NC PFAS Rulemaking Package

Appendix A

Toxicological Summary Information
and
Derivation of
15A NCAC 02L .0202
Groundwater Quality Numerical Standards

Frances Nilsen, PhD,
Bridget Shelton, MEM
North Carolina Department of
Environmental Quality

All information is current as of May 3, 2024

Table of Contents

1. Overview 1

2. Toxicological Information 2

2.1. Types of Toxicological Values 4
2.1.1. Reference Dose (RfD) 4
2.1.2. Cancer Slope Factor (CSF) 5

3. North Carolina Water Quality Standards Development Information 8

3.1. Groundwater Standards Derivation 8
3.1.1. Toxicological Requirements 8
3.1.2. Groundwater Standards Equation 8

3.2. Exposure Factors used in NC Water Quality Standards Equations 10

3.3. EPA Analytical Method 1633 10

4.1 Perfluorooctane sulfonic acid (PFOS, CASRN 1763-23-1*)* 13

4.2 Perfluorooctanoic acid (PFOA, CASRN 335-67-1) 15

3.3. Hexafluoropropylene Oxide Dimer Acid (HFPO-DA; GenX; CASRN 13252-13-6) 16

4.4 Perfluorobutane Sulfonic Acid (PFBS; CASRN 375-73-5) 19

4.5 Perfluorononanoic acid (PFNA, CASRN 375-95-1) 21

3.6. Perfluorohexanesulfonic acid (PFHxS, CASRN 355-46-4) 23

3.7. Perfluorobutanoic Acid (PFBA; CASRN 375-22-4) 25

3.8. Perfluorohexanoic Acid (PFHxA, CASRN 307-24-4) 26

5. References 28

6. Appendix 32

6.1. Supplementary Tables 32

6.2. NC SSAB PFAS Toxicity Assessment Methodology Comparison 39

6.3. Ground Water Quality Standards Calculation Sheets 40
6.3.1. PFOS 02L Numerical Standard Calculations 41
6.3.2. PFOA 02L Numerical Standard Calculations 42
6.3.3. HFPO-DA 02L Numerical Standard Calculations 43
6.3.4. PFBS 02L Numerical Standard Calculations 44
6.3.5. PFNA 02L Numerical Standard Calculations 45
6.3.6. PFHxS 02L Numerical Standard Calculations 46
6.3.7. PFBA 02L Numerical Standard Calculations 47

List of Tables

Appendix A:
Proposed PFAS Water Quality Standards Supporting Information:
Toxicological Summary Information and Derivation 15A NCAC 02L .0202 - Groundwater Quality Numerical Standards

Table 1: The proposed NC Water Quality Standards for the eight PFAS compounds in the Rulemaking Package. 11

Table 2: The toxicological information used to derive the RfD (and CSF if appropriate) for each of the PFAS compounds included in the Rulemaking package. 12

Table A - 1: A comparison between the BMD and NOAEL or LOAEL approaches to modeling Cancer Slope Factors (CSF). 32

Table A - 3: The candidate RfDs for PFOS, excerpted from the EPA Toxicity Assessment for PFOS (EPA, 2024b). 33

Table A - 4: The candidate CSF for PFOS excerpted from the EPA Toxicity Assessment for PFOS (EPA, 2024b). 34

Table A - 5: Candidate RfDs for PFOA, table excerpted from EPA Tox Assessment for PFOA (EPA, 2024c). 35

Table A - 6: The candidate CSFs for PFOA, excepted from the EPA Tox Assessment on PFOA (EPA, 2024c). 36

Table A - 7: The candidate RfDs for HFPO-DA (GenX), excepted from the EPA Tox Assessment of GenX (EPA, 2021a). 36

Table A - 8: The candidate RfDs for PFBS, excepted from EPA HH Tx Values for PFBS (EPA, 2021b) 37

Table A - 9: The RfD information that the ATDSR MRL and EPA RfD for PFNA are based on, excerpted from the ATSDR Toxicological Profile for Perfluoroalkyls (ATSDR, 2021). 37

Table A - 10: The RfD information that the ATDSR MRL and EPA RfD for PFHxS are based on, excerpted from the ATSDR Toxicological Profile for Perfluoroalkyls (ATSDR, 2021). 37

Table A - 11: The candidate RfD values based on organ/system specific effects of PFBA exposure; excerpted from the EPA IRIS Assessment of PFBA (EPA, 2022b) 38

Table A - 12: The candidate RfD values based on organ/system specific effects of PFHxA exposure; excerpted from the EPA IRIS Assessment of PFHxA (EPA, 2023a) 38

1. Overview

The intended purpose of this document is to provide a summary of the toxicological basis for the development of the PFAS water quality standards that are being proposed for the state of North Carolina. This document highlights the principal studies and health effects used in the determination of the toxicological values that are required for rulemaking. A complete description of the toxicological values and the requirements for rulemaking in North Carolina are described in subsequent sections.

There are eight PFAS compounds that are included in the NC PFAS Rulemaking Package. These PFAS were selected for rulemaking because all eight of these PFAS compounds have a significant literature base, from which health effects can be determined; the literature bases for all eight PFAS compounds have been evaluated by a federal agency; all eight PFAS compounds have health effects data to support the derivation of the necessary toxicological values, all eight PFAS compounds have been detected in NC's environmental media; and there is a final US Environmental Protection Agency (EPA) test method for measuring chemicals in different environmental media (EPA, 2024d) The PFAS compound that are included in the NC PFAS Rulemaking Package are:

- Perfluorooctane sulfonic acid (PFOS, CASRN 1763-23-1),
- Perfluorooctanoic acid (PFOA, CASRN 335-67-1),
- Hexafluoropropylene Oxide Dimer Acid (HFPO-DA; GenX; CASRN 13252-13-6),
- Perfluorobutane Sulfonic Acid (PFBS; CASRN 375-73-5),
- Perfluorononanoic acid (PFNA, CASRN 375-95-1),
- Perfluorohexanesulfonic acid (PFHxS, CASRN 355-46-4),
- Perfluorobutanoic Acid (PFBA; CASRN 375-22-4),
- Perfluorohexanoic Acid (PFHxA, CASRN 307-24-4).

Six of the eight PFAS compounds that are included in the NC PFAS Rulemaking Package are included in the EPA National Primary Drinking Water Regulation (NPDWR). The PFAS compounds included in the NPDWR are PFOS, PFOA, HFPO-DA, PFBS, PFNA, and PFHxS (Federal Register, 2023). The other two PFAS that are included in the NC PFAS Rulemaking Package are PFBA and PFHxA which have been comprehensively evaluated by the EPA and have not been included in the NPDWR.

2. Toxicological Information

The toxicological information that was used to support the NC PFAS Rulemaking Package was provided in toxicological evaluations and reports issued by a federal agency, specifically the EPA or the Centers for Disease Control and Prevention's (CDC) Agency for Toxic Substances and Disease Registry (ATSDR). When the EPA and ATSDR conduct toxicological evaluations, specific reference values that indicate the toxicity of that chemical are derived from all toxicological literature and data available for that chemical. Reviewing the existing toxicological information is a lengthy process and is done following a systematic method to achieve consistency between the reference values of each chemical and each program or agency that conducts the review. Both, the EPA and ATSDR federal programs follow the Guidelines for Development of Toxicological Profiles that were developed by the EPA and the US Department of Health and Human Services (DHHS) (Federal Register, 1987). The Guidelines provide a high-level description of the systematic process that the toxicological profiles follow. Each agency has since developed guidelines that provide greater detail throughout all steps in the process.

The Guidelines include a list of general principles that the Agencies will follow, including, that the *"primary function of the profiles is to present and interpret the available toxicological and human data on the substances being profiled; these data may be used to evaluate the significance to individuals and the public-at-large of current or potential exposures to the subject hazardous substances. The profiles also will review the adequacy of available data on the substances and will identify toxicological data needs for which research programs should be designed".* The Guidelines provide extensive details regarding the development of toxicological profiles and can be found in the Federal Register. There is a specific list of required information that the toxicological profiles must include, at a minimum (Federal Register, 1987). The required information is:

(A) An examination, summary, and interpretation of available toxicological information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

All federal toxicological evaluations that are used to support the NC PFAS Rulemaking Package were published in 2021 or more recently. The titles and citations of each evaluation are provided below in the individual PFAS descriptive sections and can be found in the reference list. Six of the eight PFAS that are included in the NC PFAS Rulemaking Package are also included in the EPA's National Primary Drinking Water Regulation (NPDWR). The remaining two of the eight PFAS compounds have been thoroughly evaluated by the EPA's Integrated Risk Information System (IRIS) program, also providing a high level of confidence in that toxicological information.

EPA National Primary Drinking Water Regulation (NPDWR) PFAS Compounds

The six PFAS compounds included in the proposed NPDWR that was announced on March 14, 2023 under the Safe Drinking Water Act (SDWA) are PFOS, PFOA, HFPO-DA, PFBS, PFNA, and PFHxS (Federal Register, 2023). The toxicological details for each of these compounds have been thoroughly evaluated by the EPA and were deemed robust enough for inclusion in a federal drinking water regulation.

The EPA's Toxicity Assessments for PFOS, PFOA, HFPO-DA, and PFBS were prepared by the Health and Ecological Criteria Division, in the Office of Science and Technology, within the Office of Water (OW) of the EPA. The pertinent toxicological information, including the reference dose (RfD), and cancer slope factor (CSF) where available, were published in the Federal Register with the proposed NPDWR and is further discussed below (Federal Register, 2023).

