. (2000) investigated the effects on the reproductive system of adult female Sprague-Dawley rats (10 per group) treated with sodium fluoride at 200 mg/L (22.58 mg/kg bw/day), 400 mg/L (18.35 mg/kg bw/day), and 600 mg/L (28.03 mg/kg bw/day) administered in drinking water for 30 days. Several rats receiving the highest dose did not survive (10/10 at 28.03 mg/kg bw/day and 7/10 at 18.35 mg/kg bw/day). Ingestion of sodium fluoride at 200 mg/L significantly reduced the number of viable fetuses. Furthermore, the number of pregnant rats with resorptions and the total number of resorptions were increased in the sodium fluoride-treated groups. There was also a significant increase in maternal organ weights. Rats that had ingested sodium fluoride showed increases in both the absolute and relative weights of the ovaries and in the relative weights of the uterus and kidney. Clinical signs of toxicity were noted in all treated groups. In another study, when exposed at 60 days of age to 100, 200, and 300 mg sodium fluoride/L in their drinking water for 10 weeks, sexually mature male Swiss mice showed significantly reduced fertility after breeding with untreated female mice. Conversely, a 4-week exposure did not reduce fertility. The numbers of implantation sites and viable fetuses were significantly reduced in females mated with males exposed to a concentration of 200 mg/L for 10 weeks. Relative weights of seminal vesicles and preputial glands were significantly increased in mice exposed to 200 and 300 mg sodium fluoride/L for 4 weeks but not in mice exposed for 10 weeks (Elbetieha et al., 2000).

Darmani et al. (2001) showed that exposure to sodium fluoride in drinking water for 12 weeks resulted in a significant reduction in the percentage of pregnancies at all concentrations used. Female mice exposed to 200 and 300 mg sodium fluoride/L showed a significant increase in relative ovary weights and a decrease in the number of viable fetuses. Exposure to 300 mg sodium fluoride/L for 12 weeks resulted in a significant decrease in the number of implantations. Exposure to sodium fluoride for four weeks did not have much effect on fertility, although there was a significant increase in the relative ovary weights and a decrease in the embryo weights in mice exposed to 300 mg sodium fluoride/L.

The oral administration (in the diet or in drinking water) of fluoride at approximately 4.5–200 mg/kg bw/day has also been reported to produce a number of adverse effects on reproductive organs in males, including a cessation of spermatogenesis, loss of stereosilica, increase in the diameter of the caput and cauda ductus epididymis, and decreases in sperm in the vas deferens and the density of epididymal epithelial cilia in rabbits (Susheela and Kumar, 1991; Kumar and Susheela, 1995); increases in seminal vesicle and prostate weights and decreases in the height of the testicular germinal epithelial cells and the cauda and caput epididymis epithelial cells in mice or rabbits (Chinoy and Sequeira, 1989a, 1989b; Kumar and Susheela, 1995); and an absence of spermatocyte maturation and degeneration and necrosis of the testicular tubules in mice (Kour and Singh, 1980). The weights of the caput and cauda epididymis in rabbits were significantly reduced, with fragmented spermatozoa; there was also a reduction in the number of secretory granules in these organs (Kumar and Susheela, 1995). Marked decreases in motility, live:dead ratio, and sperm mitochondrial activity index were also observed in guinea pigs (Chinoy et al., 1997).

Male rabbits fed sodium fluoride at doses of 20 or 40 mg/kg bw/day for 30 days had decreased body weights and significantly lowered sperm motility, sperm counts, and fertility rates (Chinoy et al., 1991). Similarly, male Swiss mice fed sodium fluoride at doses of 10 or 20 mg/kg bw/day for 30 days exhibited sperm abnormalities, significantly decreased

sperm motility and counts, and a loss of fertility (Chinoy and Sequeira, 1992; Chinoy and Sharma, 1998).

Sprando et al. (1997) did not observe any effect of sodium fluoride, administered to P-generation males and females in drinking water (25, 100, 175, or 250 mg/L) for 10 weeks, on spermatogenesis and endocrine function in P- and F1-generation male Sprague-Dawley rats. Reproductive tissues were collected from P-generation male rats after approximately 14 weeks of treatment. Pregnant females (P) were exposed to sodium fluoride via their drinking water through gestation and lactation. F1-generation weanling male rats remained within the same treatment groups as their parents. F1-generation male rats were exposed to sodium fluoride in their drinking water for 14 weeks, at which time reproductive tissues were collected. Dose-related effects were not observed within the P and F1 treatment groups in testis weights, prostate/seminal vesicle weights, non-reproductive organ weights, testicular spermatid counts, sperm production per gram of testis per day, sperm production per gram of testis, luteinizing hormone, follicle stimulating hormone, or serum testosterone concentrations. Histological changes were not observed in testicular tissues from either the P or F1 generation (Sprando et al., 1997). Another study by the same group (Sprando et al., 1998) looked at the potential effect of sodium fluoride on the testes of F1-generation male rats exposed *in utero* and during lactation to sodium fluoride in drinking water (25, 100, 175, or 250 mg/L). No differences between control and sodium fluoride-treated rats were observed with respect to absolute volume of the seminiferous tubules, interstitial space, Leydig cells, blood vessel boundary layer, lymphatic space, macrophages, tubular lumen or absolute tubular length and absolute tubular surface area, mean Sertoli cell nucleoli number per tubular cross-section, mean seminiferous tubule diameter, and mean height of the seminiferous epithelium. A statistically significant decrease in the absolute volume and volume percent of the lymphatic endothelium was observed in the groups treated with 175 and 250 mg sodium fluoride/L and in the testicular capsule in the 100 mg/L treated group (Sprando et al., 1998).

Fluoride treatment was associated with oxidative stress as indicated by an increased level of conjugated dienes in the testis, epididymis, and epididymal sperm pellet in Wistar rats exposed to sodium fluoride at 20 mg/kg bw/day orally for 29 days (n = 6), with respect to controls (n = 6). Sodium fluoride treatment also significantly reduced the relative wet weight of the testis, prostate, and seminal vesicle. Testicular $\Delta^5,3\beta$ -hydroxysteroid dehydrogenase and 17β -hydroxysteroid dehydrogenase activities, epididymal sperm count, and levels of testosterone in plasma were decreased significantly in the fluoride-exposed group (Ghosh et al., 2002).

In a study in which male and female pastel mink were exposed for seven months to a diet containing 35 mg fluoride/kg supplemented with additional fluoride in levels ranging from 33 to 350 mg/kg, survival was reduced in offspring from dams fed the highest level of supplemental fluoride, and body weights were increased in offspring of dams receiving 60 and 108 mg fluoride/kg; litter sizes and gestation periods were not altered by supplemental fluoride (Aulerich et al., 1987).

Collins et al. (1995) conducted a study to determine the effects of sodium fluoride on fetal development. Sperm-positive female rats were given 0, 10, 25, 100, 175, or 250 mg sodium fluoride/L in drinking water daily throughout gestation. Fluid consumption was significantly less in females receiving the high doses (175 and 250 mg/L). No dose-related behavioural changes

or maternal clinical signs were noted. The daily amounts of sodium fluoride ingested were 0, 1.4, 3.9, 15.6, 24.7, and 25.1 mg/kg bw. Feed consumption decreased significantly at 250 mg/L, and body weights of pregnant females reflected feed consumption trends. Exposure to sodium fluoride did not modify the mean number of viable fetuses per female. A significant decrease in the mean number of implants per litter in the 250 mg/L group was observed. There was no effect on the occurrence of *in utero* deaths or on fetal growth. There was no dose-related increase in the number of external anomalies in fetuses due to sodium fluoride ingestion. At the doses given, sodium fluoride had no effect on the development of specific bones, including sternbrae. A significant increase was seen in the average number of fetuses with three or more skeletal variations in the 250 mg/L group (25.1 mg/kg bw/day).

Heindel et al. (1996) administered sodium fluoride *ad libitum* in deionized/filtered drinking water to Sprague-Dawley-derived rats (26 per group) on gestation days (GD) 6 through 15 at levels of 0, 50, 150, or 300 mg/L and New Zealand White rabbits (26 per group) on GD 6 through 19 at levels of 0, 100, 200, or 400 mg/L. Animals were killed on GD 20 (rats) or 30 (rabbits) and examined for implant status, fetal weight, sex, and morphological development. An initial decreased maternal body weight gain was observed, but it recovered over time in both species receiving the highest dose. No clear clinical signs of toxicity were observed. Exposure to sodium fluoride during organogenesis did not significantly affect the frequency of post-implantation loss, mean fetal body weight per litter, or external, visceral, or skeletal malformations in either the rat or the rabbit. The NOAEL for maternal toxicity was 150 mg sodium fluoride/L in drinking water (approximately 18 mg/kg bw/day) for rats and 200 mg/L (approximately 18 mg/kg bw/day) for rabbits. The NOAEL for developmental toxicity was ≥ 300 mg/L (approximately 27 mg/kg bw/day) for rats and ≥ 400 mg/L (approximately 29 mg/kg bw/day) for rabbits administered during organogenesis in drinking water (Heindel et al., 1996).

Minta et al. (1998) did not observe any teratogenic effects in three groups of female rats ($n = 25$) treated with sodium fluoride solution containing 0, 20, or 40 mg/L in drinking water 3–5 weeks before pregnancy and 3 weeks after insemination. The highest dose produced fetal abnormalities (developmental retardations) in a few cases.

A multigenerational study investigated the developmental toxicity of sodium fluoride (0, 25, 100, 175, or 250 mg/L in drinking water) in caesarean-derived viral antibody-free rats exposed continuously during three generations. Numbers of corpora lutea, implants, and viable fetuses and fetal morphological development were similar in all groups, and no dose-related anomalies in internal organs were observed in F2 fetuses. Ossification of the hyoid bone of F2 fetuses was significantly decreased at 250 mg/L. The NOAEL was considered to be 175 mg/L based on developmental toxicity. Mating, fertility, and survival indices were not affected. The authors concluded that reproduction in rats was not affected by sodium fluoride up to 250 mg/L (Collins et al., 2001a, 2001b).

