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Decision-support logic diagram for the presence of per- and polyfluoroalkyl substances (PFAS) in drinking water

TRANSFER OF KNOWLEDGE

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FOREWORD

In Québec, no legal standard exists concerning the presence of perfluoroalkyl and polyfluoroalkyl substances (PFAS) in drinking water. Several organizations have published a variety of guideline values to support the assessment and management of health risks associated with these contaminants. Given this context, it proves complex to identify situations where it would be desirable to structure public health actions when PFAS are present in drinking water. The *PFAS Logic Diagram* has been developed in response to this challenge. It is primarily intended for stakeholders in public health organizations (regional public health departments, the Ministère de la Santé et des Services sociaux and the Institut national de santé publique du Québec) who may be faced with situations involving PFAS contamination of drinking water. It could also be used by other stakeholders involved in the assessment and management of these issues. It is aligned with the document entitled, *La gestion des risques en santé publique : cadre de référence* (1) (the reference framework for public health risk management, available in French only) and is also informed by the *Outil d'aide à la décision lors de dépassement de normes ou de contaminations chimiques dans l'eau potable* (2) (the decision-support tool for exceedance of standards or chemical contamination in drinking water, available in French only).

A preliminary version of the logic diagram was developed in response to a specific case of PFAS contamination of drinking water. A refined version was produced following exchanges and discussions with several regional public health departments, the Ministère de l'Environnement, de la Lutte contre les changements climatiques, de la Faune et des Parcs, as well as with a committee of experts on chemical risks in water, CERCEau. This version can be used for the initial management of various situations, and fits within the context of existing documentation. The *PFAS Logic Diagram* was developed on the basis of the knowledge available at the time of writing. It must be kept in mind that that this knowledge is rapidly evolving, as are the regulations, policies and recommendations of the recognized health organizations to whom it is relevant.

To learn more about PFAS, please consult the INSPQ web page (in French only) which contains information about these substances, sources of human exposure, their health effects and certain guideline values for PFAS in drinking water. This page contains additional information that helps elucidate the *PFAS Logic Diagram*.

TABLE OF CONTENTS

GLOSSARY

Chronic exposure: exposure to a toxic substance or contaminant over a period of several years, generally representing more than 10% of the life expectancy of the species – e.g.: > 7 years for a human whose life expectancy is set at 70 years for purposes of risk assessment (2).

Sub-chronic exposure: exposure to a contaminant over a period ranging from 30 days to 10% of a lifetime (< 7 years by default) (2).

Health-based guideline value: concentration of a chemical contaminant in an environmental setting deemed adequate for the protection of human health. This concentration has no legal value. Moreover, it is determined without consideration for the technical and economic limits associated with its application. Health guideline values are based on **toxicological reference values** (9).

Guideline value: concentration of a chemical contaminant in an environmental setting established by a recognized health or regulatory body. A guideline value may be a **health guideline value** (i.e., based solely on health considerations) or a **management-based guideline value** (2).

Management-based guideline value: concentration of a contaminant in an environmental setting established by a health or regulatory body, which is not necessarily based on health effects. These values take into account the limits of technical and economic feasibility (e.g., the analytical detection limit, the treatment system). They are used, in particular, when **health guideline values** cannot be applied or determined.

Toxicological reference value: value reflecting the potential toxicity of contaminants for human health. This is based either on a **threshold toxic effect**, or on a **non-threshold toxic effect**. In the case of threshold effects, the toxicological reference value corresponds to the reference dose or concentration. For non-threshold effects, on the other hand, the value corresponds to the unit risk (9).

1 CONTEXT

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) form a complex group of chemicals comprising thousands of fluorinated organic compounds[1]. PFAS arise exclusively from human activity and are used in a wide variety of consumer products and industrial processes. They are highly persistent and ubiquitous in the environment, often in the form of variable mixtures of several compounds. Given the toxic effects that have been associated with certain PFAS, and the current uncertainties concerning exposure levels that present a risk to human health, a number of international initiatives are aimed at banning or restricting the use of these substances in order to reduce population exposure. Moreover, local or point source contamination can add to this diffuse PFAS pollution and reach groundwater and surface water used as a drinking water supply. In some such cases, depending on the extent of contamination, drinking water can represent a significant source of exposure, as compared with diet.

In Québec, there are currently no standards regulating the presence of PFAS in water. However, a growing number of health organizations and jurisdictions around the world are proposing **guideline values**[2] for PFAS, some of which are solely health-based (**health-based guideline values**), while others take into account various application constraints (**management-based guideline values**). Guideline values have been determined for certain individual PFAS, while others apply to groups comprising varying numbers of PFAS. Increased attention has recently been focused on the presence of PFAS in drinking water, in light of the significant lowering of guideline values proposed by certain health organizations. Indeed, studies suggest that PFAS may be toxic to humans at doses similar to those resulting from some environmental exposures that were previously considered to have no significant effect. For example, government agencies have recently used epidemiological data related to effects on the immune system to determine **toxicological reference values** and **health-based guideline values** for drinking water (4,5). These values are generally very low, and alter the interpretation of the risk associated with exposure to PFAS in drinking water, such that it differs from what was generally assumed until very recently. Finally, the World Health Organization (WHO) and Health Canada recommend keeping concentrations in drinking water "as low as reasonably achievable" (6,7).

The lack of data on the toxicity of many compounds, the presence of mixtures of varying composition of individual PFAS molecules and the rapid evolution of scientific knowledge on the subject add to the complexity of the context outlined above. This is why stakeholders face many challenges in assessing and managing the risks arising from the presence of PFAS in drinking water. **The decision-support logic diagram presented here is a tool designed to support the initial management of such a situation, with the aim of rapidly identifying situations where it is desirable to structure public health actions. It proposes benchmarks for both**

[1] As defined by the Organisation for Economic Co-operation and Development (OECD) (3), the common characteristic of PFAS is that they consist of a carbon chain containing at least one fully fluorinated saturated methyl or methylene group. Various functional groups can be added to this fluorocarbon backbone, giving these molecules distinct physical, chemical and toxicological properties.