The EPA included PFNA and PFHxS in the NPDWR based on the Toxicological Profile for Perfluoroalkyls provided by the CDC's Agency for Toxic Substance and Disease Registry (ATSDR) (ATSDR, 2021; Federal Register, 2023). The profile provided by ATSDR was conducted in accordance with both ATSDR and EPA guidelines that were originally published in the Federal Register on April 17, 1987, and met recent updates regarding content and evaluation (Federal Register, 1987). The pertinent toxicological information, specifically, the RfDs for these PFAS are discussed below.

EPA Integrated Risk Information System (IRIS) PFAS Compounds

The EPA's Integrated Risk Information System (IRIS) Assessments for PFBA, and PFHxA were prepared by the Center for Public Health and Environmental Assessment (CPHEA), in the Office of Research and Development (ORD) at the EPA. The IRIS assessments provide toxicity values for health effects resulting from chronic chemical exposure as well as the RfD and CSF. The IRIS assessments meet the 1987 Guidelines as well as the recently updated guidance from EPA specific to IRIS assessments (EPA, 2022c).

Comparison of Toxicological Evaluations

DEQ conducted a comparative review of the ATSDR, EPA Health and Ecological Criteria Division, and EPA IRIS programs methods and derived PFAS values and determined that the information provided by each program was of equivalent quality. DEQ also requested feedback from the Secretaries Science Advisory Board (SAB). The SAB discussed the differences in methodologies between the toxicity assessments that the EPA and ATSDR conducted at their meeting held on April 3, 2024. The tables that the NC SSAB reviewed are provided in Appendix Section 6.2. The NC SSAB concluded that that the non-IRIS EPA assessments and the EPA's RfDs based on the CDC ATSDR assessments are adequate and of comparable fit-for-purpose to the EPA's IRIS assessments. The meeting recording where this discussion can be found here, between the 40 minute and 2-hour time stamp: 04 03 24 SSAB Meeting Recording (youtube.com).

2.1. Types of Toxicological Values

There are two types of toxicological values that are relevant to the 02L NC PFAS Rulemaking process. They are the Reference Dose (RfD), and the Cancer Slope Factor (CSF).. The RfD and the CSF come from the federal toxicity assessments. Each of these values and their derivation process is described below.

2.1.1. *Reference Dose (RfD)*

The Reference Dose (RfD) is an estimate of a daily exposure to the human population, including sensitive subgroups, that is likely to be without an appreciable risk of deleterious effects during a lifetime (EPA, 1993). The RfDs that are provided for the PFAS compounds in this document were derived by the EPA and the CDC's ATSDR. Both of these federal programs follow the Guidelines for Development of Toxicological Profiles that was developed by the EPA and the DHHS (Federal Register, 1987). Following the Guideline requirements, the available literature, and the studies that are of the highest quality and/or most appropriate toxicological endpoints are selected for further evaluation and comparison to derive a RfD. The initial evaluation of these studies requires the identification of adverse effects in a dose-response experiment, or dose-dependent epidemiology study. The concentration at which the adverse effects are observed becomes the point of departure (POD), where the model system departs homeostasis and adverse effects occur instead. The PODs from these studies are converted to a Human Equivalency Dose (POD_{HED}) using the pre-determined human clearance factor for each chemical and/or standardized modeling approaches. The most appropriate POD_{HED} is selected for derivation of the RfD.

The uncertainty of the studies that were evaluated for the POD_{HED} is accounted for systematically. There are several individual Uncertainty Factors (UF) for each type of uncertainty, all of which are combined for the total UF. The individual UFs account for:

- UF_H = the variation in sensitivity of the human population (i.e., intraspecies variability);
- UF_A = the uncertainty in extrapolating animal data to humans (i.e., interspecies variability);
- UF_S = the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure);
- UF_L = the uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and
- UF_D = the uncertainty associated with extrapolation from animal data when the database is incomplete.

The value chosen for each UF depends on the quality of the studies available, the extent of the database, and scientific judgement. The UFs are assigned a value of 1, 3, or 10 and justification of the assigned value is always provided in the EPA documentation where RfDs are derived (EPA, 2002).

$$RfD = POD_{HED}/UF_C$$

The RfD is calculated by dividing the POD_{HED} by the total or composite UF (UF_C). The overall chronic RfD is then selected from the health specific RfDs derived for each of the high-quality studies, if more than one health outcome is identified. The overall RfD that is derived is available for use in health risk assessments (EPA, 2012).

2.1.2. *Cancer Slope Factor (CSF)*

The CSF denotes the cancer risk per unit of chemical dose and is expressed as concentration of chemical dose per kilogram body weight per day (dose [mg or ng]/kg/day). The CSF can be used to compare the relative potency of different chemical substances (EPA, 1992). The CSFs that are provided for the PFAS compounds in this document were derived by the EPA following the Guidelines for Development of Toxicological Profiles developed by the EPA and the Department of Health and Human Services (DHHS) (Federal Register, 1987).

The carcinogenicity of a chemical is described in the designated "*Toxicity*" section of the profiles alongside a summary of the relevant scientific studies, and exposure scenarios (Federal Register, 1987). Following the Guideline requirements listed above, the existing literature and available data was evaluated for derivation of a CSF, in the same method that is used to evaluate literate and data for a RfD. The calculation of a CSF begins with identification of the minimum dose that led to an adverse effect, the POD, since this is the dose that caused the system to depart from homeostasis. EPA's 2005 Guidelines for Carcinogen Risk Assessment recommends modeling the dose-response data from each high-quality study based on the adverse effects observed using the widely accepted method from the publicly available Benchmark Dose Software (BMDS) program which makes use of the Benchmark Dose Approach (both described below)(EPA, 2005). The software fits models to the data from the studies to extrapolate to lower doses than those that were used in the studies.

2.1.2.1. Benchmark Dose (BMD) Approach

Health risk assessments often include an analysis of the toxicological dose-response data and health-related outcomes. The dose-response analysis includes defining a POD and extrapolating the POD for relevance to human populations (POD_{HED}). The Benchmark Dose (BMD) approach is named for modeling the dose-response data to determine the specific doses that are related to the chosen health outcome at the low end of the dose-response data – these are called "benchmark doses" or "benchmark responses" (BMDs or BMRs). The BMDs identified can be used as PODs for extrapolation of health effects data, and for comparison of the dose-response results across studies and health outcomes. The approach is similar for non-cancer and cancer outcomes. The difference in the approach between the two types of outcomes can be the selected POD, and whether a linear or non-linear extrapolation is used for dose-response modeling. The identification of a POD and the applied modeling leads to the calculation of a RfD or a CSF for use in health risk assessments (EPA, 2012).

The BMD approach was developed to address the recognized limitations of the previously used method for non-cancer outcomes, since it incorporates and conveys more information than the preceding method (i.e., the No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) approach). The NOAEL/LOAEL method is still used when there is not enough data to facilitate the BMD method. When applicable, the BMD approach provides a consistent methodology for both cancer and non-cancer outcomes, and a calculated RfD or CSF that is independent of the study design that the data was extracted from (for a more detailed comparison, see Table A-1).

2.1.2.2. BMDS Software

The Benchmark Dose Software (BMDS) has been freely available to the public from the EPA since 2000 and is routinely updated (EPA, 2022a). The BMDS facilitates the calculation of the BMD through application of mathematically fitted models to the dose-response data and makes a technical toxicological analysis and complex modeling approach seem simple. The application of the BMDS results can have far-reaching implications and should be examined by an experienced toxicologist that understands the statistical approaches used and the underlying methods of the BMD approach.

The BMDS software determines a Benchmark Response (BMR) in the dataset (typically at the lower end of the dataset) which allows for the identification of the POD and to derive a protective RfD or CSF that may be based on a POD that is below the POD that was calculated only using the experimental data, if appropriate. If the POD has been identified from an experimental animal study, dosimetric adjustments are used to convert the doses used in the animal to lifetime continuous human-equivalent doses (HEDs).

The dosimetric adjustment factors (DAF) can account for different chemical clearance rate across species; converting an internal (serum) concentration to a dose concentration (mg/kg/day) that is applicable to humans; and other conversions necessary to interpret an animal-based study for lifetime human exposures (EPA, 2012). For the purposes of this document, the DAFs used in each PFAS compounds toxicity assessment are describe in their respective sections, when applicable, and presented in Table 4 as an Overall Dosimetric Adjustment Factor (oDAF) for ease of reference and interpretation of the values in Table 4.

Non-carcinogenic Endpoints

If the toxicological endpoint of the selected POD comes from a non-carcinogenic mode of action (MOA), a variety of models can be applied to the experimental animal data, and the model that best fits the data is used to select the BMR (EPA, 2012). The selected POD can then be converted to a POD_{HED} with DAFs, if appropriate, and the RfD can be calculated as described above.