In order to examine the potential of sodium fluoride to affect serum cations in P- and F1-generation rats, Verma and Sherlin (2002) administered 40 mg sodium fluoride/kg-bw (18 mg fluoride/kg-bw) to sperm-positive pregnant female rats, either from GD 6 up to 21 days of lactation or only up to the end of gestation followed by withdrawal of the treatment during lactation (10 per group). Whereas sodium and potassium in the serum of P- and F1-generation rats increased significantly in the sodium fluoride-treated group, calcium and phosphorus

concentrations were significantly decreased. Exposure to 40 mg sodium fluoride/kg-bw in pregnant female rats caused significant alterations in cationic concentrations, which, except for calcium, recovered significantly on withdrawal of the treatment.

Shivashankara et al. (2002) investigated the extent of lipid peroxidation and response of liver antioxidant systems in rats exposed to fluoride in drinking water. Pregnant rats were exposed to 0.5, 30 and 100 mg sodium fluoride/L in drinking water from the end of second week of pregnancy up to weaning. Litters from the respective groups received the same treatment for 10 weeks after weaning. Evaluation of the oxidative stress in the liver showed that both 30 and 100 mg/L increased malondialdehyde levels in liver homogenates. Whereas liver glutathione (GSH) was reduced, GSH S-transferase and GSH peroxidase activities were induced by fluoride exposure, and ascorbic acid levels were decreased (Shivashankara et al., 2002). Increased oxidative stress in rats was also seen in another study completed later by the same group of researchers. Shivarajashankara et al. (2003) administered 0.5, 30, or 100 mg sodium fluoride/L in drinking water to rats during their fetal, weanling, and post-weaning stages of life up to puberty. Rats treated with 100 mg sodium fluoride/L showed enhanced lipid peroxidation, as evidenced by elevated malondialdehyde levels in red blood cells. Decreased levels of total and reduced GSH in red blood cells and ascorbic acid in plasma were also seen at the 100 mg/L dose. At 30 mg sodium fluoride/L, there was no appreciable change in red blood cell malondialdehyde level, but there were increased levels of total and reduced GSH in red blood cells and of ascorbic acid in plasma. The activity of red blood cell GSH peroxidase was elevated in both fluoride-treated groups. The ratio of reduced to total GSH in red blood cells and uric acid levels in plasma also decreased in both groups exposed to sodium fluoride. Red blood cell superoxide dismutase activity decreased significantly with high-fluoride treatment (Shivarajashankara et al., 2003).

Various effects on thyroid function and bone maturation were observed in suckling Wistar mice resulting from ingestion by their mothers of very high concentrations of sodium fluoride (600 mg/L) in their drinking water from the 15th day of pregnancy until the 14th day after delivery. There was a 15% decrease in body weight and a reduction in plasma free thyroxine (T4) (15%) and triiodothyronine (T3) (6%) in offspring. Also observed were 10% and 3% increases in the fluoride content of bone and urine, respectively, but not in the plasma. Calcium and phosphate levels in bone decreased by 30% and 27%, respectively. The calcium in plasma increased by 34%, the phosphorus concentration in plasma decreased by 26%, the urinary levels of calcium decreased by 25%, and those of phosphate increased by 28%. The results suggest that fluoride accelerated bone resorption activity (Bouaziz et al., 2004).

No significant changes were found in relative kidney weights of fluoride-treated female Wistar mice and their pups that were given 500 mg sodium fluoride/L (226 mg fluoride/L) in drinking water from the 15th day of pregnancy until the 14th day after delivery. Urinary fluoride excretion was three times higher in mothers treated with sodium fluoride, whereas the rate of fluoride excretion increased by only 3% in their pups. Fluoride administration strongly affected urinary and plasma parameters in 14-day-old mice and their mothers. Daily urine volume in treated groups was higher in the adult mice and their pups than in the controls. Creatinine concentrations were significantly higher in plasma and lower in urine in the treated

groups. Lipid peroxidation increased in the treated mice, while plasma and urinary uric acid levels showed a significant decline. There was also a significant increase in urinary zinc and copper levels in both mothers and pups, whereas levels in the plasma decreased (Bouaziz et al., 2005).

Female and male Wistar rats were reared and exposed to 1, 10, 50, or 100 mg sodium fluoride/L in drinking water until the second generation of rats obtained. Twenty-eight male (F2) rats were divided into four groups and were given the same treatment for six months. All F2 rats were sacrificed and autopsied at the end of the six months. Significant histopathological changes were found in the myocardial tissue of rats treated with 50 or 100 mg sodium fluoride/L. Additionally, increased activities of superoxide dismutase, GSH peroxidase, and catalase and increased thiobarbituric acid-reactive substance levels were observed in the myocardial tissues of rats treated with 10 and 50 mg sodium fluoride/L. In rats treated with 100 mg sodium fluoride/L, activities of superoxide dismutase, GSH peroxidase, and catalase decreased, while the thiobarbituric acid-reactive substance levels increased in the myocardial tissues (Cicek et al., 2005).

9.2.5 *Mutagenicity/genotoxicity*

Fluoride (as sodium fluoride) has generally produced negative results in gene mutation assays using *Escherichia coli* WP2hcr (Moriya et al., 1983), Chinese hamster V79 cells, and various strains of *Salmonella typhimurium* (Martin et al., 1979; Gocke et al., 1981; Moriya et al., 1983; Li et al., 1987d; Tong et al., 1988; NTP, 1990; Slamenova et al., 1996). Sodium fluoride did not contribute to DNA damage in peripheral blood, oral mucosa, and brain cells of male Wistar rats (Ribeiro et al., 2004). In addition, sodium fluoride was not mutagenic and did not induce gene conversion or aneuploidy in *Saccharomyces cerevisiae* D4 (Litton Bionetics, Inc., 1975; Martin et al., 1979). Sodium fluoride induced the morphological transformation of Syrian hamster embryo cells *in vitro*, but only at cytotoxic concentrations (Tsutsui et al., 1984a; Jones et al., 1988a, 1988b; Lasne et al., 1988). Sodium fluoride and potassium fluoride (KF) increased the frequency of gene locus mutations in cultured mammalian (Cole et al., 1986; Caspary et al., 1987, 1988) and human cell lines (Caspary et al., 1988; Crespi et al., 1990). The preferential increases in “small mutant colonies” (Cole et al., 1986; Caspary et al., 1987) and negative results obtained for the ouabain locus (Cole et al., 1986) in these studies are believed to indicate a mechanism based on chromosomal damage rather than point mutations (Moore et al., 1985; Department of National Health and Welfare, 1993b). The negative results observed with sodium chloride (NaCl) and potassium chloride (KCl) controls (Cole et al., 1986; Caspary et al., 1987) suggest that the genotoxic effects are due to a specific effect of the fluoride ion rather than the cations (Department of National Health and Welfare, 1993b). The specificity of the fluoride ion in inducing chromosomal aberrations in cultured rat bone marrow cells was also indicated by the observation that sodium fluoride and potassium fluoride behaved almost identically and at significantly higher variations from the results with potassium chloride and sodium chloride (Khalil, 1995). Although sodium fluoride increased unscheduled DNA synthesis in Syrian hamster embryo cells, human foreskin fibroblasts, human keratinocytes (Tsutsui et al., 1984a, 1984b, 1984c), and rat hepatocytes (Skare et al., 1986b), these results were not confirmed using more rigorous methods of quantifying DNA repair synthesis (Skare et al., 1986b; Tong et al., 1986, 1988; Department of National Health and Welfare, 1993b).

Although sodium fluoride has generally demonstrated clastogenic activity (primarily breaks, deletions, and gaps, with few exchanges) in chromosomal aberration assays using a variety of mammalian and human cell lines, some inconsistencies have been observed (Scott, 1986; Scott and Roberts, 1987; Aardema et al., 1989; Department of National Health and Welfare, 1993b). There was no significant increase in the frequencies of chromosomal aberrations of human foreskin fibroblast cells (JHU-1) induced by sodium fluoride treatment (Tsutsui et al., 1995). According to Oguro et al. (1995), fluoride clastogenicity seems unlikely to occur in humans even with very high fluoride consumption. However, significant increases in the frequencies of chromosomal aberrations were found in rat vertebral body-derived cells exposed to sodium fluoride (Mihashi and Tsutsui, 1996). Inconsistent results have also been reported for *in vitro* SCE assays in human peripheral blood lymphocytes (Kishi and Tonomura, 1984; Thomson et al., 1985; Tong et al., 1988), Chinese hamster ovary cells (Li et al., 1987d; Tong et al., 1988; NTP, 1990), and Syrian hamster embryo cells (Tsutsui et al., 1984a). Sodium fluoride exposure increased micronuclei formation in human foreskin fibroblasts (Scott and Roberts, 1987) and Chinese hamster lung cells (Li et al., 1991). Based on the *in vitro* test results, it has been suggested that fluoride-induced clastogenicity involves the inhibition of DNA synthesis and/or repair and has a threshold concentration of approximately 10 µg/mL (Department of National Health and Welfare, 1993b).

High dietary concentrations of sodium fluoride or stannous fluoride have been shown to induce recessive lethal mutations in male *Drosophila melanogaster* (Mitchell and Gerdes, 1973; Dominok and Miller, 1990). In most *in vivo* studies with rodents, oral administration of sodium fluoride produced no significant effects on the frequency of SCE (Kram et al., 1978; Li et al., 1987a, 1989) or DNA strand breaks (Skare et al., 1986a) or on the incidences of chromosomal aberrations (Martin et al., 1979; Zeiger et al., 1993), bone marrow micronuclei (Gocke et al., 1981; Albanese, 1987; Li et al., 1987b; Dunipace et al., 1989), or abnormal sperm (Li et al., 1987c; Dunipace et al., 1989). However, the increased incidences of the latter three end-points generally observed following intraperitoneal injection of sodium fluoride (Ma et al., 1986; Pati and Bhunya, 1987; Hayashi et al., 1988) may indicate differential toxicity based on route of administration (Department of National Health and Welfare, 1993b).