[2] Terms highlighted in the text are defined in the glossary at the beginning of this document (p. IV).

chronic and sub-chronic exposures, as well as for some individual PFAS and for the sum of PFAS.

In all cases, decisions concerning the management of health risks associated with PFAS contamination of drinking water should be carefully examined, in conjunction with the stakeholders involved and with consideration for the anticipated risks and the particularities of each issue identified. Communication-related issues and ethical concerns surrounding risks should also be considered by the responsible authorities.

This document first presents the scientific bases underpinning the *PFAS Logic Diagram*. It then describes the logic diagram's structure and positions it within the context of existing risk management documents in Québec. Finally, the document presents the strengths and limitations of the logic diagram, before concluding with a brief discussion of its scope of application.

2 SCIENTIFIC BASES OF THE LOGIC DIAGRAM

The *PFAS Logic Diagram* is based on considerations relative to both sub-chronic and chronic exposure. Criteria are proposed for these two exposure durations and include, for each, a management-based guideline value that applies to the sum of total PFAS and guideline values for individual substances (either health-based guideline values or management-based guideline values).

The purpose of the management-based guideline value for the sum of total PFAS is to serve as a benchmark that takes into account the presence of mixtures as well as emerging PFAS for which no toxicological reference value of confidence is currently available. Certain management-based guideline values are also proposed in the logic diagram as criteria for individual substances (more details are given in Section 3.2). The management-based guideline values adopted are based principally on current recommendations from recognized organizations.

In addition, the Institut national de santé publique du Québec (INSPQ) has developed health-based guideline values for individual substances for which a toxicological reference value of confidence[3] is available, so as to take into account the toxicological knowledge deemed most robust. The health-based guideline values were determined using the *Méthodologie d'élaboration de valeurs guides sanitaires chroniques pour les contaminants chimiques de l'eau potable* (9) (the methodology for developing chronic health guideline values for chemical contaminants in drinking water, available in French only). For sub-chronic and chronic criteria, only the health-based guideline values for individual PFAS that fall below the criterion applicable to the sum of PFAS have been included in the logic diagram, in order to avoid redundancy in the proposed benchmarks.

The criteria used in the logic diagram were determined subsequent to a review of guideline values proposed by organizations or jurisdictions in the United States, Canada and Europe. In addition, for all PFAS, toxicological reference values for the ingestion route derived by recognized health organizations were compiled using the *Méthodologie de recherche et de sélection de valeurs toxicologiques de référence publiées par les organismes reconnus* (8) (the methodology for researching and selecting toxicological reference values published by recognized organizations, available in French only) developed by the INSPQ's Équipe scientifique sur les risques toxicologiques et radiologiques (the scientific team focused on toxicological and radiological risks)[4]. More details on the compilation of these values are provided in Appendix 1.

[3] Assessing the degree of confidence for toxicological reference values (TRVs) involves analyzing the information compiled on TRVs proposed by recognized organizations. This assessment is based on professional judgement, informed by reference to certain indicators, including the transparency and consistency of the methodology used to determine the TRV. More details on this process can be found in the *Méthodologie de recherche et de sélection de valeurs toxicologiques de référence publiées par les organismes reconnus* (8) and in the *Méthodologie d'élaboration de valeurs guides sanitaires chroniques pour les contaminants chimiques de l'eau potable* (9).

[4] The document detailing the methodology is available on request.

3 DECISION-SUPPORT LOGIC DIAGRAM FOR PFAS

3.1 Context and scope of the logic diagram

Given the absence of a Québec legal standard and the variability of available guideline values, the *PFAS Logic Diagram* provides a rapid risk assessment process for the initial management of situations involving PFAS contamination of drinking water. Thus, its application makes it possible to quickly identify situations where it would be relevant to more thoroughly assess risk as part of the process leading to the analysis of the various management options set out in the document *La gestion des risques en santé publique : cadre de référence* (1), hereinafter referred to as the *Reference framework*.

More specifically, the *PFAS Logic Diagram* essentially fits within the context of ***Phase 2: Risk assessment and characterization*** of the process described in the *Reference framework* (1). The aim of the assessment carried out in this phase is to estimate the health risk for exposed populations. Characterization involves interpreting the level of risk based on professional judgement. Normally, this risk assessment and characterization phase follows ***Phase 1: Scoping and planning*** and leads to ***Phase 3: Risk acceptability and proposed management options***[5] and ***Phase 4: Decision-making, implementation and monitoring of interventions*** (see Figure A2-1 in Appendix 2 illustrating the process detailed in the *Reference framework*).

According to the *Reference framework*, other documents specific to the field of environmental health may be relevant to the assessment and characterization of particular risks. Thus, the *PFAS Logic Diagram* is also informed by the approach developed in the *Outil d'aide à la décision lors de dépassement de normes ou de contaminations chimiques dans l'eau potable* (2), hereinafter referred to as the *Decision-support tool*. Although this document was developed prior to the publication of the *Reference framework*, several steps remain contextually relevant to the logic diagram. Indeed, the latter **fits within the context of *Step 3: Risk assessment***. This implies that there are steps which precede the application of the logic diagram proposed in the present document; specifically ***Step 1: Confirmation of the result***[6] and ***Step 2: Documentation of the contamination situation and on the contaminant***[7]. It should be noted that *Step 2* could be carried out concurrently with the risk assessment step[8]. The *Reference framework* and the

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5 According to the *Reference framework*, management options may include, for example, maintaining the responsible status quo, environmental monitoring, informing the population concerned about measures to take to protect health, reducing exposure through collective or individual measures (1).