Carcinogenic Endpoints

If the toxicological endpoint of the selected POD occurs from a carcinogenic mode of action (MOA) different models are used to suit the various carcinogenic MOAs. If the mode of action is unknown or mutagenic, a linear model is used, and the slope of the line results in the CSF. Mutagenic modes of action also require the evaluation of age-dependent adjustment factors to account for the sensitivity of children to carcinogenic outcomes. If the MOA is not mutagenic or another MOA that is consistent with linear extrapolation at low doses, a non-linear model is used for low dose extrapolation. In non-linear models, the POD is determined based on the key events of carcinogenesis reported in the study. The DAFs are applied to convert the POD into the POD_{HED}. Then the CSF is calculated by dividing the selected BMR by the POD_{HED}.

$$CSF = BMR / POD_{HED}$$

2.1.2.3. Cancer Classification

During the process of evaluating a chemical for carcinogenicity, the Guidelines for Carcinogenic Risk Assessment require a discussion of the weight of the carcinogenic evidence evaluated within the assessment, and a description of the conditions for carcinogenicity based on the evidence evaluated to be provided (EPA, 2005). The five carcinogenicity descriptors and a brief description of the evidence required for each descriptor are provided below. A detailed definition of each descriptor is available in the Guidelines for Carcinogenic Risk Assessment (EPA, 2005).

- ***"Carcinogenic to Humans"*** – indicates strong evidence of human carcinogenicity and covers different combinations of evidence.
- ***"Likely to be Carcinogenic to Humans"*** – appropriate when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "Carcinogenic to Humans."; evidence covers a broad spectrum.
  - The term "likely" can have a probabilistic connotation in other contexts, but its use as a here does not correspond to a quantifiable probability of whether the chemical is carcinogenic. This is because the data that support cancer assessments generally are not suitable for numerical calculations of the probability that an agent is a carcinogen.
  - Other health agencies have expressed a comparable weight of evidence using terms such as "Reasonably Anticipated to Be a Human Carcinogen" (NTP) or "Probably Carcinogenic to Humans" (International Agency for Research on Cancer).
- ***"Suggestive Evidence of Carcinogenic Potential"*** – appropriate when the weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion.
- ***"Inadequate Information to Assess Carcinogenic Potential"*** – appropriate when available data are judged inadequate for applying one of the other descriptors. Additional studies generally would be expected to provide further insights.
- ***"Not Likely to Be Carcinogenic to Humans***" - appropriate when the available data are considered robust for deciding that there is no basis for human hazard concern.

The 2005 guidelines are the most recent guidance document for carcinogenic risk assessment from the EPA, which updates the 1986 guidance document and the guidance provided in the Federal Register in 1980 (Federal Register, 1980; EPA, 1986). Previously in the 1986 document, the cancer classifications were provided in the form of hierarchical categories that should include a narrative summary of the weight of evidence. At the time of the 1986 hierarchical categories' inception, the EPA noted that for well-studied substances, the scientific data base will have a complexity that cannot be captured by any classification scheme, and emphasized the need for an overall, balanced judgment of the totality of the available evidence (EPA, 1986). The 2005 guidelines and cancer classifications described here formally replaced the 1986 hierarchical categories, and are used to succinctly communicate the strength of the database related to carcinogenic outcomes, and should always be used in tandem with the weight of evidence evaluation and the rest of the specific toxicological documentation (EPA, 2005).

3. North Carolina Water Quality Standards Development Information

Title 15A of the North Carolina Administrative Code (NCAC) provides for the derivation of groundwater quality standards in Rule 15A NCAC 02L .0202 - Groundwater Quality Standards. The Rule details specific requirements and procedures for the application of relevant toxicological values to derive water quality criteria to protect designated uses. These requirements and procedures are discussed below.

3.1. Groundwater Standards Derivation

15A NCAC 02L .0202 defines the criteria for preserving North Carolina's groundwaters. The groundwater quality standards represent the maximum permissible concentrations of contaminants released into the land or waters, ensuring they won't pose a risk to human health or compromise the groundwater's intended best use as a source of drinking water.

3.1.1. *Toxicological Requirements*

15A NCAC 02L .0202(d) states that groundwater quality standards are established as the least of:

(1) Systemic threshold (non-cancer) concentration
(2) Concentration that corresponds to an incremental lifetime cancer risk of $1x10^{-6}$
(3) Taste threshold limit value
(4) Odor threshold limit value
(5) Maximum contaminant level
(6) National secondary drinking water standard

The first two options in the list require toxicological values, these are the RfD (1; Systemic threshold (non-cancer) concentration), and the CSF (2; Concentration that corresponds to an incremental lifetime cancer risk of $1x10^{-6}$). Since the rule text states that a groundwater quality standard shall be the least of the listed values, all calculated values should be compared to determine which is the lowest and therefore the most protective value.

The rule text also provides a list of references that shall be used in establishing groundwater standards, they are:

(1) Integrated Risk Information System (U.S. EPA),
(2) Health Advisories (U.S. EPA Office of Drinking Water),
(3) Other health risk assessment data published by the U.S. EPA, or
(4) Other relevant, published health risk assessment data, and scientifically valid peer-reviewed published toxicological data.

The eight PFAS compounds that are included in the PFAS Rulemaking Package all meet these requirements, as the toxicological values were provided by the appropriate EPA programs and in some cases were evaluated by a second federal agency (CDC).

3.1.2. *Groundwater Standards Equation*

The equation to calculate the systemic threshold or non-cancer concentration and the equation to calculate the concentration that corresponds to an incremental lifetime cancer risk of $1x10^{-6}$ are below. These equations include exposure factors that are defined in the rule.

For non-carcinogens,

Groundwater Quality Standard (GWQS) equation:
GWQS = [(RfD x WT x RSC) / WI] * 1000

For carcinogens, the equation is provided by the EPA (EPA, 2000)*,*

Groundwater Quality Standard (GWQS) equation:
GWQS = [(RL x WT) / (q1* x WI)] * 1000

Acronyms

RfD = reference dose
RL = Risk Level
WT = adult human body weight
RSC = relative source contribution
q1* = carcinogenic potency (slope) factor
WI = adult water intake

Groundwater exposure factors

WT = 70kg
WI = 2.0L / day
RSC = 0.2 for organics
RL = 1 in 10^6

3.2. Exposure Factors used in NC Water Quality Standards Equations

The exposure factors that are included in the water quality standards equations in the preceding section are important to note. The average adult human body weight (WT), average adult water intake based on the per capita estimate of community water ingestion at the 90th percentile for adults ages 21 and older (WI) (EPA, 2015).

The relative source contribution (RSC) and the risk level (RL) are provided in the EPA's Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health guidance document (EPA, 2000). The RSC is the percentage of the total exposure that comes from the source that the calculation pertains to, in this case, groundwater and surface water. The RSC is used for non-carcinogenic chemicals and there is a 10% or 20% value assigned for the RSC which is dependent upon the type of chemical (organic vs. inorganic) being calculated, since the majority of exposure generally comes from dietary sources and drinking water (EPA, 2000). Under 15A NCAC 02L .0202 (d)(1), criteria for Ground Water Quality Standards must use an RSC of 0.2 for organic substances and an RSC 0f 0.1 for inorganic substances. Since PFAS are organic substances, the RSC of 0.2 will be used to derive criteria for Groundwater Standards.

The RL is used when a chemical is known to be carcinogenic and corresponds to lifetime excess cancer risk levels. Previously, the EPA has provided guidance that surface water programs should use an RL of 10^{-7} to 10^{-5} however the publication of the Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health EPA published its national 304(a) water quality criteria at a 10^{-6} risk level, which EPA considers appropriate for the general population (EPA, 2000). NC has adopted an RL of 10^{-6} in the groundwater rules, 15A NCAC 02L .0202, for use in the derivation of water quality criteria for chemicals that are classified as carcinogenic.

3.3. EPA Analytical Method 1633

The EPA Analytical Method that will be used to detect and report the eight PFAS compounds included in the NC PFAS Rulemaking Package is Method 1633. Method 1633 the analytical method for detecting PFAS in a variety of media, including drinking water, surface water, groundwater, and complex matrix environmental mediums (EPA, 2024d). Method 1633 was validated in a multi-lab validation study that was conducted across ten independent laboratories (Willey *et al.*, 2023). Using the data gathered during the inter-lab validation study, the minimum detection limit (MDL) and the limit of quantification (LOQ) for each PFAS included in the analytical method were determined. Method 1633's quality control requirements are meeting the acceptable precent relative standard deviation (%RSD) metrics for each of the PFAS compounds through determination of a laboratory specific MDL and LOQ. The lab-specific LOQ must fall within the range of verified LOQs from the multi-lab validation report that are provided in Method 1633 (EPA, 2024d). As with any analytical method, there is inherent uncertainty in the measurements reported, and very small detections can be difficult to achieve. The range of LOQs span 1 – 16 ng/L, with %RSDs ranging from 21 – 29%, and average precent recoveries ranging from 65 – 155% (Table A-2). Since Method 1633 will be used to report PFAS concentrations based on the numeric NC WQS, the uncertainty or %RSD that is permissible in the analytical method will be considered with setting the regulatory WQS numerical values. Proposed Groundwater Quality Standards

The 15A NCAC 02L .0202(d) proposed water quality standards for the eight PFAS chemicals included in the NC PFAS Rulemaking Package and outlined above are individually discussed here. Each PFAS compound is

presented in the same fashion for ease of comparison. The sections are organized as a summary of the proposed NC Water Quality Standards based on the toxicological values (RfD, CSF) taken from the relevant federal guidance document. After the initial summary in each section, the detailed section discussing the relevant toxicological information that the EPA used to derive the RfD and CSF for each of the PFAS compounds is presented. This information is summarized in Tables 3 and 4 below.

