Expert Panel Meeting on the Health Effects of Fluoride in Drinking Water: Summary report

June 8-9, 2023

Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. Health Canada is committed to improving the lives of all of Canada's people and to making this country's population among the healthiest in the world as measured by longevity, lifestyle and effective use of the public health care system.

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Context

Health Canada works in partnership with the provinces and territories to establish the Guidelines for Canadian Drinking Water Quality. These guidelines are used by the provinces, territories and federal authorities to establish their requirements for drinking water quality based on need and context.

Health Canada identifies chemical priorities in drinking water every four to five years. The process for prioritizing chemicals examines many sources of information, including the following:

- updates in the scientific literature, risk assessment or treatment methodologies
- new actions in other countries
- input and data from the provinces, territories and other federal departments

Health Canada's prioritization process resulted in fluoride being in priority assessment group 1 based on health risk, treatment and measurement methods, and needs identified by federal, provincial and territorial authorities. The current guideline of 1.5 mg/L for fluoride in drinking water was established in 2010[1].

Health Canada is in the early stages of reviewing the Guidelines for Canadian Drinking Water Quality for fluoride. That review includes assessing new scientific studies on potential health effects associated with exposure to fluoride. New scientific studies are regularly considered in order for the government to continue to base decisions on the overall weight-of-evidence and to best protect the health of people in Canada.

To support the review, Health Canada engaged six experts to consider scientific evidence and make recommendations on fluoride exposure (in drinking water and other sources), dental fluorosis, and potential effects on neurocognitive development in children. They were also tasked with providing scientific recommendations for Health Canada to consider in deriving a health-based value for fluoride in drinking water. The experts had a panel discussion in Ottawa, ON, on June 8 and 9, 2023.

The panel received background material on how Health Canada derives a health-based value, fluoride exposure data, background science on dental fluorosis, as well as on neurocognitive effects in children, a commissioned review on fluoride and health effects from human, animal, and *in vitro* evidence, and a number of other relevant references that considered emerging science. A summary of this information is presented for each issue below followed by the consensus statements agreed upon by the panel.

The panel discussed several charge questions, with the objective of providing consensus statements, supporting statements, and recommendations for Health Canada. The panel considered information pertaining to the human health risk assessment for fluoride in drinking water. The panel did not address the benefits of fluoride

[1] Health Canada (2010). Guidelines for Canadian Drinking Water Quality. Guideline Technical Document: Fluoride. Available at:

https://www.canada.ca/content/dam/canada/health-canada/migration/healthycanadians/publications/healthy-living-vie-saine/water-fluoride-fluorure-eau/alt/water-fluoride-fluorure-eaueng.pdf

or an optimal level of fluoride in drinking water. The panel also did not consider risk management. Health Canada and the Federal-Provincial-Territorial Committee on Drinking Water will consider any risk management needs (such as drinking water treatment costs or performance) when developing the revised guideline for fluoride in drinking water.

The panel was asked to provide expert recommendations to Health Canada on the following issues:

- Fluoride exposure
- Dental fluorosis
- Neurocognitive effects
- Derivation of the health-based value

Expert panel members

David Bellinger, Harvard University and Boston Children's Hospital, Departments of Neurology, and Psychiatry. Harvard T.H. Chan School of Public Health, Department of Environmental Health

John Fawell, World Health Organization (WHO Expert Committee on the Guidelines for Drinking Water Quality, independent consultant)

Lynne Haber, Department of Environmental and Public Health Sciences, University of Cincinnati College of Medicine

Steven Levy, University of Iowa, Department of Preventive and Community Dentistry, College of Dentistry, Department of Epidemiology, College of Public Health

David Savitz, Brown University School of Public Health, Department Epidemiology

Rita Schoeny, Consultant in risk assessment and science policy. Formerly US EPA Senior Science Advisor, Office of Science Policy, Office of Research and Development and Director of Risk Assessment Forum in EPA's Office of the Science Advisor

The meeting was also attended by representatives from Health Canada and Risk Sciences International (a consulting firm), with virtual/online observers from Health Canada, Public Health Agency of Canada, and representatives of the Federal-Provincial-Territorial Committee on Drinking Water. Risk Sciences International was the facilitator of the meeting and the intermediary between the Expert Panel and Health Canada, so as to support the independence of the Panel. Risk Sciences International also did an independent systematic review titled 'Critical Review of Potential Adverse Health Effects of Fluoride in Drinking water'. The review was used by Health Canada to develop discussion material for the meeting, and will help to inform drafting of the revised drinking water guideline.

Fluoride exposure

Summary of information provided to the panel by Health Canada

Most exposure to fluoride for the general population comes from drinking water, beverages and foods prepared from drinking water, and dental products. Fluorides can also be present to a lesser extent in the atmosphere and soil. An allocation factor is a number that represents the proportion of total exposure to fluoride that can be attributed to drinking water for the most sensitive subpopulation. It is used to inform the calculation of the health-based value, which is the numerical value at which health effects could be observed.

Expert panel consensus statements

- The panel was not aware of additional data on fluoride exposure that should be considered in the risk assessment.