6 *Step 1: Confirmation of the result* involves ensuring the validity of the result obtained and the representativeness of the sample. Depending on the type of network, and if deemed necessary, a second sample may be requested to confirm the result. Samples should ideally be representative of population exposure, but low representativeness could be considered valid (e.g., data reflecting higher exposure could be used before more complete data is acquired; see also note 8).

7 *Step 2 (A: Documentation of the contamination situation* and *B: Documentation on the contaminant)* consists in further characterizing the drinking water contamination problem, by documenting the toxicity of the contaminant in question and the actual contamination situation (source, extent, etc.).

8 *Stage 2B: Documentation on the contaminant* was based on the scientific knowledge available at the time of writing. This helped determine the criteria included in the logic diagram. Knowledge of the source of

Decision-support tool propose generic approaches, while allowing for the integration of local and regional particularities.

Another advantage of the *PFAS Logic Diagram* is that it guides professional judgement as to the temporality of interventions, by making it possible to distinguish between situations where a risk could arise from sub-chronic exposure, and those where a risk could be associated with longer-term exposure (chronic exposure).

3.2 Presentation of the logic diagram

The following figure (p. 6) presents the decision-support logic diagram for PFAS contamination of drinking water. It is structured according to a sequence of decision nodes branching from two types of criteria reflecting first sub-chronic, then chronic considerations.

Sub-chronic criteria include:

a) A guideline value for the sum of total PFAS (100 ng/L);

b) Another for PFHxS (28 ng/L);

c) A hazard index of less than 1 for three substances: PFOS, PFOA and PFNA[9].

With regard to chronic criteria, these all correspond to guideline values:

a) One for a group of PFAS: the sum of total PFAS (30 ng/L);

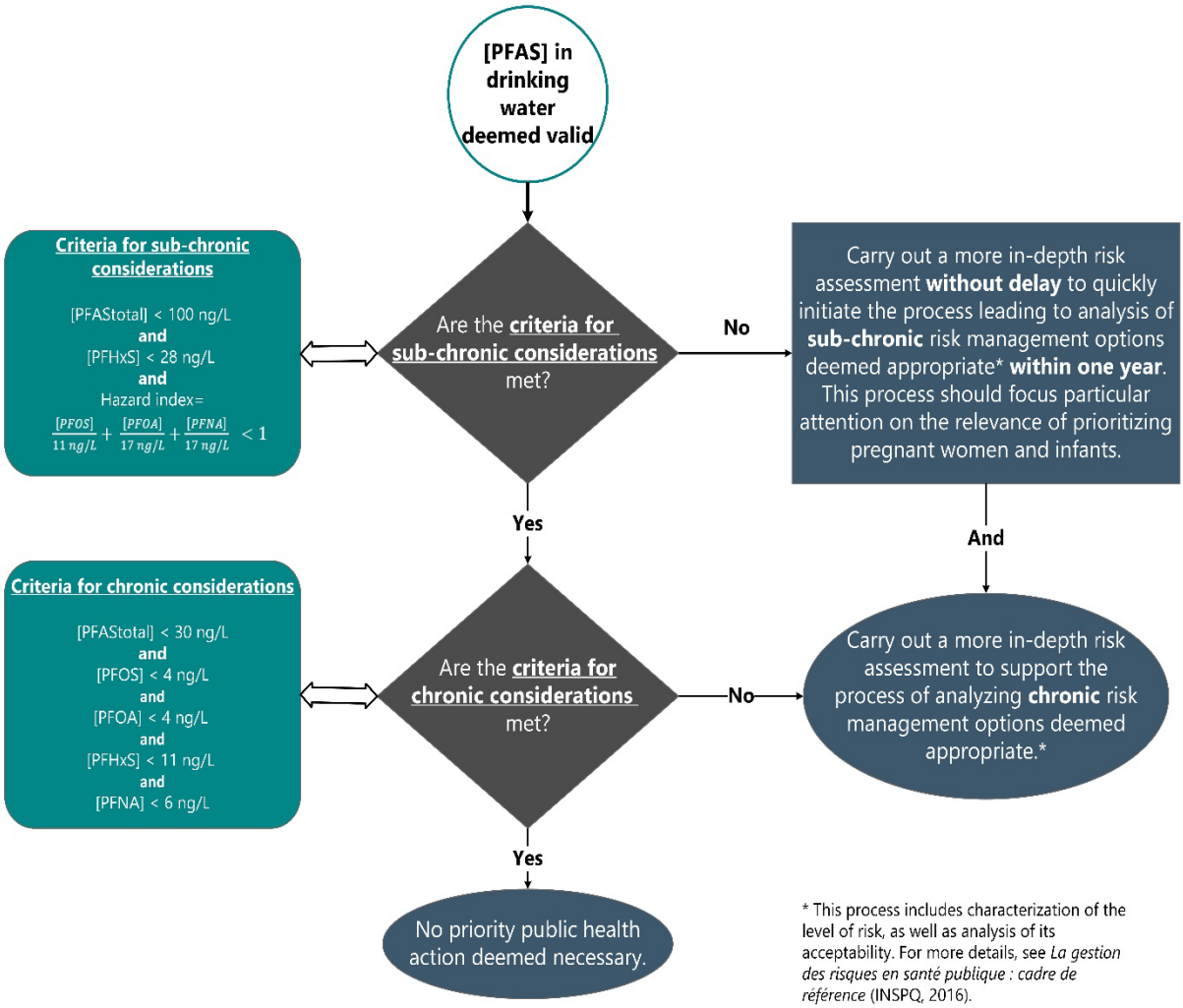
b) Four for individual substances: PFOS (4 ng/L), PFOA (4 ng/L), PFHxS (11 ng/L) and PFNA (6 ng/L).