Inconsistencies in the overall results of the studies on the genotoxicity/mutagenicity potential of fluoride do not allow for firm conclusions to be made regarding the genotoxic potential of fluoride although the balance of evidence for genotoxicity of fluoride does not support the view that fluoride is genotoxic in humans.

9.2.6 Neurotoxicity and neurobehavioural effects

A study from Mullenix et al. (1995) compared the behaviour, body weight, and plasma and brain fluoride levels after sodium fluoride exposures in Sprague-Dawley rats during late gestation, at weaning, or in adults. For prenatal exposures, dams received injections of 0.13 mg/kg NaF or saline on gestational days 14–18 or 17–19. Weanlings received drinking water containing fluoride concentrations of 0, 75, 100, or 125 mg/L for six or 20 weeks, and 3-month-old adults received water containing fluoride at 100 mg/L for six weeks. According to the results of these studies, fluoride exposures can cause sex- and dose-specific behavioural deficits with a common pattern in rats. The severity of the effect on behaviour increased directly with plasma fluoride levels and fluoride concentrations in specific brain regions. However,

results from these experiments are difficult to interpret, as the method used to assess behavioural changes is not validated. Furthermore, the extrapolation of the behavioural changes observed in the rats to cognitive deficit in humans is questionable.

In a subchronic study, Paul et al. (1998) tested the spontaneous motor activity and motor coordination in adult female Wistar rats after daily oral administration (gastric intubation) of high doses of sodium fluoride (20 or 40 mg/kg dissolved in saline) for 60 days. Whereas sodium fluoride suppressed spontaneous motor activity, there was no change in the motor coordination of these animals. Tissue and serum protein concentrations were decreased. Cholinesterase activity was decreased in the blood in a dose-related manner, but not in brain regions.

Zhao and Wu (1998) investigated the effect of sodium fluoride on acetylcholinesterase (AChE) activities in the cerebral synaptic membranes and the peripheral red blood cells of rats in *in vivo* and *in vitro* experiments. In the *in vivo* study, pregnant rats ingested fluoridated drinking water *ad libitum* (fluoride concentrations of 5, 15, or 50 mg/L) during gestation and lactation. The AChE activities of the cerebral synaptic membranes and peripheral red blood cells in maternal rats receiving fluoride concentrations of 5–50 mg/L for 60 days were elevated significantly by 30–68% and 13–32%, respectively, in a dose-dependent manner. The AChE activities in their offspring 80 days after birth were also increased (9–29% for cerebral synaptic membranes and 21–32% for red blood cells). In contrast, the AChE activities of cerebral synaptic membranes *in vitro* were inhibited by 5.0–50.0 mmol fluoride/L treatment in a time- and dose-dependent manner.

Varner et al. (1998) analysed the alterations in the nervous system resulting from chronic administration of the fluoroaluminum complex AlF_3 (aluminum fluoride) or equivalent levels of fluoride in the form of sodium fluoride. Adult male rats were administered one of three treatments for 52 weeks: the control group received double distilled deionized drinking water, the aluminum-treated group received double distilled deionized drinking water with 0.5 mg aluminum fluoride/L; and the sodium fluoride group received 2.1 mg sodium fluoride/L in double distilled deionized drinking water. The effects of the two treatments on cerebrovascular and neuronal integrity were qualitatively and quantitatively different; these alterations were greater in animals in the aluminum fluoride group than in the sodium fluoride group and greater in the sodium fluoride group than in controls.

Long et al. (2002) investigated the changes in neuronal nicotinic acetylcholine receptors (nAChRs) in the brain of rats receiving fluoride at either 30 or 100 mg/L in their drinking water for seven months. A significant reduction in the number of [3H]epibatidine binding sites in the brain of rats exposed to 100 mg fluoride/L was observed; however, no alteration was noted after exposure to 30 mg/L. The level of nAChR α 4 subunit protein in the brains of rats was significantly lowered by exposure to fluoride at 100 mg/L but not 30 mg/L, whereas the expression of the nAChR α 7 subunit protein was significantly decreased by both levels of exposure.

Albino mice treated with sodium fluoride at 30, 60, or 120 mg/L in drinking water for 30 days had degenerative changes in hippocampal subregions of the brain, particularly in the CA3, CA4, and dentate gyrus. Fluoride-treated animals also performed poorly in motor coordination tests and maze tests, compared with the groups exposed to 30 or 60 mg/L in the same conditions (Bhatnagar et al., 2002).

The possibility that chronic oral ingestion of fluoride in water could modify peripheral pain sensitivity was studied in two strains of adult male rats that were given sodium fluoride in drinking water (Sprague-Dawley rats at 75 and 150 mg/L for 15 weeks; Lou rats at 150 mg/L for 27 weeks). Using classical behavioural evaluation methods of pain symptoms, only slight tendencies to a thermal hyperalgia and a mechanical allodynia were observed in Sprague-Dawley rats (Balayssac et al., 2002).

Several neurohistopathological effects were observed in brain tissues at autopsy from albino rabbits that had been subcutaneously injected for 15 weeks with 0, 5, 10, 20, or 50 mg sodium fluoride/kg-bw per day. According to the authors, the neurotoxic changes observed in the brain suggested that there was a direct action of fluoride upon the nerve tissue responsible for central nervous system problems such as tremors, seizures, and paralysis, indicating brain dysfunction at the two highest doses (Shashi, 2003).

Shah and Chinoy (2004) examined the effects of oral administration of sodium fluoride and/or arsenic trioxide (As_2O_3) at 5 and 0.5 mg/kg bw doses, respectively, for 30 days on the physiology and histology of the brain (cerebral hemisphere) in adult mice of Swiss strain. The observed significant decline in levels of DNA, RNA, and AChE activity in the brain of mice treated with sodium fluoride, arsenic trioxide, and sodium fluoride plus arsenic trioxide was related to its altered histology (Shah and Chinoy, 2004). Sodium fluoride and/or arsenic trioxide were also administered orally to mice for 30 days, at doses of 5 and 0.5 mg/kg bw, respectively, to study the biochemical effects on the brain. According to the authors, the data suggest that metabolic changes associated with the treatments could be the result of free radical toxicity rendering the brain more susceptible to injury (Shah and Chinoy, 2004).

Guan et al. (1998) analysed brain membrane lipids in rats after being fed either 30 or 100 mg fluoride/L in drinking water for three, five, and seven months. The protein content of a brain treated with fluoride decreased, whereas the DNA content remained stable during the entire period of investigation. After seven months of fluoride treatment, the total brain phospholipid content decreased by 10% and 20% in the 30 and 100 mg fluoride/L groups, respectively. Vani and Reddy (2000) examined the activities of enzymes involved in free radical metabolism and membrane function in whole brain and gastrocnemius muscle of female mice treated with sodium fluoride (20 mg/kg bw) for 14 days. Body weight and somatic index were decreased, whereas fluoride levels were significantly increased in both brain and gastrocnemius muscle. The effect of fluoride on enzymes was greater in the muscle than in the brain, which corroborates the claim of greater accumulation of fluoride in muscle than in brain. A decline in AChE activity was also observed in the gastrocnemius muscle, which was accompanied by a significant increase in levels of glycogen and a concomitant decrease in phosphorylase activity following administration of 5 mg sodium fluoride/kg-bw in female mice for 30 days (Chinoy et al., 2004).

Overall, the various neurohistopathological, neurochemical, or biochemical changes reported in animal studies following fluoride administration were subtle and involved high doses of fluoride or certain physiological or environmental conditions (NRC, 2006; Tardif, 2006).

9.2.7 *Other health effects*

Some studies have been conducted to assess the effects of fluoride on other organs or systems. In order to elucidate the effect of various concentrations of iodine and fluoride on the pathogenesis of goitre and fluorosis in mice, Zhao et al. (1998) treated a total of 288 mice

divided into nine groups, each receiving a different iodide/fluoride mixture in drinking water. The concentrations of iodide were as follows: iodine deficiency at 0.0 µg/L, iodine normal at 20.0 µg/L, iodine excess at 2500.0 µg/L; and those of fluoride were as follows: fluoride deficiency 0.0 mg/L; fluoride normal 0.6 mg/L, and fluoride excess, 30.0 mg/L. Fluoride excess induced dental fluorosis and increased fluoride content in the bone. Fluoride affected the thyroid changes induced by iodine deficiency or iodine excess. After 100 days of treatment, fluoride showed some stimulatory effect on the thyroid in iodine-deficient conditions and inhibitory effect in iodine excess conditions. After 150 days, the effects of fluoride on the thyroid reversed compared with those at 100 days. Difference in iodine intake could also increase the toxic effects of fluoride excess on the incisors and bones. Excessive fluoride caused fluorosis of incisors and limb bones. According to the authors, iodine and fluoride have mutually interacting effects on both goitre and fluorosis in experimental mice (Zhao et al., 1998).

The impact of surgically induced renal insufficiency was examined in uraemic and sham-operated control rats receiving 0, 5, 15, or 50 mg fluoride/L (corresponding to 0, 11, 33, and 110 mg sodium fluoride/L) in their drinking water for three or six months. Significantly higher levels of fluoride in the tissues of the animals with renal insufficiency were observed. There were no clinically adverse, fluoride-induced, extraskelatal physiological, biochemical, or genetic effects of chronic exposure to common levels of fluoride in these rats (Dunipace et al., 1998b).