- The panel agreed that air and soil are not major components of fluoride exposure for the purpose of this assessment.

- Given variation in intakes and challenges in precise derivation of an allocation factor, the panel agreed that the informed default approach is appropriate, considering the two sources: drinking water (including beverages and food prepared using drinking water) and dental products. Considering both sources to be of equal importance, the panel agreed that an allocation factor of 0.5 is appropriate for the derivation of the health-based value.

Dental fluorosis

Summary of information provided to the panel by Health Canada

Dental fluorosis is the most widely studied and recognised health effect resulting from oral exposure to fluoride. A study from 1942 led by a scientist named H.T. Dean is still considered to provide the best available data to assess the risk of dental fluorosis from exposures to fluoride in drinking water. Dental fluorosis is caused by a hypo-mineralization of teeth during the period when enamel develops, which can result in mottled enamel, with a chalky white appearance or brown staining or pitting in areas of the teeth with higher fluoride concentrations. The very mild form of dental fluorosis is difficult to detect, even by experienced dental personnel. This form is not associated with any health consequences, except for a decrease in prevalence of caries (often called dental cavities). Cosmetic effects are generally not of concern with very mild or mild forms of fluorosis. Moderate dental fluorosis may be associated with staining; however, this form has not been associated with health effects such as a loss of tooth function, as is the case with severe dental fluorosis. Moderate dental fluorosis was defined with Dean's Index (a guide for assessing the presence and severity of mottled enamel) as "All tooth surfaces affected; marked wear on biting surfaces; brown stain may be present". It is considered to be an adverse effect for the purpose of this risk assessment, based on its potential for aesthetic concern.

The 1942 study by Dean[2] provided the key data for estimating the lower limit of the benchmark dose (to be used as a point of departure), which indicates the exposure at which moderate and severe dental fluorosis rates increase in the population by 1%. This was estimated as 1.56 mg/L fluoride in drinking water.

Expert panel consensus statements

- Taking into account the robustness of the scientific database on dental fluorosis, the panel agreed with the use of moderate dental fluorosis as an endpoint of concern. This recognizes moderate dental fluorosis may include staining, which can be of aesthetic and therefore psychological concern.

- The panel knew of no additional evidence that would argue against the use of moderate dental fluorosis as an endpoint of concern.

- The panel agreed with the use of Dean (1942) for derivation of the point of departure for fluoride based on dental fluorosis. The panel acknowledged that this is an older study, but it was conducted at a time when the only source of exposure to fluoride was through drinking water, which increases trust in the data analysis.

- The panel recommended 0-4 years as the period of greatest susceptibility.

[2] Dean, T. (1942). The investigation of physiological effects by the epidemiological method. National Institute of Health, U.S. Public Health Service, Bethesda, MD.

- The panel agreed with the use of a 1% lower limit benchmark dose of 1.56 mg F/L as the point of departure for deriving the health-based value.

Supporting statement

In considering aesthetic effects, the most sensitive period of exposure to fluoride from drinking water is the period of development/mineralization for the most visible permanent teeth (the 4 maxillary incisors). This occurs from birth to age 4 years, and especially from age 1 to 3 years, with resulting aesthetic effects becoming apparent later in life, once the permanent teeth have erupted. The next most visible permanent teeth are the 2 maxillary canines, and the most sensitive risk period for this is approximately age 2 to 7 years. After 8 years of age, there is essentially no risk of dental fluorosis. Thus, there is no increased risk of dental fluorosis from fluoride intake during late childhood, adolescence, or adulthood.

Neurocognitive effects

Summary of information provided to the panel by Health Canada

A growing body of evidence suggests that fluoride in drinking water may be associated with reduced IQ scores in children at fluoride levels that may be found in Canadian drinking water. Health Canada commissioned an independent systematic review, which concluded that, on the basis of the weight of evidence, cognitive dysfunction (specifically, reduced IQ scores in children) should be considered as a candidate endpoint when setting the health-based value for fluoride in drinking water[3].

A report from the U.S. National Institutes of Health National Toxicology Program (NTP) suggested that evidence for neurological effects of fluoride in children is less consistent at levels below 1.5 mg F/L than at above that level, based on a review of numerous epidemiologic studies[4]. Following its systematic review of available literature, including the NTP report, Risk Sciences International (2023) identified a provisional point of departure of 1.5 mg F/L for neurocognitive effects[5]. Risk Sciences International acknowledged that the actual point of departure for this endpoint may be considerably lower (based on recent analyses, which included a high-quality Canadian birth cohort[6]. Although fluoride has been reported to affect the regulation of various enzymes, no specific mechanisms were found for the effect of fluoride on learning, memory or other cognitive or neurodevelopmental outcomes.

Expert panel consensus statement

- Based on several considerations, the panel agreed there is not a sufficient basis at this time to recommend a specific point of departure and health-based value for neurocognitive effects.