More details about these criteria can be found further on in this section and in Appendix 3.

contamination is sometimes required to enable identification of the most effective and realistic management options, but the step of documenting the contamination situation *(Step 2A*) can be complex and sometimes costly. However, this should not form an obstacle to risk assessment and management. Depending on professional judgement, it is therefore possible that actions may be implemented initially on the basis of results deemed valid, even if incomplete, and that more sustainable management options may be examined on the basis of additional results obtained at a later date.

[9] The hazard index is calculated by dividing the concentration in drinking water by the proposed health guideline value for each of these three substances (i.e., 11 ng/L for PFOS and 17 ng/L for PFOA and PFNA).

Figure 1 Decision-support logic diagram for PFAS contamination of drinking water



The first decision node prompts comparison of PFAS concentrations in drinking water deemed valid with sub-chronic exposure criteria. When one or more sub-chronic criteria are not met, the risk assessment should be refined without delay, so as to rapidly initiate the process leading to analysis of the sub-chronic risk management options[10] deemed appropriate. Where applicable, a one-year period is allowed for the analysis and implementation of these options. This period of time is adequate assuming there is an agreement to reduce, in the short term, the exposure to PFAS in drinking water of the population concerned. The process should pay particular attention to the relevance of targeting pregnant women and infants as a priority, especially if the criteria for individual PFAS (including the hazard index) are not met[11] or if the in-depth risk assessment

[10] This is the process detailed in the *Reference framework*, which includes characterizing the level of risk, as well as analyzing the acceptability of the risk, prior to analyzing management options.

[11] The goal is to reduce the risk of health effects, which forms the basis for the determination of sub-chronic criteria for individual PFAS (refer to the following subsection and to Appendix 3).

highlights the importance of doing so. In cases where these population subgroups are prioritized, the aim is to reduce, in the short term, any intake through drinking water that would add to the unavoidable exposure of an unborn child or infant due to the body burden accumulated by the mother during her lifetime prior to pregnancy[12]. An assessment of longer-term risk management options should follow after these initial actions, so as to limit chronic exposure for the entire population served. The ultimate goal should be, with time, to meet chronic criteria.

If sub-chronic criteria have been met, concentrations in drinking water are compared to chronic criteria, as prompted by the second decision node in the logic diagram. If one or more of these criteria are not met, a more in-depth risk assessment will need to be carried out to support the process of analyzing chronic risk management options deemed relevant by the responsible authorities. In this case, management may call for interventions that are more sustainable, but require a longer time frame to establish. This step generally includes consultation with the stakeholders involved and affected by the decision to be made. In addition, it must take into account a whole range of dimensions that influence health risk and its management, and that extend beyond drinking water contamination alone.

Finally, a more in-depth risk assessment can be as much about refining the exposure estimate as refining the risk estimate; the *Reference framework* and the *Decision-support tool* can guide stakeholders or responsible authorities in this regard.

Sub-chronic criteria

Sub-chronic criteria include a management-based guideline value for the sum of total PFAS and four health-based guideline values developed for four PFAS whose toxicity has been best characterized. The management-based guideline value is set at 100 ng/L for the sum of total PFAS[13] and is based on the value proposed by the European Union for the sum of 20 PFAS, in its drinking water directive (13). At this concentration, drinking water intake would represent between 41% and 73%[14] as measured against average dietary intake, depending on the age group concerned.

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[12] It should be noted that breastfeeding women are not included in this list, since generally the molecules likely to accumulate in breast milk are essentially attributable to the mother's accumulated body burden (10–12), and are much less attributable to the mother's recent exposure through drinking water intake. For this reason, targeting breastfeeding women is unlikely to have much impact on the exposure of the breast-fed child. Moreover, the many health benefits of breastfeeding for both baby and mother are well known and have been demonstrated. Consequently, it is still recommended that breastfeeding mothers and those planning to breastfeed pursue this course of action.

[13] The value of 100 ng/L applies to the sum of PFAS as determined using a certified and standardized analytical method, such as that of the Centre d'expertise en analyse environnementale du Québec (CEAEQ) or U.S. EPA methods 533 and 537.1.

[14] This is according to a preliminary analysis based on the drinking water intake rates for the various age groups set out in the INSPQ's *Méthodologie d'élaboration de valeurs guides sanitaires chroniques pour les contaminants chimiques de l'eau potable* (9) and using as a comparison the average upper and lower bounds of average dietary exposure specific to similar age groups, estimated by the EFSA (4).

On the other hand, certain situations where total PFAS concentrations do not reach the value of 100 ng/L could still present a risk associated with a sub-chronic exposure duration when, for example, the PFAS mixture is dominated by certain individual substances that are toxic at low concentrations. Based on the availability of toxicological reference values judged to be of a high level of confidence[15] and from which health-based guideline values derived are of less than 100 ng/L, certain substances have been identified and included in the logic diagram. Thus, the criterion used for PFHxS is 28 ng/L. This is a sub-chronic health guideline value derived by the INSPQ for endocrine effects liable to affect the whole population. For PFOS, PFOA and PFNA, the expected effects target development of the unborn child and result from prenatal exposure. To take account of the potential additivity of effects, the proposed criterion for these three substances is expressed as a hazard index, since they all target a developmental effect. The hazard index corresponds to the sum of the ratios between the concentration of each substance and the health guideline value derived for that substance (i.e., 11 ng/L for PFOS and 17 ng/L for PFOA and PFNA). This hazard index must be less than 1. More details on these health-based guideline values derived by the INSPQ for the *PFAS Logic Diagram* can be found in Appendix 3.