Sondhi et al. (1995) treated adult Swiss Albino mice 6–7 weeks old with drinking water *ad libitum* containing sodium fluoride (100 mg/L) for 30 days. The organo-somatic index decreased significantly on days 7 and 15; the total protein and cholesterol values declined significantly, whereas those of glycogen, acid and alkaline phosphatase activities increased significantly on day 7 and up until day 30. The crypt cells (intestines) exhibited cytoplasmic degranulation and vacuolation. Hydropic degeneration in lamina propria and muscular tissue, an increase in the number of goblet cells, broken tips of villi, nuclear pyknosis, and abnormal mitoses were observed.

A controlled longitudinal experimental study was carried out in gerbils by Luke (1997) to determine whether fluoride affects the biosynthesis of melatonin during pubertal development, using the excretion rate of urinary 6-sulphatoxymelatonin (aMT6s) as the index of pineal melatonin synthesis. Gerbils of the high-fluoride (HF) group received 2.3 mg F/kg bw/day orally from birth until 24 days, whereafter the HF and the low-fluoride (LF) groups received food containing 37 and 7 mg F/kg respectively from prepubescence to adulthood (measured at 7, 9, 11½ and 16 weeks). The HF group excreted significantly less aMT6s than the LF group until the age of sexual maturation. Fluoride was associated with a significant acceleration of pubertal development in female gerbils using body weights, age of vaginal opening and accelerated development of the ventral gland. At 16 weeks, the mean testes weight of HF males was significantly less ($p < 0.002$) than that of the LF males. In this study, fluoride was associated with low circulating levels of melatonin, which lead to an accelerated sexual maturation in female gerbils. According to authors, further investigation is required to determine whether fluoride interferes with pineal function in humans.

Wang et al. (2000) analysed the cellular membrane lipids of the liver after long-term fluoride treatment in Wistar rats supplied with drinking water containing either 30 or 100 mg fluoride/L (as sodium fluoride) for seven months. Total liver phospholipid content decreased in

rats treated with the high dose of fluoride due to a lower content of phosphatidylethanolamine, phosphatidylcholine, and phosphatidylserine. Among the fatty acid compositions of phosphatidylethanolamine and phosphatidylcholine in the livers of fluoride-treated animals, the proportion of polyunsaturated fatty acids (20:4 and 22:6) decreased, whereas saturated fatty acids (16:0 and 18:0) increased. No changes could be detected in the amounts of liver cholesterol and dolichol. Total ubiquinone contents in rat liver were reduced by 11% in the group treated with 30 mg fluoride/L and by 42% in the group treated with 100 mg fluoride/L. In the subclasses of ubiquinone, both ubiquinone-9 and ubiquinone-10 amounts decreased after fluoride treatment. According to the authors, these modifications of membrane lipids could be induced by oxidative stress, which might be an important factor in the pathogenesis of chronic fluorosis.

Overall, the animal studies that looked at potential systemic effects associated with fluoride exposure showed that exposure to sufficiently high fluoride concentrations or doses (much higher than those reported or expected in humans) produced various adverse effects in different organs or systems. These effects are unlikely to pose a risk to humans exposed to relatively high levels of fluoride (even at 4 mg/L, according to NRC, 2006), except in susceptible individuals, who may accumulate more fluoride than healthy people. In fact, some sub-groups in the population could potentially be more susceptible to the toxic effects of fluoride, for example people with kidney problems, osteoporosis, or poor nutrition. Similarly, some sub-populations may be exposed to a greater amount of fluoride on a daily basis, such as those working outdoors, living in hot climates, or living in proximity to fluoride-emitting facilities (ATSDR, 2003). However, for most of these aforementioned sub-populations, there are very limited data to support or refute an increased susceptibility to fluoride, and there are no data to suggest that exposure to fluoride at typical levels found in Canadian drinking water (e.g. at the maximum acceptable concentration of 1.5 mg/L) would result in adverse effects in these potentially susceptible populations.

10.0 Dental effects

10.1 Dental fluorosis

Dental fluorosis is a permanent hypomineralization of tooth enamel due to fluoride-induced disruption of tooth development (Smith, 1988; Cutress and Suckling, 1990; Fejerskov et al., 1990; Burt, 1992). It has been recognized since the turn of the century in people with high exposure to naturally occurring fluoride in drinking water (Clark, 2006). Dental fluorosis occurs only when exposure to fluorides happens during tooth formation and becomes apparent upon eruption of the teeth. In the mildest forms, only the outermost layer of enamel is affected, producing diffuse white lines across the tooth surface (Fejerskov et al., 1990). As the severity increases, deeper layers are affected and the porosity increases, leading to a chalky white appearance (Fejerskov et al., 1990; NRC, 1993). Eventually, chewing and other forces erode the surface enamel, producing pits that can become stained by various food constituents (Fejerskov et al., 1990). H.T. Dean's fluorosis index, shown in Table 2, was developed in 1942 and remains a universally accepted classification system (American Dental Association, 2005).

Table 2: Fluorosis classification (Dean’s Index)^a

Classification	Criteria: description of enamel
Normal	Smooth, glossy, pale creamy-white translucent surface
Questionable	A few white flecks or white spots
Very mild	Small opaque, paper-white areas covering less than 25% of the tooth surface
Mild	Opaque white areas covering less than 50% of the tooth surface
Moderate	All tooth surfaces affected; marked wear on biting surfaces; brown stain may be present
Severe	All tooth surfaces affected; discrete or confluent pitting; brown stain present

^a Adapted from American Dental Association (2005).

The very mild form of fluorosis is barely detectable, even by experienced dental personnel. The literature suggests that there are no health consequences associated with mild fluorosis, other than a lower number of caries experienced. The literature would also demonstrate that there is no real cosmetic problem arising from the mild forms of dental fluorosis. Moderate and severe forms of dental fluorosis do not appear to produce adverse dental health effects, such as the loss of tooth function (Clark, 2006). However, the recent review done by NRC (2006) in the United States indicated that severe enamel fluorosis compromises the health-protective function of the enamel, which is to protect the dentin and the pulp of the teeth from decay and infection, by causing structural damage to the tooth. Hence, the damage to teeth caused by severe enamel fluorosis is a toxic effect that the majority of expert committee members judged to be consistent with prevailing risk assessment definitions of adverse health effects (NRC, 2006).

Epidemiological studies of various age cohorts of children exposed to different fluoride concentrations in drinking water have identified the later maturation stage rather than the earlier secretory stage as the period of enamel development most sensitive to the occurrence of dental fluorosis (Burt, 1992). As the milder forms of dental fluorosis are the ones most often seen in North America (Clark, 1994), the anterior teeth, particularly the maxillary central incisors, are believed to be the most important ones for judging the risk of dental fluorosis (Burt, 1992; NRC, 1993; Limeback, 1994). An analysis of small groups of Hong Kong school children before and after a reduction in the fluoride concentration in the community drinking water supply concluded that there is a minimal risk to the maxillary central incisors before 18 months of age, but that 22–26 months of age represents the period of greatest risk (Evans and Stamm, 1991). A recent review of literature also indicated that the period for susceptibility to dental fluorosis is during the first four years of life (Clark, 2006). However, for anterior teeth, which are the greatest aesthetic concern, the risk period appears to be the first three years of life (Evans and Stamm, 1991; Ishii and Suckling, 1991; Levy et al., 2002; NRC, 2006). Because the severity of fluorosis is related to the duration, timing, and dose of fluoride intake, cumulative exposure during the entire maturation stage, not merely during critical periods of certain types of tooth development, is probably the most important exposure measurement to consider when assessing the risk of fluorosis (DenBesten, 1999). Hence, the fluorosis prevalence would be more strongly related to a fluoride intake that is elevated for all of the first three years of life (Hong et al., 2006a). Furthermore, fluoride intake expressed as mg/kg-body weight/day declines substantially

after 6 months of age and remains more or less steady after that (Levy et al., 2001). As most permanent teeth start forming later in life, the risk of enamel fluorosis in permanent dentition is low if the higher exposure is only in the first six months. According to the findings and recommendations from the expert panel meeting held in Canada, extended periods (e.g., multiple years) of exposure to fluoride are associated with increased fluorosis risk, and a higher exposure in the first year of life may not be as much of a concern if it is followed by low exposure (Health Canada, 2008). After about four years of age, there is no longer a risk of dental fluorosis (Evans and Stamm, 1991; Limeback, 1994; Stookey, 1994; Hong et al., 2006a,b).

In the 1940s and 1950s, the major sources of fluoride were from drinking water and food. Since then, numerous sources of fluoride have become available, including dental products containing fluoride (e.g., toothpastes and mouth rinses) and fluoride dietary supplements. The inappropriate/unsupervised use of these products in excess of recommended levels can contribute significantly to total fluoride intake. For example, a recent article reviewing twins that were both exposed to fluoridated water has demonstrated swallowing toothpaste at a young age was the main factor contributing to fluorosis of concern in a fluoridated area (Limeback, 2007). As well, many infant formula preparations contain high levels of fluoride. Many of these are supplied in concentrated formulations and, when reconstituted with fluoridated water, can lead to an increased risk of dental fluorosis.

In 1992, a conference involving experts from Canada and the United States resulted in the proposal of several new guidelines for the appropriate use of fluoride products (Limeback et al., 1998). These experts in preventive dentistry recognized that the prevalence of dental fluorosis was increasing during the 1970's and into the 90's (Clark, 2006). The group concluded that water fluoridation continues to have unique advantages from the perspectives of distribution, equity, compliance, and cost-effectiveness over other fluoride technologies and that it would be a backward step to consider abandoning or de-emphasizing water fluoridation without first eliminating most other sources of fluoride, many of which are used or consumed on an elective basis and are often used inappropriately. The group made recommendations to reduce the exposure to fluorides for children under the age of 6 years due to evidence showing that the prevalence of dental fluorosis had increased in North America (including Canada) during the 1970s and 1980s.