Table 1: The proposed NC Water Quality Standards for the eight PFAS compounds in the Rulemaking Package.

PFAS	Federal Guidance Document	Proposed Water Quality Standards [a] (ng/L)
		02L GW
PFOS	EPA Office of Water Human Health Toxicity Assessment (draft until 03/24)	0.7 (RfD)
		0.9 (CSF)
PFOA		0.21 (RfD)
		0.001 (CSF)
HFPO-DA	EPA OW Human Health Toxicity Assessment (2021)	10*
PFBS	EPA OW Human Health Toxicity Assessment (2021)	2,000
PFNA	ATSDR Minimal Risk Level (2021); EPA MCLG Summary (2023)	10*
PFHxS		10
PFBA	EPA IRIS Assessment (2022)	7,000
PFHxA	EPA IRIS Assessment (2023)	4,000

[a] Rounded using the EPA Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (EPA, 2000).
*Value based on EPA established a maximum contaminant level (MCL) in April 2024 (EPA, 2024a).

Appendix A:
Proposed PFAS Water Quality Standards Supporting Information:
Toxicological Summary Information and Derivation 15A NCAC 02L .0202 - Groundwater Quality Numerical Standards

Table 2: The toxicological information used to derive the RfD (and CSF if appropriate) for each of the PFAS compounds included in the Rulemaking package.

PFAS	Critical Effect	POD	Overall Dosimetry Adjustment Factor (oDAF)	POD_{HED} (mg/kg/day)	Total UF	RfD^{f} (mg/kg/day)	Federal Guidance Document
PFOS	**Developmental:** PFOS in first and second trimesters and decreased birth weight (Wikström *et al.*, 2020) **Cardiovascular:** Increased serum total cholesterol (Dong *et al.*, 2019)	*Not Applicable, POD_{HED} was identified from human epidemiology studies.*		0.000001	10 [b]	0.0000001; (CSF = 39.5)	EPA Office of Water Human Health Toxicity Assessment (draft until March 2024)
PFOA	**Immune:** PFOA at age 5 on anti-diphtheria antibody concentrations at age 7; PFOA at age 5 and anti-tetanus antibody concentrations at age 7 (Budtz-Jørgensen and Grandjean, 2018) **Developmental:** PFOA in first and second trimesters and decreased birth weight (Wikström *et al.*, 2020) **Cardiovascular:** Increased serum total cholesterol (Dong *et al.*, 2019)	*Not Applicable, POD_{HED} was identified from human epidemiology studies.*		0.000000275	10 [b]	0.00000003; (CSF = 0.0000000293)	
HPFO-DA	**Hepatic:** Liver constellation of lesions in parental female mice (Dupont, 2010)	0.09*	0.14	0.01	3000 [b-e]	0.000003	EPA OW Human Health Toxicity Assessment (2021)
PFBS	**Developmental:** Decreased serum total T4 in newborn (PND1) mice (Feng *et al.*, 2017)	22*	0.0043	0.095	300 [b-d]	0.0003	EPA OW Human Health Toxicity Assessment (2021)
PFNA	**Developmental:** Decreased body weight and developmental delays in mice (Das *et al.*, 2015)	6.8 ^	0.0001518	0.001	300 [c]	0.000003	ATSDR Minimal Risk Level (2021); EPA MCLG Summary (2023)
PFHxS	**Thyroid:** Thyroid follicular epithelial hypertrophy/hyperplasia in rats (Butenhoff *et al.*, 2009)	73.2^	0.000064	0.0047	3000 [b-e]	0.000002	
PFBA	**Hepatic:** Increased hepatocellular (liver) hypertrophy **Thyroid:** Decreased total T4 (Butenhoff *et al.*, 2012)	5.6*	0.229	1.27	1000	0.001	EPA IRIS Assessment (2022)
PFHxA	**Developmental:** Decreased F1 body weight at PND 0 in rats (Loveless *et al.*, 2009)	10.6*	0.0045	0.048	100	0.0005	EPA IRIS Assessment (2023)

[*] Dose concentration (mg/kg/day); [^] Internal serum concentration (ug/ml); [b] UF based on interspecies extrapolation; [c] UF based on database limitations; [d] UF based on variation in the human population; [e] UF based on experimental duration extrapolation. [f] RfDs were rounded to one significant figure by EPA and ATSDR.

4.1 Perfluorooctane sulfonic acid (PFOS, CASRN 1763-23-1)

NC Water Quality Standards Proposed Values

The proposed 02L groundwater standard for PFOS is 0.7 ng/L (Table 1).

The proposed standard value is derived from the oral reference dose (RfD) of 0.0000001 mg/kg-day published by the EPA in the *Toxicity Assessment and Proposed Maximum Contaminant Level Goal for Perfluorooctane Sulfonic Acid (PFOS) in Drinking Water* (EPA, 2024b). The RfD was based on the developmental and cardiovascular endpoints of low birth weight and increased total cholesterol seen in epidemiological studies.

A Cancer Slope Factor (CSF) of 39.5 mg/kg/day was also published by the EPA in the *Toxicity Assessment and Proposed Maximum Contaminant Level Goal for Perfluorooctane Sulfonic Acid (PFOS) in Drinking Water* (EPA, 2024b). The CSF was derived from studies that reported carcinomas in rodents. PFOS has been classified as a "*Likely Human Carcinogen*" by the EPA, and the EPA has established a Maximum Contaminant Level Goal of zero for PFOS due to its carcinogenic classification (EPA, 2024b)(Table 4). When the surface water and groundwater standards calculations are calculated using each the CSF and the RfD, the non-cancer RFD-based equation provides a smaller value than the CSF-based value (Table 3; Appendix Section 6.3.1).

Either of the resulting health-based standards (CSF-based or RfD-based) are below the lowest quantifiable concentration or practical limit of analytical quantification (PQL) based on the national multi-laboratory validation conducted by the Department of Defense (DOD) and EPA in developing the final test method 1633 (Willey *et al.*, 2023). The multi-laboratory range of validated limits of quantification (LOQ) for PFOS by Method 1633 ranges from 1 – 4 ng/L and has a percent recovery that ranges from 70% - 140%, which equates to approximately ± 29 % uncertainty or relative standard deviation (RSD) (Willey *et al.*, 2023; EPA, 2024d).

Principal Study, Critical Effect, and Reference Dose (RfD) Selection

There were two high-quality studies identified for PFOS out of the ten studies that were evaluated for RfD development. These two critical studies are epidemiological studies that report the relationship between PFOS exposure and decreased birth weight following maternal exposure, and elevated cholesterol in a highly exposed human population (Dong *et al.*, 2019; Wikström *et al.*, 2020), Table A-3).

The developmental effects were identified by an association between PFOS concentration in maternal serum and infant birth outcomes, specifically decreased birth weight (Wikström *et al.*, 2020). The POD where the decreased birth weight was observed was 1.13×10^{-6} mg/kg/day (EPA, 2024b). The POD was divided by a UF of 10 to account for human variability, which resulted in a RfD of 1.13×10^{-7}, which was rounded to one significant figure for the final value of the RfD to be 1.0×10^{-7}, or 0.0000001 mg/kg/day PFOS.

The cardiovascular effect of increased cholesterol was identified in both the Center for Disease Control and Prevention's (CDC) National Health and Nutrition Examination Survey (NHANES) population and a highly exposed population (The C8 Health Project study population). The candidate RfDs from each study were similar and the overall RfD calculated for this cardiovascular outcome was the same as both studies (1.0 x

10^{-7}, or 0.0000001 mg/kg/day PFOS). Dong *et al.*, 2019 was chosen as the principal study since there was greater confidence in the analysis of this study in comparison to the other C8 population study that was evaluated by the EPA (EPA, 2023; Table A-3).

There were seven other studies and health outcomes evaluated for selection as the critical effect and principal study to support the PFOS RfD. The health outcomes evaluated in these other studies included immune effects, specifically diminished vaccine response in children, and hepatic effects that resulted in liver enzyme changes. Both health outcome specific RfDs are 2.0 x 10^{-7}, which is slightly greater than the selected RfD of 1.0 x 10^{-7} based on the Dong et al. 2019 study that reported increased cholesterol with PFOS exposure.

Cancer Slope Factor (CSF) Development

There were two studies identified for CSF development by the EPA. These two studies highlight the carcinogenic effect of PFOS in rodents, specifically hepatocellular adenomas and carcinomas, and pancreatic cell carcinomas (Table A-4). The data from both studies was determined to be of high quality by the US EPA (EPA, 2024b).

The CSF for PFOS was developed following the method described previously in section *2.1.2. Cancer Slope Factor (CSF).* The POD for dosed animals was converted into a POD_{HED} by multiplying the POD by the human clearance value for PFOS (0.128; EPA, 2023c). The POD_{HED} is equivalent to the constant exposure, by bodyweight, that would result in a serum concentration equal to the POD based on the study (EPA, 2024b). The BMDL for PFOS was calculated using the standardized method in EPA's BMDS program with multistage models for tumor dose-response data. A BMR of 10% was chosen based on EPA's BMD Technical Guidance to account for additional risk factors unaccounted for in the data or subsequent calculations (EPA, 2024b). The CSF was calculated by dividing the BMR of 10% by the POD_{HED}. The CSF was selected based on the lowest POD reported from the animal studies, which was calculated to be 39.5 $(mg/kg/day)^{-1}$ (Table A-4).