Chronic criteria

The chronic criteria include a management guideline value for the sum of total PFAS, set at 30 ng/L, the Health Canada objective[16] (7). At this concentration, drinking water intake would result in an exposure corresponding to between 12% and 22%,[17] depending on the age group concerned, of the average dietary intake of total PFAS.[18] In addition, it seems appropriate to also set guideline values for certain individual PFAS whose toxic effects have been better characterized. Depending on their relative concentrations in certain mixtures, the sum of PFAS could remain below 30 ng/L, yet include a single substance whose concentration would exceed its individual guideline value, and this should be avoided. A management-based guideline value for PFOS and one for PFOA, as well as a health-based guideline value for PFHxS and one for PFNA, are therefore proposed.

More recent toxicological reference values for PFOS and PFOA are based on effects on the immune system[19] and result in extremely low health guideline values,[20] that sometimes fall below certain analytical detection limits (4,5). With regard to prioritizing interventions using the *Decision-support tool*, such values are practically inapplicable, since drinking water interventions

[15] See footnote 3.

[16] At the time this document was written, Health Canada's objective was the subject of a public consultation (7).

[17] The distribution of concentrations found in 463 drinking water samples collected from 376 Québec municipalities in the study by Munoz et al. (14) produced an average of 4.8 ng/L, a median of 2 ng/L and a 95th percentile of 13 ng/L. Exposure resulting from the intake of drinking water with a concentration corresponding to this 95th percentile would represent between 5% and 9% of exposure resulting from general dietary intake.

[18] See footnote 14.

[19] A few epidemiological studies have shown a decrease in antibody levels and other markers of post-vaccination immunity in children exposed to PFOA and PFOS. For more information, see the INSPQ's web page on PFAS.

[20] For example, the U.S. EPA *Health Advisory* has proposed health guideline values of 0.02 ng/L for PFOS and 0.004 ng/L for PFOA using toxicological reference values of 7.9 x10^{-9} mg/kg/day and 1.5 x 10^{-9} mg/kg/day respectively (5). It should be noted that these values are provisional, and are therefore subject to revision.

would be indicated as soon as concentrations of PFOS and PFOA were detected. For these two substances, the management-based guideline value was therefore set at 4 ng/L, as proposed by the U.S. EPA (15), which takes into account analytical detection limits. Moreover, this concentration would correspond to an expected proportion of dietary intakes of between 36% and 79% for PFOA and between 11% and 15% for PFOS[21].

The two health-based guideline values for PFHxS and PFNA were derived by adjusting the sub-chronic toxicological reference values used previously for a chronic exposure duration. This was done by adding an appropriate uncertainty factor, based on the critical effect. The values set as criteria for this logic diagram are 11 ng/L for PFHxS and 6 ng/L for PFNA. More details on these chronic health guideline values derived by the INSPQ for the *PFAS Logic Diagram* can be found in Appendix 3.

3.3 Strengths and limitations of the proposed logic diagram

One of the advantages of the *PFAS Logic Diagram* is that it is relatively simple to use, making it possible to identify situations where it would be appropriate to perform a more exhaustive health risk assessment. This helps provide public health actors with rapid responses, and thus guide them through the process leading to analysis of the options for managing potential sub-chronic or chronic risks. As such, it is a tool applicable for use during the initial management of a situation involving PFAS contamination of drinking water. The logic diagram also fits within the context of tools already being used within Québec's network of public health actors, which facilitates its implementation.

The logic diagram does not propose different management options for the various contamination profiles or situations that may be encountered. Analysis of the various management options is entrusted to the responsible authorities (refer to the *Reference framework*). However, it is important to note that the removal of PFAS from drinking water presents significant challenges, and that management options for this type of contamination involve a high level of complexity. Appropriate treatment technologies for PFAS removal are costly, sometimes difficult to implement, and vary in effectiveness depending on the nature of the targeted contamination (7). In addition, effective water treatment involves concentrating PFAS residues in matrices that must be properly managed to avoid recontamination of the environment during disposal of these matrices. Furthermore, point-of-use treatments are the responsibility of individuals, and do not always represent effective and equitable solutions. As regards alternative water sources, these can be hard to find and present their own logistical challenges. Moreover, bottled water generates an additional load of waste, which is difficult to justify from a sustainable development perspective, without necessarily being free from contamination. As mentioned in the preface, this logic diagram is subject to rapidly evolving new scientific knowledge and additional management considerations. The criteria could be adapted or other substances could be added based on these developments. It is important to note that criteria were selected using a simplified approach, in order to quickly equip

[21] See footnote 14.

stakeholders. A further limitation of the logic diagram is inherent in any toxicological risk assessment process; namely, uncertainties affect the choice of critical effects and the derivation of toxicological reference values and guideline values. Finally, the uncertainties specific to the assessment of a mixture of substances, whose components do not necessarily have the same physico-chemical or toxicity properties, are highly applicable in the case of PFAS.

Indeed, the applicability of the logic diagram rests on the premise that the PFAS concentration data being assessed are valid. However, obtaining such data can prove complex in situations where the characterization of the contamination is uncertain (diffuse contamination, variable over time, having begun at an unknown time, unidentified source or multiple sources, analytical challenges for characterization, etc.). Since the *PFAS Logic Diagram* is designed to allow for a rapid risk assessment, initial recourse to data reflecting high exposure is appropriate in the immediate absence of representative population data.

4 CONCLUSION

The rationale for producing this document derives from the complexity of assessing and managing the health risks associated with PFAS in drinking water. Its purpose is to provide public health actors with the tools they need for the initial management of this type of situation. More specifically, the *PFAS Logic Diagram* offers a rapid approach to risk assessment using generic benchmarks based on the sub-chronic and chronic exposure of populations. Exceedance of these benchmarks points toward the relevance of carrying out a more in-depth risk assessment to support the process of analyzing risk management options. Finally, the *PFAS Logic Diagram* is intended to support the professional judgement of public health actors, and thus serves as a complement to other documents and tools related to chemical contamination of drinking water that are available to these professionals.