In 1992, an Advisory Review Panel of dental researchers also examined the available data on the relationship between total daily fluoride intake and the prevalence of dental caries and dental fluorosis in children (Advisory Review Panel, 1993). The data reviewed ranged from the studies of Dean et al. (1941, 1942), conducted in the 1940s with children 12–14 years of age who were lifelong residents of 21 United States communities and whose drinking water contained naturally occurring fluoride, to more modern studies using children of various ages from fluoridated and non-fluoridated communities in Canada, the United States, Australia, and other countries (Clark, 1993; Ismail, 1993). The critical studies for defining the dose–response relationship between total daily fluoride intake and dental caries/fluorosis were found to be those of Dean et al. (1941, 1942), supplemented with data compiled in 1958 on 12- to 14-year-old children from 20 United States communities (Eklund and Striffler, 1980). The panel concluded that these older dose–response studies were more applicable than modern ones because the age ranges of the children in the modern studies varied; the modern studies have relatively few data on dental fluorosis and caries prevalence in communities with fluoride concentrations in drinking

water below 1.0 mg/L; and most of the modern studies have not accounted for the confounding effect of sources of fluoride that were not available in the 1940s (e.g., toothpaste, mouth rinses, gels) (Advisory Review Panel, 1993). The group of experts gathered for this project reaffirmed the position of the previous working group that water fluoridation, relative to other fluoride technologies, continues to have unique advantages from the perspectives of distribution, equity, compliance, and cost-effectiveness in the reduction of dental caries.

In the 1940s, about 10 percent of the Canadian population displayed very mild and mild dental fluorosis when the concentration of fluoride found naturally in drinking water was about 1 mg/L. Over the last 55 years, in areas where fluoride is added to the drinking water to bring the total level of fluoride to approximately 1 mg/L (optimally fluoridated areas), there have been increases in the total prevalence of dental fluorosis. Also, in non-fluoridated areas, there is clear evidence that the total prevalence of dental fluorosis has increased over the preceding 40 years (Clark, 1994).

More recently Health Canada supported the National Oral Health Component of the Canadian Health Measures Survey (CHMS) (Health Canada, 2010b). The survey collected measures from approximately 5,600 people of the Canadian population aged 6–79 years. Survey development and testing occurred during 2003–06, with data collection occurring from March 2007 to February 2009. In addition to many other dental considerations, dental fluorosis was measured, by trained dentists, using Dean's Index for all children ranging from six to 12 years old. Dean's Index was the original index used to quantify the prevalence of dental fluorosis, and therefore offers the most relevant historical comparisons. The results from this survey showed that about 85% of the children have teeth that are normal or questionable. Only 12.0% had dental fluorosis classified as very mild and 4.4% as mild. So few Canadian children had moderate or severe fluorosis that, even combined, the prevalence is too low to allow reporting (less than 0.3%) (Health Canada, 2010b). These results suggest that the changes made to the fluoride recommendations in the 1990's have resulted in reduced fluoride intake for infants and young children to the extent that fluorosis prevalences are markedly reduced.

Heller et al. (1997) investigated the relationships between caries experience and dental fluorosis at different fluoride concentrations in drinking water (<0.3, 0.3 to <0.7, 0.7 to 1.2 and >1.2 mg/L), and the impact of other fluoride products. This study used data from the 1986–87 National Survey of Oral Health of United States schoolchildren conducted by the National Institute of Dental Research. Oral examinations were conducted in schoolchildren and adults (n = 40,693) aged 4–22 years old. Dental fluorosis prevalence was 13.5%, 21.7%, 29.9% and 41.4% for children who consumed drinking water with fluoride concentrations of <0.3, 0.3 to <0.7, 0.7 to 1.2 and >1.2 mg/L, respectively. According to the authors, increasing water fluoride level was consistently and strongly associated with lower decayed or filled surfaces (dfs) and lower permanent decayed, missing, or filled surfaces (DMFS) scores, but little decline in caries levels was observed between 0.7 and 1.2 mg/L F. According to the authors, a suitable trade-off between caries and fluorosis appears to occur around 0.7 mg/L F. At this level, caries experience and fluorosis severity appear to be as low or lower than that seen at 1.0 mg/L. The authors have also noticed that the use of fluoride supplements was associated with increased dental fluorosis (Heller et al., 1997).

According to the York review report (McDonagh et al., 2000), dental fluorosis is the most widely and frequently studied of all negative effects of water fluoridation. A significant dose–response relationship was identified through a regression analysis. The prevalence of dental fluorosis at a water fluoride level of 1.0 mg/L was estimated to be 48% (95% CI = 40–57%); for fluorosis of aesthetic concern (defined by the report as Dean’s score of mild or worse), it was predicted to be 12.5% (95% CI = 7.0–21.5%). The prevalence of dental fluorosis at a water fluoride level of 2.0 mg/L was estimated to be 61% (95% CI = 51–69) and for fluorosis of aesthetic concern it was predicted to be 24.7% (95% CI = 14.3–39.4). Furthermore, the results of all the research on dental fluorosis suggest that it is perhaps more appropriate to focus on the prevalence of either moderate and severe scores or mild to severe scores of dental fluorosis, as these scores are more representative of conditions that may demonstrate an aesthetic concern. The literature quite clearly presents disparate findings, and it is perhaps the fluorosis scores in the “questionable” and “very mild” ranges that create the variance, when in fact they have little impact on the public concern of aesthetics (McDonagh et al., 2000).

To summarize the recent fluorosis data from across Canada, there is evidence that fluorosis prevalence in some parts of Canada is lower than the values that prompted the initiatives in 1994 and 1998 to review existing fluoride recommendations (Clark, 2006). It appears that in most areas of eastern Canada, including Ontario, the prevalence of all levels of dental fluorosis is quite low (between 3% and 28% affected); in western Canada, in contrast, the prevalence appears to be higher. There is evidence in some instances—for example, in the Niagara region—of a dramatic decrease in prevalence between 1994 and 1998. After fluoridation was ended in Comox, Courtenay, and Campbell River, British Columbia, in 1992, the prevalence and severity of TFI scores decreased significantly after the 1993–94 survey when compared both to the 1996–97 and to the 2002–03 survey cycles. Notably, the decrease was attributed to changes in the use of fluoride toothpastes and supplements in addition to the loss of community water fluoridation (Clark, 2006).

The experts from the fluoride expert panel meeting recommend monitoring the prevalence of dental fluorosis in the Canadian population on an on-going basis, based on a clear definition for “moderate dental fluorosis,” and using a common rating system that is compatible and/or comparable between researchers (Health Canada, 2008). Although elucidated over 60 years ago, the caries preventative effects of fluoridated drinking water are consistently evident in historical studies of fluoridated versus non-fluoridated communities. The caries preventative effects arise primarily through a post-eruptive mechanism and have been demonstrated not only in children, but in adults as well. Although the effectiveness of water fluoridation may have decreased over time, this has been attributed to other sources of fluoride (e.g., toothpaste and other fluoridated dental products) that have become available in both fluoridated and non-fluoridated communities since the time of the original research on water fluoridation. There is also a “halo” or “diffusion” effect that occurs when foods and beverages processed in a fluoridated community are consumed in a non-fluoridated one and vice-versa. This halo effect results in increased fluoride intake by people in nonfluoridated communities, providing them increased protection against dental decay, and failure to account for this effect may result in an underestimation of the total benefit of water fluoridation.

According to the findings and recommendations from the Expert Panel Meeting on fluoride recently held in Canada, from a health perspective, there is no reason to be concerned about the actual prevalence of very mild and mild dental fluorosis in Canada (Health Canada, 2008).

With respect to the occurrence of dental fluorosis, analysis of the original data of Dean et al. (1941, 1942) showed that children from the 1940s consuming drinking water containing ≤ 1.6 mg fluoride/L experienced low rates of very mild (22%) and mild (4%) dental fluorosis, but no moderate or severe dental fluorosis. The total daily fluoride intake for these children (i.e., from air, soil, food, and water) can be considered to represent the maximum daily fluoride intake that is unlikely to result in moderate to severe dental fluorosis.

10.2 Effectiveness of water fluoridation

According to the *World Oral Health Report 2003* (WHO, 2003), dental caries remain a major public health problem in most industrialized countries, affecting 60–90% of schoolchildren and the vast majority of adults. Dental caries result from the localized dissolution of tooth enamel by acids produced by bacterial deposits (plaque). The period of greatest susceptibility to caries is believed to extend from the time teeth first emerge to full eruption for both the primary and permanent dentition (Thylstrup, 1990). Initially, the ability of fluoride to prevent the formation of clinically detectable caries was thought to be primarily due to pre-eruptive incorporation, producing improved crystal stability and reduced enamel solubility (Beltran and Burt, 1988; Groeneveld et al., 1990). Fluoride was also shown to inhibit plaque bacterial acid production (Grembowski et al., 1992). However, reviews of clinical studies of water fluoridation and fluoride's effects on mineralization indicate that fluoride's major anticariogenic effect is post-eruptive, through the inhibition of demineralization and the enhancement of remineralization of early caries lesions (Groeneveld et al., 1990; Thylstrup, 1990). Consistent with this post-eruptive mechanism are observations of significantly less decayed and filled tooth surfaces in adults exposed to fluoridated drinking water from ages 15 to 34 (Grembowski et al., 1992) and significantly lower coronal and root caries incidences for adults >65 years of age residing in fluoridated communities for at least 30–40 years compared with lifelong residents of non-fluoridated communities (Hunt et al., 1989). According to a recent meta-analysis by Griffin (2007), the caries preventative effects arise primarily through a post-eruptive mechanism and have been demonstrated not only in children, but in adults as well.