Maximum Contaminant Level (MCL) Information

In April 2024, the EPA established a National Primary Drinking Water Regulation (NPDWR) with an MCL for PFOS of 4 ng/L (EPA, 2024a). This MCL value is greater than the calculated numerical standard would be using the RfD, and so the value derived from the RfD is proposed for rulemaking in accordance with 15A NCAC 02L .0202(d) (0.7 ng/L, Table 1).

4.2 Perfluorooctanoic acid (PFOA, CASRN 335-67-1)

NC Water Quality Standards Proposed Values

The proposed 02L groundwater standard is 0.001 ng/L (Table 1).

The proposed WQ standard values are derived from the Cancer Slope Factor (CSF) of 0.0000000293 mg/kg/day published by the EPA in the *Toxicity Assessment and Proposed Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) in Drinking Water* (EPA, 2024c). The CSF and the RfD were both derived from human epidemiology studies (Table 4). The CSF-based water quality standards were selected because PFOA has been classified as a "Likely Human Carcinogen" by the EPA, and the EPA has established a Maximum Contaminant Level Goal of zero for PFOS due to its carcinogenic classification (EPA, 2024b).

When the surface water and groundwater standards calculations are calculated using each the CSF and the RfD, the cancer CSF-based equation provides a value that is at least 2 orders of magnitude lower than the non-cancer RfD-based equation (Table 3, Appendix Section 6.3.2).

Either of the resulting health-based standards (CSF-based or RfD-based) are below the lowest quantifiable concentration or practical limit of analytical quantification (PQL) based on the national multi-laboratory validation conducted by the Department of Defense (DOD) and EPA in developing the final test method 1633 (Willey *et al.*, 2023). The multi-laboratory range of validated limits of quantification (LOQ) for PFOA by Method 1633 ranges from 1 – 4 ng/L and has a percent recovery that ranges from 65% - 155%, which equates to approximately ± 27% uncertainty or relative standard deviation (RSD) (Willey *et al.*, 2023; EPA, 2024d).

Principal Study, Critical Effect, and Reference Dose (RfD) Selection

There were three high quality studies identified for PFOA out of the nine studies that were initially evaluated for RfD development. These studies documented the relationship between PFOA exposure and (i) decreased vaccine response in children, (ii) decreased birth weight following maternal exposure, and (iii) increased cholesterol levels in a highly exposed human population, respectively (Budtz-Jørgensen and Grandjean, 2018; Dong *et al.*, 2019; Wikström *et al.*, 2020). All three of these adverse health outcomes had the same POD and health-effect specific derived RfD (Table A-5).

The developmental effects were identified through an association between PFOA concentration in maternal serum and infant birth outcomes. Specifically, two studies documented a reduction in birth weight that was correlated with increasing PFOA concentration in maternal serum (Sagiv *et al.*, 2018; Dong *et al.*, 2019; Wikström *et al.*, 2020). The POD for birth outcomes was chosen from the Wikström *et al.*, 2020 study (2.92×10^{-7} mg/kg/day) because it was more conservative and protective than the POD reported in the Sagiv *et al.*, 2018 study (1.21×10^{-6} mg/kg/day). The POD value of 2.92×10^{-7} mg/kg/day was divided by an uncertainty factor of 10 to account for human variability, which resulted in the health-outcome specific RfD of 3.0×10^{-8} mg/kg/day PFOA (EPA, 2023b; Table A-5).

The cardiovascular effect of increased cholesterol was identified in both the NHANES population and a highly exposed population, the C8 Health Project study population (Steenland and Woskie, 2012; Dong *et*

al., 2019). The POD value was chosen from the Dong *et al.*, 2019 based on higher confidence in the analysis of this study and that the POD of 2.75 x 10^{-7} mg/kg/day was more protective. The POD was divided by an uncertainty factor of 10 to account for human variability, which resulted in the health-outcome specific RfD of 3.0 x 10^{-8} mg/kg/day PFOA, which is the same value as the developmental health outcome RfD.

The immune effects that were identified in response to PFOA exposure included decreased vaccine response in children, specifically decreased anti-tetanus and anti-diphtheria antibody responses. The PODs for the immune-related health outcomes were 3.05 x 10^{-7} mg/kg/day and 2.92 x 10^{-7} mg/kg/day, respectively (Budtz-Jørgensen and Grandjean, 2018). Each POD was divided by an uncertainty factor of 10 to account for human variability, which resulted in the health-outcome specific RFD value of 3.0 x 10^{-8} mg/kg/day PFOA for both immune outcomes.

As the health-outcome specific RfDs from each of the three high-quality studies were the same (3.0 x 10^{-8} mg/kg/day) so this value was selected as the overall RfD for PFOA. All other health-outcome specific RfDs that were considered were within one order of magnitude of this value (EPA, 2023b, Table A-5).

Cancer Slope Factor (CSF) Development

Both human epidemiology studies and animal model studies were evaluated in determining the CSF for PFOA. The animal-derived CSFs ranged from 8 to 53 $(mg/kg/day)^{-1}$ for PFOA based on testicular, hepatocellular, and pancreatic adenomas (EPA, 2024c). Two human epidemiology studies were examined, and both demonstrated a positive relationship between PFOA exposure and kidney cancer (EPA, 2023b; Table A-6).

The CSF for PFOA was developed following the method described in section *2.1.2. Cancer Slope Factor (CSF).* The study that reported the most conservative POD for kidney cancer was chosen for use in the calculation of the CSF for PFOA. The POD reported in this study was 3.52 x 10^{-3} ng/kg/day. Since this value was derived from a human study, the POD does not need to be converted to a POD_{HED}. The POD was divided by the human clearance value for PFOA (0.120; EPA, 2023b) to convert the internal dose-derived POD to an external dose CSF, resulting in a calculated CSF value of 0.0293 $(ng/kg/day)^{-1}$ for PFOA.

Maximum Contaminant Level (MCL) Information

In April 2024, the EPA established a National Primary Drinking Water Regulation (NPDWR) with an MCL for PFOA of 4 ng/L (EPA, 2024a). This MCL value is greater than the calculated numerical standard would be using the CSF, and so the value derived from the CSF is proposed for rulemaking in accordance with 15A NCAC 02L .0202(d) (0.001 ng/L, Table 1).

3.3. Hexafluoropropylene Oxide Dimer Acid (HFPO-DA; GenX; CASRN 13252-13-6)

NC Standards Proposed Values

The proposed 02L groundwater standard is 10 ng/L (Table 1).

All the proposed standard values are derived from the Reference Dose (RfD) of 0.000003 mg/kg/day published by the EPA in the *Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3) Also Known as "GenX Chemicals"* (EPA, 2021a). This RfD was selected based on liver effects (constellation of lesions including cytoplasmic alteration, hepatocellular single-cell and focal necrosis, and hepatocellular apoptosis) reported in an oral reproductive and developmental toxicity study with exposure of 53 - 64 days in mice (Dupont, 2010) (Table 4). The calculations that were used in the standards development equations are presented in Appendix Section 6.3.3.

Principal Study, Critical Effect, and Reference Dose (RfD) Selection

Several studies were evaluated to identify specific health outcomes to use for RfD development by the EPA. The studies evaluated report a consensus that liver is the most sensitive organ to HFPO-DA exposure. To filter the data for the effects that had systemic impact on the hepatic system, and were therefore considered more adverse, the effects that were observed at a gross and histological or pathological level were selected for further evaluation. Adverse liver effects were observed at low doses (5 mg/kg/day) in 28/day, 90/day, and reproduction/developmental oral exposure studies in mice (Dupont, 2010). The 28/day study was not considered any further since the longer duration studies also demonstrated adverse effects at low doses (EPA, 2021, Table A-7). The EPA's BMDS program was used to calculate the PODs based on 10% of the BMDL of the three doses used in the 90/day study. The BMDS software provided a POD for the male and female responses observed in the study, 0.14 and 0.09 mg/kg/day, respectively (EPA, 2021a).

The POD_{HED} values were calculated in two steps following EPA's guidance. First, by applying a dosimetry adjustment factor (DAF) specific to body weight (rather than clearance factors as used in PFHxA's DAF calculation) to the animal POD dose.

$$DAF = (BWa^{1/4}/BWh^{1/4})$$

where:
BWa = Animal Bodyweight.
BWh = Human Bodyweight.

A BWh of 80 kg was used with male and female mouse body weights of 0.0372 and 0.0349, and yielded DAFs of 0.15 and 0.14 mg/kg/day, respectively. Second, by using the DAF in the POD_{HED} calculation below, the POD_{HED}s for males and female were calculated to be 0.02 and 0.01 mg/kg/day, respectively.

$$POD_{HED} = \text{POD animal dose (mg/kg/day)} \times DAF$$

The RfDs were then calculated by dividing the total UF of 3000 (3 for interspecies extrapolation, 10 for human variability, 10 for duration extrapolation, and 10 for database deficiencies) from the POD_{HED} (Table 7). The resulting candidate RfDs were 7×10^{-6} and 3×10^{-6}, for males and females respectively. The more conservative candidate RfD was chosen as the overall chronic RfD for HFPO-DA, at 3×10^{-6} mg/kg/day of HFPO-DA.