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APPENDIX 1 COMPILATION OF TOXICOLOGICAL REFERENCE VALUES AND GUIDELINE VALUES

COMPILATION OF TOXICOLOGICAL REFERENCE VALUES

The methodology used to research and select toxicological reference values (TRVs) published by recognized organizations (8) was developed by the INSPQ's Équipe scientifique sur les risques toxicologiques et radiologiques[22]. The aim of this process is to identify several TRVs established by various recognized organizations, classified as what are termed primary and secondary sources.[23]

Briefly, primary sources are public health reference organizations that have detailed a reproducible methodology for developing TRVs, whose supporting documents are subject to a peer or an expert committee review process. These are international or national organizations. As regards secondary sources, these belong to national or regional organizations (e.g., provinces, U.S. states) whose methodology for developing TRVs is not as thoroughly detailed as that of primary sources, and whose supporting documents have not necessarily been peer-reviewed.

In addition to the sources listed in Table A1-1 and A1-2 (p. 15), TRVs proposed by the U.S. EPA's *Drinking Water Health Advisories* have been compiled (5,16). Using the criteria described above, "final" documents were classified as primary sources, while interim documents were classified as secondary sources. **The compilation of TRVs for PFAS was carried out between late January and mid-February 2023.**

[22] The detailed methodology is available on request.

[23] It should be noted that, in the past, TRVs proposed by organizations classified as primary and secondary sources have regularly been used by the Équipe scientifique sur les risques toxicologiques et radiologiques (ESRTR), based on the quality of the work carried out by these institutions.

Table A1-1 Primary sources of toxicological reference values (TRVs)

Organization	Source of TRV
Anses	Anses toxicity reference values (TRVs)
Anses	Avis et rapports sur Avis du comité d'experts spécialisé (CES) "Eaux" (expert committee on water)
ATSDR	Minimal risk levels for hazardous substances (MRL)
EFSA	Scientific reports and opinions published in the *EFSA Journal*
WHO	*Drinking-water quality guidelines*
WHO/CICAD	Concise international chemical assessment documents (CICADs)
WHO/JECFA	Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)
WHO/JMPR	Inventory of evaluations performed by the Joint Meeting on Pesticide Residues (JMPR)
U.S. EPA	Integrated Risk Information System (IRIS)
U.S. EPA	Human health benchmarks for pesticides (HHBP)

Anses: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (France); ATSDR: Agency for Toxic Substances and Disease Registry; EFSA: European Food Safety Authority; WHO: World Health Organization; U.S. EPA: United States Environmental Protection Agency.

Table A1-2 Secondary sources of toxicological reference values (TRVs)

Organization	Source of TRV
MDH	Human health-based water guidance table
OEHHA	Toxicity criteria on chemicals evaluated by OEHHA
Health Canada	Guidelines for Canadian Drinking Water Quality – Technical documents
Health Canada (PMRA)	Proposed decisions (PRDs, PRVDs, etc.)
TCEQ	Final development support documents (DSDs) – Effects screening levels (ESLs), inhalation reference values (ReVs) and inhalation unit risk factors (URFs)
U.S. EPA	Provisional peer-reviewed toxicity values (PPRTVs) assessments[A]

PMRA: Pest Management Regulatory Agency; MDH: Minnesota Department of Health; OEHHA: California Office of Environmental Health Hazard Assessment; TCEQ: Texas Commission on Environmental Quality.

[A] This source is considered secondary because of its "provisional" nature.

In all, 37 specific TRVs[24] were compiled for 10 individual PFAS and a single TRV for the sum of four PFAS (PFOA, PFOS, PFNA and PFHxS).

[24] TRVs were considered "substance-specific" when they were based on toxicological studies documenting that same substance; i.e., they did not use other PFAS as "proxies" in the TRV derivation process.

COMPILATION OF GUIDELINE VALUES FOR DRINKING WATER

All guideline values[25] (for individual substances and for the sum of PFAS) proposed by organizations classified as primary and secondary sources were compiled. In addition, the following documents were consulted, since they contained recent reviews of guideline values in the United States and Europe:

- Cordner et al. (2019). Guideline levels for PFOA and PFOS in drinking water: The role of scientific uncertainty, risk assessment decisions, and social factors (17).
- Post. (2021). Recent US state and federal drinking water guidelines for per-and polyfluoroalkyl substances (18).
- WHO. (2022). PFOAS and PFOA in Drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality (Version for public review) (6).
- Teymoorian et al. (2023). Tracking PFAS in drinking water: A review of analytical methods and worldwide occurrence trends in tap water and bottled water (19).

The compilation of guideline values for drinking water was also carried out between late January and mid-February 2023.