Many epidemiological studies have been conducted around the world to estimate the prevalence of dental caries. In North America, Burt (1994) studied data on caries prevalence in the permanent and primary dentitions of children from Mexico, the United States, and Canada. He concluded that caries prevalence and severity in the permanent dentition were continuing to decline in the general populations of Canada and the United States, but that the caries prevalence experienced in the primary dentition had stabilized since around 1986–1987. Burt (1994) further noted that there were considerable geographic variations in caries experience in the general populations of the United States and Canada; the highest prevalence and severity were found in Quebec. Caries were more prevalent and severe in the indigenous populations than in the general population, but there were indications of a caries decline in the permanent dentitions of those indigenous groups. He concluded that caries prevalence will probably

decline further in the general populations of Canada and the United States before it reaches an irreducible minimum, but that point may not be far away, because caries experience is already very low in many localities. However, Speechley and Johnston (1996) suggested that in Ontario, caries prevalence may be increasing, at least in the primary dentition of the youngest elementary school children. According to recent results of a study on the dental health of elementary schoolchildren in Quebec (1998–1999), the prevalence of dental cavities is approximately 42% and 56% in kindergarten and 7–8 years old children, respectively. Furthermore, kindergarten children in Quebec have 40% more cavities compared to children of the same age in Ontario and United States (Brodeur et al., 2001).

The National Oral Health Component of the Canadian Health Measures Survey (CHMS) measured dental caries in the Canadian population. The DMFT index was used to assess dental caries experience by counting the number of decayed (D), missing (M), and filled (F) permanent teeth (T). The mean DMFT count for adolescents in this survey was 2.49, of which only 0.37 teeth actually presented with active disease (decayed - DT). Results suggest that about 50% of children aged six to 11 have evidence of decay in primary or permanent teeth in Canada. However, since the index represents only a count of accumulated disease, these results might over-estimate the actual active disease.

Maupome et al. (2001) compared the prevalence and incidence of caries between fluoridation-ended and still-fluoridated communities in British Columbia. The prevalence of caries decreased over time in the fluoridation-ended community while remaining unchanged in the fluoridated community. While numbers of filled surfaces did not vary between surveys, sealed surfaces increased at both study sites. Caries incidence expressed in terms of decayed, missing and filled tooth surface index (DMFS) was not different between the still-fluoridating and fluoridation-ended communities. There were, however, differences in caries experienced when DMFS components and surfaces at risk were investigated in detail. The results suggest a complicated pattern of disease following cessation of fluoridation. Multiple sources of fluoride besides water fluoridation make it more difficult to detect changes in the epidemiological profile of a population with a generally low caries experience, as well as living in an affluent setting with widely accessible dental services.

According to the York review (McDonagh et al., 2000), the best available evidence suggests that fluoridation of drinking water supplies does reduce caries prevalence, as measured both by the proportion of children who are caries free and by the mean change in dmft/DMFT³ score. The degree to which caries are reduced, however, is not clear from the data available. The range of the mean difference in the proportion of caries-free children is -5.0% to 64%, with a median of 14.6% (interquartile range 5.05–22.1%). The range of mean change in dmft/DMFT score was 0.5–4.4 (median 2.25) teeth. It is estimated that a median of six people need to receive fluoridated water for one extra person to be caries-free. The best available evidence from studies following withdrawal of water fluoridation indicates that caries prevalence increases,

³ The dmft/DMFT Index is an indicator of dental disease that is obtained by calculating the number of decayed, missing, and filled teeth. The dmft/DMFT Index relates to whole primary teeth (dmft) or permanent teeth (DMFT). It is made up of the number of teeth with active untreated decay. It allows comparisons to be made of the number of children who have experienced caries or have active cases.

approaching the level of the low-fluoride group. Furthermore, there appears to be some evidence that water fluoridation reduces the inequalities in dental health across social classes in 5- and 12-year-olds, using the dmft/DMFT measure. However, the small number of studies, differences between them, and their low quality rating suggest caution in interpreting these results (McDonagh et al., 2000).

Petersen and Lennon (2004) noted that despite great improvements in the oral health of populations across the world, problems with dental caries still persist, particularly among poor and disadvantaged groups in both developed and developing countries. According to the *World Oral Health Report 2003* (WHO, 2003) water fluoridation where technically feasible and culturally acceptable has substantial advantages in public health. Experts from the fluoride Expert Panel Meeting were all in agreement that community drinking water fluoridation is still an effective public health measure to reduce the prevalence of dental caries in the Canadian population (Health Canada, 2008).

The dose-response data from Dean et al. (1941, 1942) and Eklund and Striffler (1980) suggest a relatively small decline in dental caries incidence in 12- to 14-year-olds when fluoride concentrations in drinking water increased from 0.8 to 1.2 mg/L, compared with much larger declines for fluoride concentrations from 0 up to 0.8 mg/L. This decrease in the slopes of the dose-response curves and the fact that Dean et al. (1941, 1942) observed the occurrence of only the very mild to mild forms of dental fluorosis at concentrations of 0.8–1.2 mg/L led the Advisory Review Panel (1993) to select this range as an optimal range of fluoride concentrations. In 1992, the panel concluded that at the time of the research by Dean et al. (1941, 1942), children who consumed drinking water containing fluoride at concentrations of 0.8–1.2 mg/L combined with intakes of fluoride from air, food, and soil were obtaining an optimal daily fluoride intake for the prevention of dental caries (Advisory Review Panel, 1993). However, as fluoride prevents dental caries through both pre- and post-eruptive mechanisms (Beltran and Burt, 1988; Groeneveld et al., 1990; Thylstrup, 1990) in both children and adults (Hunt et al., 1989; Grembowski et al., 1992), it is likely that there is a relatively wide range of optimal daily fluoride intakes, depending on the age group considered. The study from Heller et al. (1997) showed that the sharpest declines in dmfs and DMFS in children were associated with increases in water fluoride levels between 0 and 0.7 mg/L, with little decline between 0.7 and 1.2 mg/L.

According to findings and recommendations of the expert panel meeting (Health Canada, 2008), it is now unlikely necessary to determine a range for the optimal target concentration of fluoride, partly because seasonal variability in drinking water consumption appears to be less significant now than before, with more indoor temperature control and fewer people working outdoors. Where municipalities choose to fluoridate their water supplies as a public health measure for the prevention of dental caries, Health Canada's Chief Dental Health Officer has reviewed the available science on dental effects, and sought external expert advice from the scientific dental community. As a result, the optimal concentration of fluoride in drinking water for dental health has been determined to be 0.7 mg/L. This concentration provides optimal dental health benefits and is well below the MAC to protect against adverse effects. The consumption of drinking water at a level of 0.7 mg/L fluoride combined with average daily fluoride intakes from other sources to which Canadian consumers are commonly exposed should convey the beneficial dental effects of fluoride to all age groups. The scientific basis for this number is

provided by a study from Heller (1997), which concluded that under modern conditions of exposure, 0.7 mg/L of fluoride in drinking water provides a suitable trade off between the risk of dental fluorosis and the protective effect against dental caries. This recommendation is also in line with the results from a previous analysis by Eklund and Striffler (1980), which indicated that the effectiveness of water fluoridation seems to plateau at a concentration higher than 0.6 mg/L of fluoride in drinking water. The Irish Forum on Fluoridation (2002) also concluded that 0.7 mg/L was the optimal target level.

11.0 Classification and assessment

The weight of evidence from existing epidemiological studies does not support an association between cancer morbidity or mortality and the consumption of fluoride in drinking water. Most of these studies are of the ecological or geographical correlation type, and their limitations preclude them from providing conclusive evidence on an exposure–response relationship. Some case-control studies were published more recently on a possible link between fluoride exposure from drinking water and the risk of osteosarcoma. Only one of these, Bassin et al. (2006), showed a positive association with fluoride exposure in young boys. However, this article only presents a partial view of an on-going study, and no conclusions can be drawn until the entire study has been published and reviewed.

A comprehensive bioassay sponsored by the NTP (1990) provided limited evidence for the carcinogenicity of fluoride based on the observation of a significant dose–response trend for the occurrence of osteosarcomas in male F344/N rats consuming drinking water containing 25–175 mg sodium fluoride/L. However, a pairwise comparison of osteosarcoma incidence in the high-dose versus control males was not significant, and no dose–response trend for the occurrence of osteosarcoma was observed in female rats or male and female B6C3F1 mice exposed to the same concentrations of fluoride in drinking water. A carcinogenicity bioassay in which male and female Sprague-Dawley rats and CD-1 mice were administered sodium fluoride at doses of 4–25 mg/kg bw/day in the diet found no statistically significant dose–response relationship for osteosarcomas in either sex of both species (Maurer et al., 1990, 1993). However, reviews have noted several limitations of this second bioassay, including high levels of minerals, ions, and vitamins in the diet and drinking water; poor survival rate leading to an early termination of the study; and infection of the mice with a retrovirus. Recently, the supplemental study completed by the NTP (2006) in male F344/N rats did not find an association between the exposure of 250 mg/L of fluoride in drinking water for two years and increased risk in bone tumors or other neoplastic lesions.

Fluoride generally did not increase chromosomal aberrations, micronuclei formation, SCE, or DNA strand breaks when administered orally to rodents. These results in animals are supported by recent epidemiological studies. Based on the scientific data available to date, as well as the findings and recommendations from the Expert Panel Meeting on Fluoride (Health Canada, 2008), the weight of evidence does not support a link between fluoride and increased risks of cancer. According to the criteria for classification of carcinogenicity (Health Canada,

1994), and using the available scientific information, fluoride is classified in Group VI – Unclassifiable with respect to carcinogenicity in humans. This corresponds to the International Agency for Research on Cancer (IARC) classification which classifies fluorides (inorganic, used in drinking-water) in Group 3: Not classifiable as to its carcinogenicity to humans (IARC, 1982).