Cancer Slope Factor (CSF) Development

The EPA has not classified HFPO-DA for carcinogenicity. The cancer potency factor is not available. Therefore, a human exposure concentration associated with an incremental lifetime cancer risk estimate of 1 x 10^{-6} cannot be calculated.

Maximum Contaminant Level (MCL) Information

In April 2024, the EPA established a National Primary Drinking Water Regulation (NPDWR) with an MCL for HFPO-DA of 10 ng/L (EPA, 2024a). This MCL value is lesser than the calculated numerical standard would be using the RfD, and so the value derived from the MCL is proposed for rulemaking in accordance with 15A NCAC 02L .0202(d) (10ng/L; Table 1).

4.4 Perfluorobutane Sulfonic Acid (PFBS; CASRN 375-73-5)

NC Standards Proposed Values

The proposed 02L groundwater standard is 2,000 ng/L (Table 1).

All the proposed standard values are derived from the Reference Dose (RfD) of 0.0003 mg/kg/day published by the EPA in the *Human Health Toxicity Values for Perfluorobutane Sulfonic Acid (CASRN 375-73-5) and Related Compound Potassium Perfluorobutane Sulfonate (CASRN 29420-49-3)* (EPA, 2021b). This RfD was selected based on developmental effects (decreased thyroid hormones in newborn mice) reported in an oral reproductive and developmental toxicity study (Feng *et al.*, 2017) (Table 4). The calculations that were used in the standards development equations are presented in Appendix A Section 6.3.4.

Principal Study, Critical Effect, and Reference Dose (RfD) Selection

There were three high-quality studies evaluated to derive the RFD from. These studies reported the relationship between PFBS exposure and numerous developmental effects, kidney effects, and thyroid effects (Lieder, Chang, *et al.*, 2009; Lieder, York, *et al.*, 2009; Feng *et al.*, 2017; NTP, 2019) (Table A-8). The EPA's BMDS program was used to calculate the POD_{HED} based on 10% of the BMDL for all health outcomes associated with these three critical studies (EPA, 2021b). Since the thyroid effects were observed in two species, in both sexes, and across life stages and different exposure durations in two separate high-quality studies, the thyroid effects were selected as the health outcome that the overall RfD would be based on (Feng *et al.*, 2017; NTP, 2019). The thyroid effects observed in the Feng *et al.*, 2017 study that included gestational exposure to PFBS for 20 days were more biologically significant than the NTP, 2019 study, so it was selected as the principal study the RfD would be based on.

The DAF that was used to convert the POD to the POD_{HED} included the sex-specific animal half-life values for both mouse and rat, and the average serum elimination half-life value for humans (EPA, 2021b). The BMDS software was used to determine the dose concentration that is ½ of a standard deviation from the control dose, since there is no information regarding what a biologically significant level of change is for PFBS in the sensitive developmental life stage. The developmental endpoints were entered into the BMDS software separately to find the best fit model and data for RfD derivation. The female mouse thyroid endpoints yielded the best fit model in the BDMS process, do the species and sex-specific DAF = 0.0043 was used to convert the POD to the POD_{HED} (EPA, 2021b).

The calculated POD_{HED} for PFBS based on the doses used in the Feng *et al.*, 2017 study was 0.095 mg/kg/day. The POD_{HED} was then divided by the total UF of 300 (3 for interspecies differences, 10 for database deficiencies, and 10 for human variability) and resulted in the overall RfD of 3×10^{-4} mg/kg/day PFBS.

Cancer Slope Factor (CSF) Development

The EPA has not classified PFBS for carcinogenicity. The cancer potency factor is not available. Therefore, a human exposure concentration associated with an incremental lifetime cancer risk estimate of 1×10^{-6} cannot be calculated.

Maximum Contaminant Level (MCL) Information

In April 2024, the EPA established a National Primary Drinking Water Regulation (NPDWR) for PFAS mixtures containing at least two or more of PFHxS, PFNA, HFPO-DA, and PFBS using a unitless Hazard Index (EPA, 2024a). No individual maximum contaminant level has been established for PFBS, so the value derived from the RfD is proposed for rulemaking, in accordance with 15A NCAC 02L .0202(d) (2,000 ng/L; Table 1).

4.5 Perfluorononanoic acid (PFNA, CASRN 375-95-1)

NC Standards Proposed Values

The proposed 02L groundwater standard is 20 ng/L (Table 1).

All the proposed standard values are derived from the Reference Dose (RfD) of 0.000003 mg/kg/day published by the EPA in the Federal Register and in the ATSDR Toxicological Profile for Perfluoroalkyls as an intermediate Minimal Risk Level (MRL) (ATSDR, 2021; Federal Register, 2023). This RfD was selected based on decreased body weight and developmental delays in mice (Das *et al.*, 2015) (Table 4). The calculations that were used in the standards development equations are presented in Appendix Section 6.3.5.

Principal Study, Critical Effect, and Reference Dose (RfD) Selection

There were three developmental studies evaluated to derive the MRL from. These studies reported the relationship between PFNA exposure and effects on offspring weight, survival, and postnatal development (Wolf *et al.*, 2010; Rogers *et al.*, 2014; Das *et al.*, 2015). The lowest internal serum concentration in mice that corresponded to the Lowest Observable Adverse Effects Level (LOAEL) for developmental effects was 10.9 ug.ml and the value corresponding to the No Observable Adverse Effects Level (NOAEL) was 6.8 ug/ml PFNA in mouse serum (Das *et al.*, 2015, Table A-9). Since the lowest observable adverse effects were seen in the Das *et al.*, 2015 study it was selected as the principal study that the MRL and subsequent RfD would be derived from , (ATSDR, 2021; Federal Register, 2023). Since the NOAEl was identified in mouse serum, which represents the internal dose the mouse received, rather than the dose given orally, different adjustment factors are used to account for the internal dose conversion into a HED. The $NOAEL_{HED}$ was calculated by multiplying the internal mouse serum concentration (6.8 ug/ml) by the 2.5-year elimination half-life (7.59×10^{-4}) and the volume distribution (0.2 ml/kg) and dividing the result by the gastrointestinal absorption factor (1). This results in the $NOAEL_{HED}$ of 0.001 mg/kg/day (ATSDR, 2021).

The calculated MRL was derived by multiplying the total UF of 30 (3 UF for extrapolation from animals to humans with dosimetry adjustment, 10 UF for human variability) by the modifying factor (MF) of 10 (for database limitations), and then dividing the $NOAEL_{HED}$ by the quotient. The calculated MRL for PFNA is 0.001 mg/kg/day.

$$MRL = NOAEL_{HED} \div (UFs \times MF)$$

The EPA notes that ATSDR MRLs and EPA RfDs are not necessarily equivalent (e.g., intermediate-duration MRL vs. chronic RfD; EPA and ATSDR may apply different uncertainty/modifying factors) and are developed for different purposes. In this case, EPA did not apply an additional UFs to calculate the HBWC for PFNA because the critical effect is identified in a developmental population (EPA, 2000). The MF used by ATSDR is equivalent to the database UF term used by the EPA, so that form of uncertainty was already accounted for in the ATDSR calculation. To derive the EPA's NPDWR value for PFNA of 10 ng/L, the 90th percentile two/day average water ingestion for lactating women (13 to < 50 years), 0.0469 L/kg/day, was used in their calculation, to match the developmental effects of the principal study and critical effect in the ATSDR profile.

Cancer Slope Factor (CSF) Development

The EPA and ATSDR have not classified PFNA for carcinogenicity. The cancer potency factor is not available. Therefore, a human exposure concentration associated with an incremental lifetime cancer risk estimate of 1×10^{-6} cannot be calculated according to the requirements of 15A NCAC 02L .0202(a)(2)(B).

Maximum Contaminant Level (MCL) Information

In April 2024, the EPA established a National Primary Drinking Water Regulation (NPDWR) with an MCL for PFNA of 10ng/L (EPA, 2024a). Since the MCL value is equal to the value derived from the RfD, value derived from the RfD is proposed for rulemaking in accordance with 15A NCAC 02L .0202(d) (10 ng/L; Table 1).

3.6. Perfluorohexanesulfonic acid (PFHxS, CASRN 355-46-4)

NC Standards Proposed Values

The proposed 02L groundwater standard is 10 ng/L (Table 1).

All the proposed standard values are derived from the Reference Dose (RfD) of 0.000002 mg/kg/day published by the EPA in the Federal Register and in the ATSDR Toxicological Profile for Perfluoroalkyls as an intermediate Minimal Risk Level (MRL) of 0.00002 mg/kg/day (ATSDR, 2021; Federal Register, 2023). There is an order of magnitude difference between the ATSDR MRL and the EPA RfD, which is described in detail below. Both values were based on the same critical thyroid effects observed in rats (Butenhoff et al 2009a, Table 4). The calculations that were used in the standards development equations are presented in the Appendix Section 6.3.6.