Supporting statement

Several studies have raised concern regarding the potential neurocognitive effects of fluoride at community exposure levels, but questions remain regarding whether the weight of evidence supports a causal relationship. Some of these studies suggest adverse effects at lower exposure levels than those that cause dental fluorosis, and that possibility should not be ignored. Less weight should be given to the ecological and cross-sectional studies relative to the few prospective cohort studies of individuals exposed to fluoride levels in the range of concern with longitudinal measurements of neurocognitive function. The science concerning neurocognitive

[3] Risk Sciences International (2023). Critical Review of Potential Adverse Health Effects of Fluoride in Drinking Water. Report prepared for Health Canada (unpublished).

[4] National Toxicology Program. 2022. DRAFT NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review (September 2022 version). [accessed 17 April 2023]. https://ntp.niehs.nih.gov/whatwestudy/assessments/noncancer/ongoing/fluoride/index.html.

[5] Risk Sciences International (2023).

[6] Risk Sciences International (2023).

effects and fluoride is rapidly evolving, and consideration should be given to new studies as they become available.

The following type of information would contribute to resolving the issue of possible neurocognitive effects resulting from fluoride exposure in the dose-range of interest. Consideration should be given to mining existing cohorts or initiating new studies to address the issue. These additional large, high-quality studies should include longitudinal measurement from conception, with observations in the lower exposures spanning the range experienced by sensitive subpopulations of interest, following children into childhood. The studies should incorporate more domains of cognitive function (e.g., executive function, visual-spatial skills, problem-solving). Studies should ideally include detailed personal exposure profiles representing fluoride exposure from all relevant routes. Consideration should be given to the use of standardized collection of several days of 24-hour total urine as a biomarker of fluoride exposure. Attention should be given to potential confounders (e.g., lead, arsenic, manganese) and effect modifiers (e.g., such as calcium and iodide) that could obfuscate or alter the association of fluoride and possible cognitive effects.

Understanding the mode of action by which fluoride might induce neurocognitive effects would be useful and could help in the interpretation of results from epidemiologic studies.

Derivation of the Health-Based Value

Summary of information provided to the panel by Health Canada

Based on the weight of evidence from a systematic review of epidemiologic, animal, and in vitro studies, dental fluorosis and neurocognitive effects (specifically, IQ deficits in children) were identified as the most sensitive endpoints of concern for updating the Health Canada guideline technical document on fluoride in drinking water.

Selection of a point of departure is a critical step in the development of a health-based value. The point of departure for neurocognitive effects (i.e., IQ reduction) is not yet well defined because of uncertainties, including the shape of the exposure-response curve at low concentrations of fluoride in drinking water. Therefore, moderate dental fluorosis was selected as the key endpoint of concern with a point of departure of 1.56 mg F/L in drinking water.

The tolerable daily intake is normally calculated by dividing daily intake on a µg/kg/day basis by an uncertainty factor. Since the point of departure in this case is already a measurement in drinking water, this step (and calculation of the health-based value) can be simplified by applying an uncertainty factor directly to the point of departure to account for the database deficiencies about the potential occurrence of neurotoxicity from exposure to fluoride at low doses.

Therefore, the drinking water concentration (DWC) is calculated by dividing the point of departure (POD) by the uncertainty factor (UF).

$$DWC = POD / UF$$

A health-based value (HBV) for fluoride in drinking water would be calculated by multiplying this DWC by an allocation factor (AF) to account for exposure to fluoride from other sources.

$$HBV = DWC \times AF$$

Consensus statement

- The panel agreed with the choice of moderate dental fluorosis as the key endpoint and Dean (1942) as the key study. Although effects on neurocognitive endpoints have been reported in the scientific literature at lower fluoride exposure levels than moderate dental fluorosis, at this time, the evidence is not considered sufficient to use neurocognitive endpoints as the basis for deriving a point of departure.

- The panel agreed with the derivation of the lower limit of the 1% benchmark dose for moderate dental fluorosis and its use as the point of departure.

- Given the uncertainty about possible neurocognitive effects at low levels of exposure, the panel recommended the use of an uncertainty factor for database deficiency for deriving the health-based value but was unable to recommend a specific numeric uncertainty factor, leaving this decision to Health Canada.

- The panel agreed with the choice of children as the most sensitive subpopulation for the risk of moderate dental fluorosis and recommended that an age range of 0-4 years be considered to reflect the most sensitive subpopulation.

- The panel agreed with the use of an allocation factor of 0.5 for the age group of 0-4 years.

Summary of key recommendations for developing a health-based value

As outlined above, the expert panel reached consensus on answers to several key questions that will guide the development of a health-based value for fluoride in drinking water. The expert panel agreed on the following:

1. an appropriate health endpoint of moderate dental fluorosis as the key health effect on which to base a human health risk assessment for fluoride in drinking water,

2. a point of departure of 1.56 mg/L,

3. an allocation factor of 0.5 (representing the relative source contribution of drinking water to total fluoride exposure), and

4. the need for application of an uncertainty factor to the calculation in order to account for the database deficiency as it relates to potential neurocognitive effects.

The panel did not reach a consensus on the magnitude of the uncertainty factor that should be applied, leaving Health Canada to determine this value.