Dental fluorosis is the most widely and frequently studied of all adverse effects of fluoride. It is the effect occurring at the lowest level of fluoride exposure in the population. Mild and very mild dental fluorosis are not considered to be adverse effects, whereas moderate dental fluorosis is found to be an adverse effect, based on its potential aesthetic concern, and is used as the endpoint of concern in this risk assessment. Although there is some controversy as to whether the more severe forms of dental fluorosis represent an aesthetic or a health effect, a limited number of surveys have shown that laypeople can detect different degrees of dental fluorosis, and both clinicians and laypeople view the more severe forms as socially embarrassing to the children afflicted (Riordan, 1993a,b; Clark, 1995). Furthermore, the report from the recent review done by the NRC in the United States (2006) indicated that the damage to teeth caused by severe enamel fluorosis is a toxic effect that the majority of expert committee members judged to be consistent with prevailing risk assessment definitions of adverse health effects (NRC, 2006). Health Canada considers moderate dental fluorosis (according to Dean's index) to be an adverse effect, based on its potential aesthetic concern. The best available dose–response relationship data on dental fluorosis for use in the risk assessment are still considered to be those from Dean et al. in the 1940's, supplemented with data compiled in by Eklund and Striffler in 1980 (see Section 10.1).

In 1993, an Advisory Review Panel of dental researchers reviewed the available data on the relationship between daily fluoride intake in childhood and the occurrence of dental fluorosis. At that time, based on the conclusions of this review and data on the period of greatest risk for dental fluorosis in the anterior permanent teeth, Health Canada estimated that a daily fluoride intake less than or equal to 122 µg/kg bw/day for children 22–26 months old (i.e., period of greatest risk) was unlikely to result in moderate to severe dental fluorosis in the anterior permanent teeth.

In 2007, Health Canada convened a panel of experts to provide recommendations on the path forward based on currently available science. The panel recommended that the tolerable daily intake (TDI) of fluoride should be based mainly on estimated total fluoride intake from fluids and foods recorded in the 1940s – when children were exposed to no other major sources of fluoride (Health Canada, 2008). This was deemed appropriate because exposure to fluoride in the 1940s was accompanied by a low incidence (~10%) of mild and very mild dental fluorosis (Clark, 2006). The 1940s estimates are used for calculating the TDI to prevent moderate dental fluorosis (according to Dean's index), for a 1- to 4-year-old child:

- fluoride intake of 1.6 mg/L from drinking water, the level at which there was no moderate dental fluorosis in the 1940s, according to Dean's data;
- the best food intake value to represent the situation in the 1940s; and
- the assumption that the intake of fluoride from soil and air is about the same today as it was in the 1940s.

Based on Dean's data, the TDI can be calculated as follows:

$$\begin{aligned} \text{TDI} &= 98.5 \mu\text{g/kg bw/day} + 5.4 \mu\text{g/kg bw/day} + 1.19 \mu\text{g/kg bw/day} + 0.01 \mu\text{g/kg bw/day} \\ &\approx 105 \mu\text{g/kg bw/day} \\ &\approx 0.105 \text{ mg/kg bw/day} \end{aligned}$$

where:

- 98.5 $\mu\text{g/kg bw/day}$ is the fluoride intake from drinking water in the 1940s: 1.6 mg/L, with a drinking water ingestion rate of 0.8 L/day and a body weight of 13 kg (Health Canada, 1994), $(1600 \mu\text{g/L} \times 0.8 \text{ L/day})/13 \text{ kg} = 98.5 \mu\text{g/kg bw/day}$;
- 5.4 $\mu\text{g/kg bw/day}$ is the fluoride intake from food in the 1940s: based on the new calculations from Dabeka (2007b), assuming a 1940s diet for a 1- to 4-year-old child living in a community with $\approx 1.5 \text{ mg fluoride/L}$ in the drinking water would have been approximately 27 $\mu\text{g/kg bw/day}$ (see Table B-5). Knowing that about 80% of the intake of fluoride from food was coming from beverages (which is already included in the figure of 0.8 L/day), the breakdown amount comes to 5.4 $\mu\text{g/kg bw/day}$ for food intake only;
- 1.19 $\mu\text{g/kg bw/day}$ is the fluoride intake from soil (the same as today); and
- 0.01 $\mu\text{g/kg bw/day}$ is the fluoride intake from air (the same as today).

Adding all the sources of exposure relevant to Dean's time, the updated TDI is about 105 $\mu\text{g/kg bw/day}$. This value is the same as the one that had been proposed by the Advisory Review Panel (1993), based on the absence of moderate dental fluorosis. It is also close to the tolerable upper intake level of 100 $\mu\text{g/kg bw/day}$ established by the Institute of Medicine (IOM) in United States for infants, toddlers, and children through 8 years of age, based on the same endpoint (IOM, 1997). No uncertainty factor was applied in the derivation of the TDI, because the daily intake level was based on studies in the most susceptible age group in the human population. The health-based value (HBV) for fluoride can be calculated as follows:

$$\begin{aligned} \text{HBV} &= \frac{0.105 \text{ mg/kg bw/day} \times 13 \text{ kg bw} \times 0.50}{0.8 \text{ L/d}} \\ &\approx 0.9 \text{ mg/L (rounded)} \end{aligned}$$

where:

- 0.105 mg/kg bw/day is the TDI, as derived above;
- 13 kg bw is the average body weight of a 1 to 4 year-old;
- 0.50 is the allocation factor based on the exposure assessment data (see Table 1): of all media of exposure, drinking water represents 50% of the total daily intake of fluoride for the 1 to 4 year-old age group – the other 50% coming mainly from food and toothpaste ingestion; and
- 0.8 L/d is the ingestion rate of drinking water for the 1 to 4 year-old age group.

There seems to be some discrepancy between the estimated level of effect for fluoride in the population and the true levels of moderate and severe dental fluorosis in the population. Using recent exposure data from the Iowa Fluoride Study, Levy et al. (2006) estimated that over 20% of infants aged 1.5 to 9 months had a combined total fluoride intake above 0.100 mg/kg bw/day. However, this is much higher than the percentages of infants having moderate/severe dental fluorosis (~1%). One would expect to find a similar proportion of infants with exposure above 0.100 mg/kg bw/day and infants having moderate/severe dental fluorosis. For all children aged 24–48 months, the percentage ingested combined total fluoride over the 0.100 mg/kg bw/day threshold was 6%–8%. These percentages are also much higher than the percentages of the children having moderate/severe fluorosis (~1%). From these results, Levy et al. (2006) noted that the 0.10 mg/kg bw/day may not be the lower border of over-ingestion of fluoride relevant to moderate/severe dental fluorosis in these age groups. Hence the TDI of 105 µg/kg bw/day may be overly conservative in order to protect against the moderate and severe forms of dental fluorosis. These very low levels of moderate and severe dental fluorosis have also been observed in the recent Canadian survey (Health Canada, 2010b), which corroborates the fact that the total daily intake of fluoride in the Canadian population is lower than the calculated TDI.

Skeletal fluorosis is the most serious adverse health effect clearly associated with prolonged exposure to high levels of fluoride in drinking water. Potentially adverse effects associated with skeletal fluorosis are likely to be observed at intakes greater than approximately 0.20 mg/kg bw/day of fluoride (Department of National Health and Welfare, 1993b). Some of the evidence supporting this intake level included a small number of case reports of crippling skeletal fluorosis following fluoride intakes of approximately 0.215–0.285 mg/kg bw/day for 20 years and the observation of stage I skeletal fluorosis in osteoporosis patients treated with fluoride at doses of 0.260–0.389 mg/kg bw/day. Also, the 0.20 mg/kg bw/day effect level is within the range of daily intakes predicted (based on modelling) to result in bone fluoride concentrations associated with adverse skeletal effects in humans (Environment Canada and Health Canada, 1993). A review from the IOM (1997) in the United States pointed out that most epidemiological research suggest that an intake of at least 10 mg/day for 10 or more years is needed to produce clinical signs of the milder forms of skeletal fluorosis.

Based on a comprehensive review of available data, the weight of evidence does not support a link between exposure to fluoride in drinking water at 1.5 mg/L and any adverse health effects, including those related to cancer, immunotoxicity, reproductive/developmental toxicity, genotoxicity and/or neurotoxicity. In addition, the weight of evidence does not support a link between fluoride and intelligence quotient deficit, as there are significant concerns regarding the available studies, including quality, credibility, and methodological weaknesses. These conclusions are in agreement with the findings and recommendations of the 2007 expert panel meeting on fluoride held in Canada (Health Canada, 2008).

11.1 International considerations

Several agencies have reviewed the toxicity of fluoride and have established a guideline or a standard value for fluoride in drinking water. The World Health Organization first established a guideline for fluoride in drinking water of 1.5 mg/L in 1984, based on increased risk of objectionable dental fluorosis. WHO reaffirmed the same guideline in 1993 and in 2004, stating that there was no evidence to suggest that the guideline value needed to be revised. WHO mentioned that where intakes are likely to approach or be greater than 6 mg/day, it would be appropriate to consider setting a standard or local guideline at a concentration lower than 1.5 mg/L (WHO, 2004). In Australia, the guideline value of 1.5 mg/L has been established to protect children from the risk of dental fluorosis. The Australian government mentioned that at concentrations between 1.5 and 2.0 mg/L, mottling of teeth due to dental fluorosis may occur, sometimes to an objectionable degree (NHMRC, 2004). The United States EPA's Maximum Contaminant Level (MCL) for fluoride in drinking water is 4 mg/L (currently under review). This level was set to protect against crippling skeletal fluorosis, with a secondary MCL of 2 mg/L to protect against dental fluorosis, which United States EPA considers a "cosmetic" rather than adverse effect (U.S. EPA, 1986). The California MCL for fluoride in drinking water is 1.4 to 2.4 mg/L, depending on the ambient temperature (California Health and Safety Code, Title 22). The European Union Drinking Water Directive (1998) recommends a standard value of 1.5 mg/L for supplies with naturally occurring fluoride and of 1.0 mg/L for fluoridated supplies.