Principal Study, Critical Effect, and Reference Dose (RfD) Selection

There were four laboratory studies that were evaluated to derive the MRL from. These studies reported the relationship between PFHxS exposure and effects on the thyroid and liver of exposed rodents, and decreased litter size in (Butenhoff *et al.*, 2009; Bijland *et al.*, 2011; Chang *et al.*, 2018; Ramhøj *et al.*, 2018) The health effect that was selected as the critical effect was changes to the thyroid, since some epidemiology studies have shown a link between thyroid effects and PFHxS exposure in humans (Wen *et al.*, 2013). The laboratory study that the thyroid effects were observed in, Buttenhoff et al 2009, was selected as the principal study. The LOAEL in this study was 3 mg/kg/day of PFHxS, and the NOAEL was 1 mg/kg/day (ATSDR, 2021). The $NOAEL_{HED}$ was calculated by multiplying the internal mouse serum concentration (73.22 ug/ml) by the human clearance value (2.23×10^{-4}) and the volume distribution (0.2 ml/kg) and dividing the result by the gastrointestinal absorption factor (1). For the purposes of this document, the oDAF in Table 3 is 0.000064, which is the product of the human clearance value and the volume distribution. The $NOAEL_{HED}$ of 0.0047 mg/kg/day is the product of the internal serum concentration and the oDAF. (ATSDR, 2021).

The calculated MRL was derived by multiplying the total UF of 30 (3 UF for extrapolation from animals to humans with dosimetry adjustment, 10 UF for human variability) by the modifying factor (MF) of 10 (for database limitations), and then dividing the $NOAEL_{HED}$ by the quotient. The calculated MRL for PFHxS is 0.00002 mg/kg/day.

$$MRL = NOAEL_{HED} \div (UFs \times MF)$$

The EPA notes that ATSDR MRLs and EPA RfDs are not necessarily equivalent (e.g., intermediate-duration MRL vs. chronic RfD; EPA and ATSDR may apply different uncertainty/modifying factors) and are developed for different purposes. In this case, EPA did apply an additional UF to calculate the HBWC for PFHxS because the critical effect is identified in an adult rat population and not a developmental population, which was the case for PFNA (EPA, 2000). The MF used by ATSDR is equivalent to the database UF term used by the EPA, so that form of uncertainty was already accounted for in the ATDSR calculation. The EPA added a UF of 10 for extrapolation of the exposure duration, since the laboratory study was a sub chronic exposure (ATSDR, 2021; Federal Register, 2023). To derive the EPA's NPDWR value for PFHxS all the

combined UFs were divided from the $NOAEL_{HED}$, resulting in an RfD of 0.000002 mg/kg/day, a value one order of magnitude smaller than the ATSDR MRL (Federal Register, 2023)(Table A-10).

Cancer Slope Factor (CSF) Development

The EPA and ATSDR have not classified PFHxS for carcinogenicity. The cancer potency factor is not available. Therefore, a human exposure concentration associated with an incremental lifetime cancer risk estimate of 1×10^{-6} cannot be calculated.

Maximum Contaminant Level (MCL) Information

In April 2024, the EPA established a National Primary Drinking Water Regulation (NPDWR) with an MCL for PFHxS of 10ng/L (EPA, 2024a). The MCL value is lesser than the value derived from the RfD, so the MCL value is proposed for rulemaking in accordance with 15A NCAC 02L .0202(d) (10 ng/L; Table 1).

3.7. Perfluorobutanoic Acid (PFBA; CASRN 375-22-4)

NC Standards Proposed Values

The proposed 02L groundwater standard is 7,000 ng/L (Table 1).

All the proposed standard values are derived from the Reference Dose (RfD) of 0.001 mg/kg/day published by the EPA in the *IRIS Toxicological Review of Perfluorobutanoic Acid (PFBA, CASRN 375-22-4) and Related Salts* (EPA, 2022b). This RfD was selected based on decreased thyroid hormones and increased liver weight and hypertrophy (Butenhoff *et al.*, 2012)(Table 4). The calculations that were used in the standards development equations are presented in Appendix Section 6.3.7.

Principal Study, Critical Effect, and Reference Dose (RfD) Selection

Two high-quality studies were selected for further evaluation and RfD calculation. These studies report liver and thyroid effects from a 90/day exposure to PFBA in rodents (Butenhoff *et al.*, 2012; Feng *et al.*, 2017) and developmental effects from a gestational exposure lasting 17 days in rodents (Das *et al.*, 2015). The specific endpoints that were considered for RfD development in the Buttenhoff et al. 2012a study were increased liver weight and hypertrophy and decreased thyroid hormones (EPA, 2022b). The endpoints that were considered for RfD derivation from the Das et al. 2008 study were perinatal mortality, and delayed developmental effects including eye opening, vaginal opening, and preputial separation ((EPA, 2022b), Table A-11).

The PODs were determined using the EPA's BMDS where the BMD and 95% lower confidence limit on the BMD (BMDL) were estimated using a BMR to represent a minimal, biologically significant level of change of 10% based on the data presented in the Buttenhoff et al. 2012a study. The POD was determined to be 5.56 mg/kg/day PFBA. The DAF used was the quotient of the human clearance value and the species and sex-specific animal clearance value (0.229). The POD_{HED} of 1.27 was calculated by multiplying the POD by the DAF. The RfD was derived by dividing the POD_{HED} of 1.27 mg/kg/day by an uncertainty factor of 1000 (10 for variation in sensitivity among the human population, 3 for interspecies extrapolation, 10 for extrapolation of a subchronic effect level to a chronic effect level, and 3 for database deficiencies).

Cancer Slope Factor (CSF) Development

The EPA has not classified PFBA for carcinogenicity. The cancer potency factor is not available. Therefore, a human exposure concentration associated with an incremental lifetime cancer risk estimate of 1×10^{-6} cannot be calculated.

Maximum Contaminant Level (MCL) Information

There is currently no MCL for PFBA in the NPDWR (EPA, 2024a), so the value derived from the RfD is proposed for rulemaking in accordance with 15A NCAC 02L .0202(d) (7,000 ng/L; Table 1).

3.8. Perfluorohexanoic Acid (PFHxA, CASRN 307-24-4)

NC Standards Proposed Values

The proposed 02L groundwater standard is 4,000 ng/L (Table 1).

All the proposed standard values are derived from the Reference Dose (RfD) of 0.0005 mg/kg/day published by the EPA in the *IRIS Toxicological Review of Perfluorohexanoic Acid [PFHxA, CASRN 307-24-4] and Related Salts* (EPA, 2023a). This RfD was selected based developmental effects, specifically decreased postnatal weight, observed in a gestational 12/day oral exposure study in rodents (Loveless *et al.*, 2009) (Table 4). The calculations that were used in the standards development equations are presented in Appendix Section 6.3.8.

Principal Study, Critical Effect, and Reference Dose (RfD) Selection

There were five high-quality studies evaluated for RfD derivation. Of these five studies, two of the studies included early life exposures related to developmental health effects, which are most appropriate for estimating effects of lifetime exposure, so those two studies were evaluated further as well as the study that detailed decreases in female adult rodent red blood cell counts ((Loveless *et al.*, 2009; Iwai and Hoberman, 2014; Klaunig *et al.*, 2015),Table A-12).

These studies exposed rodents to PFHxA during critical windows of development. The developmental effects evaluated for POD derivation were decreased postnatal body weight and increased perinatal mortality (EPA, 2023a).

The PODs were determined using the EPA's BMDS where the BMD and BMDL were estimated using a BMR of 5% relative deviation from the control mean, instead of the 95% used in the derivation of the PFBA values. The BMR of 5% is used for developmental effects to account for health impacts occurring at this sensitive life stage (EPA, 2012). The POD derived based on these BMDS calculations was 10.62 (mg/kg-d), which was then multiplied by a Dosimetry Adjustment Factor (DAF) which was calculated from the ratio of human to animal clearance factors for PFHxA (1.84×10^{-3} L/kg-hr divided by 0.383 L/kg-hr [based on the Loveless *et al.*, 2009 study] = 0.0048 DAF) and applied to the POD.

$$\text{DAF} = \frac{\text{Human Clearance Factor}}{\text{Animal Clearnce Factor}}$$

To calculate the POD_{HED} of PFHxA, the POD of 10.62 mg/kg/day was multiplied by the DAF of 0.0048 L/kg-hr and then multiped by the normalization factor to convert the dosed chemical from sodium salt to free acid (molecular weight of the free acid divided by the molecular weight of the salt; 314/336 = 0.935), to result in a POD_{HED} of 0.048 mg/kg/day of PFHxA.

$$POD_{HED} = \text{POD animal dose (mg/kg/day)} \times \text{DAF}$$

The RfD of 0.0005 mg/kg/day was derived by dividing the POD_{HED} of 0.048 mg/kg/day by an uncertainty factor of 100 (3 for variation in sensitivity among the human population, 10 for interspecies extrapolation, 1 for extrapolation of a subchronic effect level to a chronic effect level, and 1 for database deficiencies).

Cancer Slope Factor (CSF) Development

The EPA has not classified PFHxA for carcinogenicity. The cancer potency factor is not available. Therefore, a human exposure concentration associated with an incremental lifetime cancer risk estimate of 1×10^{-6} cannot be calculated.

Maximum Contaminant Level (MCL) Information

There is currently no MCL for PFHxA in the NPDWR (EPA, 2024a), so the value derived from the RfD is proposed for rulemaking in accordance with 15A NCAC 02L .0202(d) (4,000 ng/L; Table 1).

5. References

ATSDR, C. (2021) 'Toxicological Profile for Perfluoroalkyls'. Available at: https://www.atsdr.cdc.gov/ToxProfiles/tp200.pdf (Accessed: 22 December 2023).