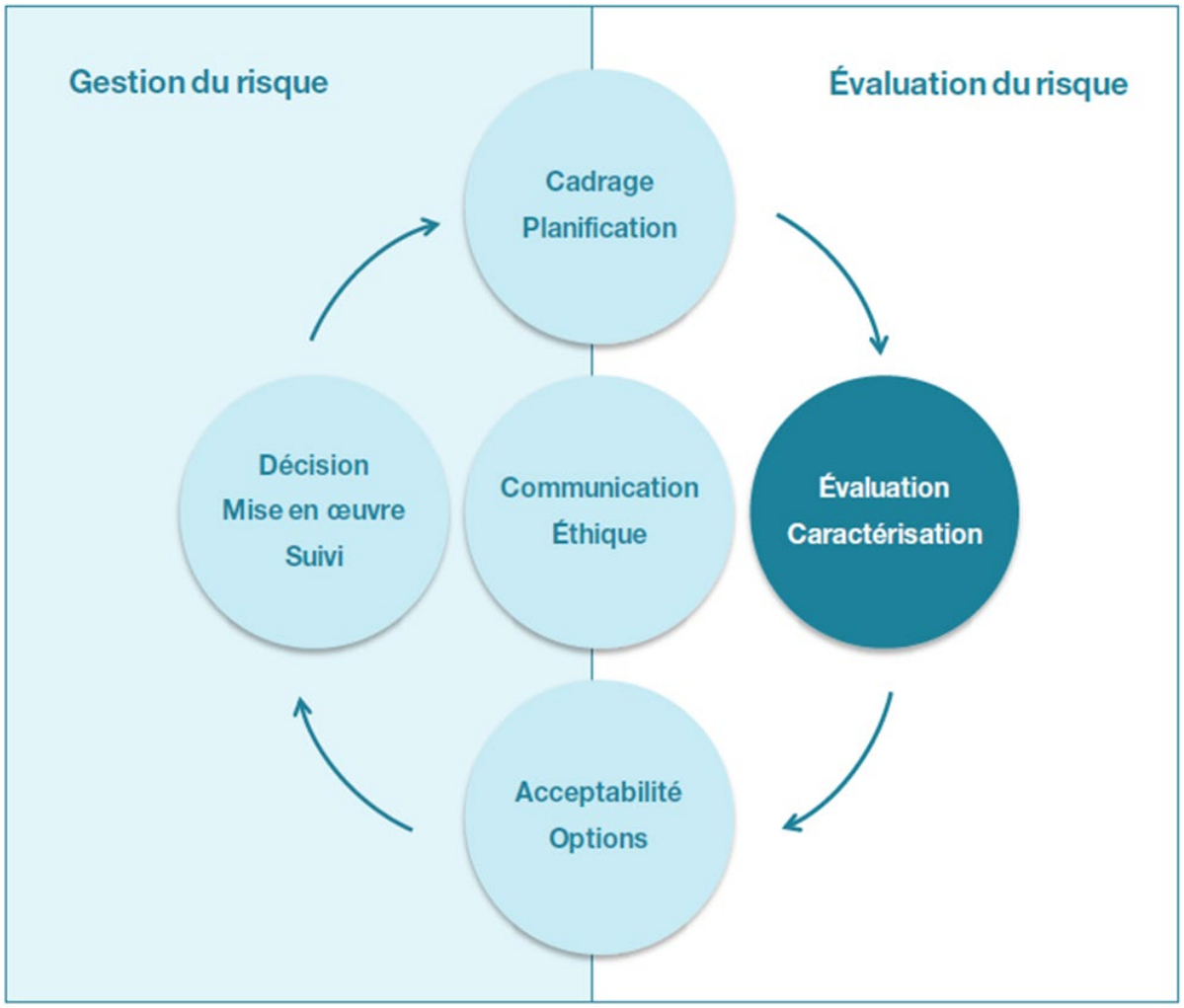
Finally, the U.S. EPA's proposal, published in March 2023 (15), for a regulatory framework including non-enforceable, health-based *maximum contaminant level goals* (MCLGs) and mandatory *maximum contaminant levels* (MCLs) was also included in the compilation process.

In total, 125 guideline values were compiled. Most of these were for individual PFAS, including 20 different substances. Fourteen guideline values were for the sum of PFAS (either for the sum of some PFAS or for the sum of "total" PFAS measured).

[25] Including health and management guideline values, either final or under consultation.

APPENDIX 2 PUBLIC HEALTH RISK MANAGEMENT PROCESS IN THE *REFERENCE FRAMEWORK*

Figure A2-1 Phases of the process detailed in the *Reference framework* for public health risk management in Québec



Source: INSPQ, 2016.

APPENDIX 3 DERIVATION OF HEALTH GUIDELINE VALUES FOR THE LOGIC DIAGRAM

Health-based guideline values (HGVs) for sub-chronic and chronic exposure were derived by applying the INSPQ's *Méthodologie d'élaboration de valeurs guides sanitaires chroniques pour les contaminants chimiques de l'eau potable* (9). All HGVs were determined assuming a default relative water contribution of 20%. The applicable water intake volume corresponds to the greatest degree of protection, for the relevant age category, based on the critical effect and duration of exposure (sub-chronic or chronic). The reference doses[26] selected are the toxicological reference values (TRVs) deemed the most robust according to the simplified approach of the *Méthodologie standardisée* developed by the Équipe scientifique sur les risques toxicologiques et radiologiques (8)[27]. More details about the methodological choices made for each substance with regard to water intake and reference doses can be found in subsequent sections.

$$HGV_{with\ threshold} = RfD \times RSC / V_{water}$$

where:

$HGV_{with\ threshold}$ = Health-based guideline value based on a toxic effect with dose threshold (mg/l);

RfD = Reference dose (or maximum daily dose, mg/kg-day);

RSC = Relative source contribution of drinking water (unitless);

V_{water} = Volume of water consumed daily, adjusted for body weight (l/kg-day).

Sub-chronic health guideline values

The TRVs selected are the values proposed by the ATSDR in 2021 for sub-chronic exposure to PFOA, PFOS, PFHxS and PFNA (20). These values are the only ones of all the TRVs compiled that have been derived specifically for sub-chronic exposure[28] for these four substances. These TRVs are based on animal studies on the critical effect deemed most sensitive and toxicologically robust by the ATSDR. More information on these TRVs is given in Table A3-1 (p. 19).

[26] Namely, the ingestion toxicological reference values (TRVs) for threshold effects.

[27] Document available on request.

[28] These TRVs were derived for an "*intermediate*" exposure duration based on the ATSDR's classification; i.e., an exposure of 15 to 364 days.