12.0 Rationale

Moderate dental fluorosis has been chosen as the endpoint of concern for fluoride. It is not considered to be a toxicological end-point because it is not a health concern, but it is significant because it correlates with cosmetic problems. Dental fluorosis is the effect occurring at the lowest level of exposure in the population, and is the most widely and frequently studied of all adverse effects of fluoride. However, very mild and mild dental fluorosis are not considered to be adverse effects, either from a health or from a cosmetic perspective. Health Canada has calculated a health-based value of 0.9 mg/L for fluoride in drinking water, which is deemed protective against any potential adverse health effect from fluoride.

Based on the health-based value, the Federal-Provincial-Territorial Committee on Drinking Water has chosen to risk manage this value to a MAC of 1.5 mg/L for fluoride in drinking water, incorporating the following considerations:

- The current MAC of 1.5 mg/L for fluoride is still considered unlikely to cause moderate dental fluorosis in the Canadian population. The recent CHMS data have shown that the prevalence of Canadian children with moderate dental fluorosis is too low to be reported.
- The current MAC of 1.5 mg/L is also considered to be protective against all potential adverse health effects, including cancer, bone fracture, immunotoxicity, reproductive/developmental toxicity, genotoxicity, and/or neurotoxicity. Mild to moderate dental fluorosis is not considered to be an adverse health effect.
- The maximum acceptable concentration is established to ensure levels of fluoride do not exceed this value in treated drinking water. Naturally-occurring levels of fluoride above this value could be expected to be found in groundwater, which generally affects well owners and would require residential scale treatment.

- Where natural levels of fluoride in drinking water are exceeding the health-based value, the increased water treatment costs that would have to be incurred by those communities and private wells would be excessive.
- At current exposure levels, Canada is not a country cited in the international literature as having wide areas with elevated fluoride concentrations. Based on data provided by provinces and territories, fewer than 2% of the population would receive community water at levels over 1.0 mg/L. The situation in Canada is such that only a tiny minority of supplies is likely affected by excess fluoride and there appear to be few or no very high fluoride sources.

However, the Committee encouraged efforts to control fluoride intake from sources such as toothpaste ingestion and efforts to obtain other up-to-date estimates of daily fluoride intake in Canada.

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Appendix A: List of acronyms

AA	activated alumina
AChE	acetylcholinesterase
BMD	bone mineral density
bw	body weight
CEPA	Canadian Environmental Protection Act
CI	confidence interval
DMFS	decayed, missing, or filled surfaces of permanent teeth
DMFT	decayed, missing, or filled permanent teeth
DNA	deoxyribonucleic acid
ED	electrodialysis
EDR	electrodialysis reversal
EPA	Environmental Protection Agency (United States)
GD	gestation day
GSH	glutathione
HBV	health-based value
IQ	intelligence quotient
LD ₅₀	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MAC	maximum acceptable concentration
MDL	method detection limit
nAChR	nicotinic acetylcholine receptor
NCI	National Cancer Institute (United States)
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program (United States)
OR	odds ratio
PBPK	physiologically based pharmacokinetic
PQL	practical quantitation limit
RNA	ribonucleic acid
RR	relative risk
SCE	sister chromatid exchange
SD	standard deviation
SEER	Surveillance, Epidemiology and End Results
SIDS	sudden infant death syndrome
TDI	tolerable daily intake
TDS	total diet study

Appendix B: Tables

Table B-1: Provincial/territorial estimates for community water fluoridation coverage^a

Province	Total population	Population with fluoridated water	Population without fluoridated water	Percentage with fluoridated water (%)	Percentage without fluoridated water (%)
British Columbia	4 113 000	152 241	3 960 759	3.7	96.3
Alberta	3 290 350	2 457 406	832 944	74.7	25.3
Saskatchewan	968 157	356 096	612 061	36.8	63.2
Manitoba	1 148 401	803 116	345 285	69.9	30.1
Ontario	12 160 282	9 229 015	2 931 267	75.9	24.1
Quebec	7 546 131	489 420	7 067 711	6.4	93.7
New Brunswick	729 498	188 607	540 891	25.9	74.2
Nova Scotia	913 462	519 031	394 431	56.8	43.2
Prince Edward Island	135 851	32 174	103 677	23.7	76.3
Newfoundland and Labrador	505 469	7 572	497 897	1.5	98.5
Nunavut	29 474	0	29 474	0.0	100.0
Northwest Territories	41 464	23 400	18 034	56.4	43.6
Yukon	30 372	0	30 372	0.0	100.0
National totals	31 611 911	14 258 078	17 364 803	45.1	54.9

^a This information was collected from Provincial or Territorial Environment Ministries and then verified by the Dental Directors of each province and territory. The Ministries of Environment provided detailed data on the community fluoridated, or the water plants well as population numbers (Health Canada, 2009).

Table B-2: Estimated dietary intake of fluoride by children over 1 year of age and adults in Canadian communities with fluoride levels of about 1 mg/L and 0 mg/L in their food processing water and beverages^a

Diet	Dietary intake (µg/kg bw/day)										
	1-4 years M+F	5-11 years M+F	12-19 years M	20- 39 years M	40-64 years M	65+ years M	12-19 years F	20-39 years F	40-64 years F	65+ years F	All ages M+F
Fluoride in water at 1 mg/L, with tea	26	21	20	38	47	41	19	42	48	43	32
No fluoride in water, with tea	16	14	13	24	31	29	13	27	33	31	21
TDS ^b estimate, Toronto, with tea	17	14	12	21	24	20	11	21	23	21	17
Fluoride in water at 1 mg/L, no tea	22	16	12	17	15	12	10	15	14	11	12
No fluoride in water, no tea	13	10	7	7	6	5	6	6	6	5	6
TDS estimate, Toronto, no tea ^c	15	12	9	11	10	7	7	8	8	6	8

^a Adapted from Dabeka et al. (2007a). Does not include fluoride intake from straight tap water consumption.

^b TDS stands for "Total Diet Study." Fluoride levels in Toronto drinking water were 0.54 mg/L, and water used to process food had fluoride concentrations of 0.28 mg/L.

^c The concentration of fluoride in coffee from the Toronto composite was used in place of the concentration of fluoride in tea.

Table B-3: Estimated dietary intake of fluoride by infants as a function of fluoride level in their community drinking water and the type of infant formula fed to them^a

Diet ^b	Fluoride in water status	Dietary intake (µg/kg bw/day)				
		0–1 months	2–3 months	4–6 months	7–9 months	10–12 months
All formulas	Fluoride in water ^c	33	37	21	26	24
	No fluoride in water ^d	14	16	12	14	13
TDS estimate, Toronto ^e		18	21	12	15	13
Ready-to-use milk-based formula	Fluoride in water	26	28	28	27	30
	No fluoride in water	21	23	22	22	21
Powdered milk-based formula	Fluoride in water	119	120	115	97	85
	No fluoride in water	19	21	20	20	20
Ready-to-use soy-based formula	Fluoride in water	69	70	68	60	55
	No fluoride in water	64	65	63	54	46
Powdered soy-based formula	Fluoride in water	102	111	102	92	81
	No fluoride in water	15	17	17	18	18
Breast milk	Fluoride in water	12	14	15	17	21
	No fluoride in water	6	8	9	11	12

^a Adapted from Dabeka et al. (2007a).

^b Except for the “All formulas” and for the “TDS estimate,” all dietary intake estimates were calculated assuming that the only milk or formula type fed to the infant was that described in the table. For the powdered formula, a dilution of 8.5 g (water) + 1.5 g (powder) was used to estimate the concentration of fluoride in the formula as fed, assuming water contains fluoride at 1 mg/L or 0 mg/L. The fluoride concentrations used for human milk were 0.013 mg/L and 0.009 mg/L, geometric means obtained previously in Canada for mothers living in communities with fluoridated and non-fluoridated water, respectively (Dabeka et al., 1986).

^c For foods and beverages with important water components (such as canned soups, pasta, rice, frozen juices, coffee, tea, infant formula, and cereals), the water used was fluoridated (0.99 mg fluoride/L).

^d For foods and beverages with important water components (such as canned soups, pasta, rice, frozen juices, coffee, tea, infant formula, and cereals), the water used was fluoride-free (0 mg fluoride/L).

^e TDS stands for “Total Diet Study.” Fluoride levels in Toronto drinking water were 0.54 mg/L, and water used to process food had fluoride concentrations of 0.28 mg/L.

Table B-4: Estimated dietary intakes of infants living in the 1940s in communities with differing concentrations of fluoride in drinking water^a

Fluoride concentration in drinking water (mg/L)	Average dietary intakes (µg/kg bw/day)					
	0–1 months	2–3 months	4–6 months	7–9 months	9–12 months	All ages 0–12 months
	M+F	M+F	M+F	M+F	M+F	M+F
0	9	11	11	12	12	11
1	57	52	33	31	25	36
1.5	81	72	45	40	32	48

^a Adapted from Dabeka et al. (2007b).

Table B-5: Estimated dietary intakes of children 1 year of age and older and adults living in the 1940s in communities with differing concentrations of fluoride in drinking water^a

Fluoride concentration in drinking water (mg/L)	Average dietary intakes (µg/kg bw/day)										All ages >1 year old M+F
	1–4 years	5–11 years	12–19 years	20–39 years	40–64 years	65+ years	12–19 years	20–39 years	40–64 years	65+ years	
	M+F	M+F	M	M	M	M	F	F	F	F	
0	14	11	10	16	20	18	9	18	21	19	16
1	23	19	17	30	35	30	15	31	35	31	26
1.5	27	22	20	37	42	36	18	38	42	36	32

^a Adapted from Dabeka et al. (2007b).

Table B-6: Estimated dose of fluoride ingested from fluoridated dentifrice per day in children aged 6 to 144 months old^a

Age (months)	N ^b	Average ingested dose µg/kg bw/day
6	13	30
12	214	20
24	558	30
36	577	30
48	582	40
60	603	40
72	587	40
84	531	40
96	514	30
102	474	30
108	434	30
120	504	30
132	342	30
144	137	20

^a Adapted from Levy et al. 2006.

^b N = number of subjects. Only subjects brushing with fluoridated toothpaste are included in the table.