Table A3-1 Toxicological reference values (TRVs), reference doses (RfD), selected for sub-chronic exposure, proposed by the ATSDR in 2021

Substance	Details of TRV					
	TRV (mg/kg/day)	Key study	Species	Critical effect (type of effect)	POD_{HED} (mg/kg/day)	UF_{total}
PFOA	3×10^{-6}	Koskela et al., 2016 (21)	Mouse	Skeletal alterations in offspring (developmental)	8.2×10^{-4}	300 (UF_A: 3; UF_H: 10; UF_L: 10)
PFOS	2×10^{-6}	Luebker et al., 2005 (22)	Rat	Delayed eye opening and reduced body weight of offspring (developmental)	5.2×10^{-4}	300 (UF_A: 3; UF_H: 10; UF_{BD}: 10)
PFHxS	2×10^{-5}	Butenhoff et al., 2009 (23)	Rat	Hypertrophy/hyperplasia of the thyroid follicular epithelium (endocrinal)	4.7×10^{-3}	300 (UF_A: 3; UF_H: 10; UF_{BD}: 10)
PFNA	3×10^{-6}	Das et al., 2015 (24)	Mouse	Reduced body weight and developmental delays (developmental)	1.0×10^{-3}	300 (UF_A: 3; UF_H: 10; UF_{BD}: 10)

RfD: dose of contaminant to which an individual can be exposed over a given exposure period without risking threshold toxic effects. This concentration is determined by the quotient between the starting point (POD) and the product of all uncertainty factors deemed appropriate. **POD:** point of departure, dose associated with a toxic effect presumed to be critical. This is derived from a dose-response relationship determined in an epidemiological study or a study carried out on laboratory animals. **HED:** human equivalent dose. **UF:** series of uncertainty factors applied to the POD associated with a threshold effect. These factors make it possible to consider the uncertainty generated by using extrapolated data to determine a TRV applicable to conditions different from those under which the POD was obtained. **UF_A:** interspecies extrapolation factor. **UF_H:** extrapolation factor for human interindividual variability. **UF_L:** extrapolation factor from a LOAEL. **UF_{BD}:** factor for gaps in available data. The ATSDR uses the term *modifying factor*.

All the parameters used to calculate sub-chronic HGVs are shown in Table A3-2 (p. 20). The critical effects tied to PFOS, PFOA and PFNA target the fetal development of the unborn child. Key studies for all three substances have reported developmental effects in rodent offspring following exposure of mothers during or prior to gestation (20). Consequently, the most relevant water intake volume for these three substances is that for pregnant women. However, the lifetime weighted water intake was selected for the derivation, since this intake volume is slightly more protective than that for pregnant women[29]. In the case of PFHxS, the critical effect is on the thyroid gland. The study was carried out on adult male rats exposed for 42 days. This critical effect was deemed relevant for all age groups. The water intake volume used to determine the HGV for this substance is therefore the most protective; i.e. that for infants. This intake volume

[29] The intake rate for pregnant women specified in the *HGV methodology* is 0.033 L/kg-day, while the lifetime rate corresponds to 0.035 L/kg-day. The derived HGV is barely modified by this methodological choice.

has been chosen to protect the general population, which could suffer from this effect and which is protected by the conservative choice of the infant intake rate, a rate that can only be present for a sub-chronic period during an individual's lifetime.

Table A3-2 Derived sub-chronic health guideline values (HGVs) and parameters used

Substance	Details of HGV			
	HGV (ng/L)	TRV (mg/kg/day)	RSC	V_{water} (L/kg-day)
PFOA	**17**	3×10^{-6}	20%	0.035 (lifetime)
PFOS	**11**	2×10^{-6}	20%	0.035 (lifetime)
PFHxS	**28**	2×10^{-5}	20%	0.144 (infants)
PFNA	**17**	3×10^{-6}	20%	0.035 (lifetime)

Chronic health-based guideline values

The ATSDR has not established a chronic TRV for these four compounds, and does not extrapolate from sub-chronic to chronic exposure durations. Chronic HGVs were not calculated for PFOA and PFOS, because the management-based values of 4 ng/L proposed by the U.S. EPA were deemed adequate. The chronic HGVs for PFHxS and PFNA were derived by adjusting the ATSDR's sub-chronic toxicological reference values (20) used previously, by adding an appropriate uncertainty factor based on the critical effect. For the PFHxS (endocrinal effect), a default uncertainty factor of 10 – to account for extrapolation from a sub-chronic study – was applied in accordance with the *HGV methodology*. For PFNA, the critical effect targets development and is therefore associated with a specific, restricted exposure window. Due to gaps in knowledge about the relationship between exposure and potential chronic effects for this substance, an additional uncertainty factor of 3 was added.
Given that the HGV is for chronic exposure (over 7 years), the lifetime water intake is deemed most relevant for both substances. All the parameters used to calculate chronic HGVs are shown in Table A3-3 (p. 21).

It should be noted that these two HGVs are very comparable to the HGVs recently proposed by the U.S. EPA in its regulatory framework under consultation (i.e., a HGV of 9 ng/L for PFHxS and of 10 ng/L for PFNA) (15).

Table A3-3 Derived chronic health guideline values (HGVs) and parameters used

Substance	Details of HGV			
	HGV (ng/L)	TRV (mg/kg/day)	RSC	V_{water} (L/kg-day)
PFHxS	**11**	2×10^{-6} **A**	20%	0.035 (lifetime)
PFNA	**6**	1×10^{-6} **B**	20%	0.035 (lifetime)

A TRV proposed by the ATSDR after application of an additional uncertainty factor of 10 (endocrinal effect).

B TRV proposed by the ATSDR after application of an additional uncertainty factor of 3 (developmental effect).

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