Bijland, S. *et al.* (2011) 'Perfluoroalkyl sulfonates cause alkyl chain length–dependent hepatic steatosis and hypolipidemia mainly by impairing lipoprotein production in APOE* 3-Leiden CETP mice', *Toxicological Sciences*, 123(1), pp. 290–303.

Budtz-Jørgensen, E. and Grandjean, P. (2018) 'Application of benchmark analysis for mixed contaminant exposures: Mutual adjustment of perfluoroalkylate substances associated with immunotoxicity', *PLoS One*, 13(10), p. e0205388.

Butenhoff, J.L. *et al.* (2009) 'Gestational and lactational exposure to potassium perfluorooctanesulfonate (K+PFOS) in rats: Developmental neurotoxicity', *Reproductive Toxicology*, 27(3–4), pp. 319–330. Available at: https://doi.org/10.1016/j.reprotox.2008.12.010.

Butenhoff, J.L. *et al.* (2012) 'Chronic dietary toxicity and carcinogenicity study with potassium perfluorooctanesulfonate in Sprague Dawley rats', *Toxicology*, 293(1), pp. 1–15. Available at: https://doi.org/10.1016/j.tox.2012.01.003.

Chang, S. *et al.* (2018) 'Reproductive and developmental toxicity of potassium perfluorohexanesulfonate in CD-1 mice', *Reproductive toxicology*, 78, pp. 150–168.

Darrow, L.A., Stein, C.R. and Steenland, K. (2013) 'Serum Perfluorooctanoic Acid and Perfluorooctane Sulfonate Concentrations in Relation to Birth Outcomes in the Mid-Ohio Valley, 2005–2010', *Environmental Health Perspectives*, 121(10), pp. 1207–1213. Available at: https://doi.org/10.1289/ehp.1206372.

Das, K.P. *et al.* (2015) 'Developmental toxicity of perfluorononanoic acid in mice', *Reproductive toxicology*, 51, pp. 133–144.

DeWitt, J.C. *et al.* (2009) 'Immunotoxicity of Perfluorooctanoic Acid and Perfluorooctane Sulfonate and the Role of Peroxisome Proliferator-Activated Receptor Alpha', *Critical Reviews in Toxicology*, 39(1), pp. 76–94. Available at: https://doi.org/10.1080/10408440802209804.

Dong, Z. *et al.* (2019) 'Using 2003–2014 US NHANES data to determine the associations between per-and polyfluoroalkyl substances and cholesterol: Trend and implications', *Ecotoxicology and environmental safety*, 173, pp. 461–468.

Dupont, D.C.C. (2010) *DuPont-18405-1037: An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice.*

EPA (1986) 'Guidelines for Carcinogen Risk Assessment'. Available at: https://cfpub.epa.gov/ncea/raf/car2sab/guidelines_1986.pdf.

EPA (1992) 'EPA's Approach for Assessing the Risks Associated with Chronic Exposure to Carcinogens. Background Document 2.' Available at: https://www.epa.gov/iris/epas-approach-assessing-risks-associated-chronic-exposure-carcinogens (Accessed: 22 December 2023).

EPA (1993) 'Reference Dose (RfD): Description and Use in Health Risk Assessments Background Document 1A'. Available at: https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments (Accessed: 22 December 2023).

EPA (2000) 'Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health'. Office of Science and Technology, Office of Water. Available at: https://www.epa.gov/sites/default/files/2018-10/documents/methodology-wqc-protection-hh-2000.pdf (Accessed: 2 January 2024).

EPA (2002) 'A Review of the Reference Dose and Reference Concentration Process'. Available at: https://www.epa.gov/sites/default/files/2014-12/documents/rfd-final.pdf.

EPA (2005) 'Guidelines for Carcinogen Risk Assessment'. Available at: https://archive.epa.gov/raf/web/pdf/cancer_guidelines_final_3-25-6.pdf (Accessed: 3 January 2024).

EPA (2012) 'Benchmark Dose Technical Guidance'. Available at: https://www.epa.gov/sites/default/files/2015-01/documents/benchmark_dose_guidance.pdf (Accessed: 22 December 2023).

EPA (2015) 'Human Health Ambient Water Quality Criteria: 2015 Update'. Available at: https://www.epa.gov/sites/default/files/2015-10/documents/human-health-2015-update-factsheet.pdf (Accessed: 31 January 2024).

EPA (2021a) 'Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3) Also Known as "GenX Chemicals"'. Available at: https://www.epa.gov/system/files/documents/2021-10/genx-chemicals-toxicity-assessment_tech-edited_oct-21-508.pdf (Accessed: 22 December 2023).

EPA (2021b) 'Human Health Toxicity Values for Perfluorobutane Sulfonic Acid (CASRN 375-73-5) and Related Compound Potassium Perfluorobutane Sulfonate (CASRN 29420-49-3)'. Available at: https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=542393 (Accessed: 22 December 2023).

EPA (2022a) 'Benchmark Dose Software VERSION 3.3 USER GUIDE'. Available at: https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=545595 (Accessed: 22 December 2023).

EPA (2022b) 'IRIS Toxicological Review of Perfluorobutanoic Acid (PFBA, CASRN 375- 22-4) and Related Salts'. Available at: https://iris.epa.gov/static/pdfs/0701tr.pdf (Accessed: 22 December 2023).

EPA (2022c) 'ORD Staff Handbook for Developing IRIS Assessments'. Available at: https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=545991 (Accessed: 16 February 2024).

EPA (2023a) 'IRIS Toxicological Review of Perfluorohexanoic Acid [PFHxA, CASRN 307-24-4] and Related Salts'. Available at: https://iris.epa.gov/static/pdfs/0704tr.pdf (Accessed: 22 December 2023).

EPA (2024a) 'Final PFAS National Primary Drinking Water Regulation'. Available at: https://www.epa.gov/system/files/documents/2024-04/pfas-npdwr-presentation_4.9.24_overview.pdf.

EPA (2024b) 'Human Health Toxicity Assessment for Perfluorooctane Sulfonic Acid (PFOS) and Related Salts'. Available at: https://www.epa.gov/system/files/documents/2024-04/main_final-toxicity-assessment-for-pfos_2024-04-09-refs-formatted_508c.pdf (Accessed: 3 May 2024).

EPA (2024c) 'Human Health Toxicity Assessment for Perfluorooctanoic Acid (PFOA) and Related Salts'. Available at: https://www.epa.gov/system/files/documents/2024-04/main_final-toxicity-assessment-for-pfoa_2024-04-09-refs-formatted.pdf (Accessed: 3 May 2024).

EPA (2024d) 'Method 1633; Analysis of Per- and Polyfluoroalkyl Substances (PFAS) in Aqueous, Solid, Biosolids, and Tissue Samples by LC-MS/MS. .' Available at: https://www.epa.gov/system/files/documents/2024-01/method-1633-final-for-web-posting.pdf (Accessed: 2 January 2024).

Federal Register (1980) 'Environmental Protection Agency Water Quailty Criteria Documents'.

Federal Register (1987) 'Notice of the First Priority List of Hazardous Substances That Will Be the Subject of Toxicological Profiles and Guidelines for Development of Toxicological Profiles'. Available at: https://tile.loc.gov/storage-services/service/ll/fedreg/fr052/fr052074/fr052074.pdf (Accessed: 22 December 2023).

Federal Register (2023) 'Environmental Protection Agency. 40 CFR Parts 141 and 142. PFAS National Primary Drinking Water Regulation Rulemaking.' Available at: https://www.govinfo.gov/content/pkg/FR-2023-03-29/pdf/2023-05471.pdf (Accessed: 2 January 2024).

Feng, X. *et al.* (2017) 'Exposure of Pregnant Mice to Perfluorobutanesulfonate Causes Hypothyroxinemia and Developmental Abnormalities in Female Offspring', *Toxicological Sciences*, 155(2), pp. 409–419. Available at: https://doi.org/10.1093/toxsci/kfw219.

Gallo, V. *et al.* (2013) 'Serum perfluoroalkyl acids concentrations and memory impairment in a large cross-sectional study', *BMJ Open*, 3(6), p. e002414. Available at: https://doi.org/10.1136/bmjopen-2012-002414.

Iwai, H. and Hoberman, A.M. (2014) 'Oral (gavage) combined developmental and perinatal/postnatal reproduction toxicity study of ammonium salt of perfluorinated hexanoic acid in mice', *International Journal of Toxicology*, 33(3), pp. 219–237.

Klaunig, J.E. *et al.* (2015) 'Evaluation of the chronic toxicity and carcinogenicity of perfluorohexanoic acid (PFHxA) in Sprague-Dawley rats', *Toxicologic pathology*, 43(2), pp. 209–220.

Lau, C. *et al.* (2006) 'Effects of Perfluorooctanoic Acid Exposure during Pregnancy in the Mouse', *Toxicological Sciences*, 90(2), pp. 510–518. Available at: https://doi.org/10.1093/toxsci/kfj105.

Lieder, P.H., York, R.G., *et al.* (2009) 'A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+ PFBS) in Sprague Dawley rats', *Toxicology*, 259(1–2), pp. 33–45.

Lieder, P.H., Chang, S.-C., *et al.* (2009) 'Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague–Dawley rats', *Toxicology*, 255(1–2), pp. 45–52.

Loveless, S.E. *et al.* (2009) 'Toxicological evaluation of sodium perfluorohexanoate', *Toxicology*, 264(1), pp. 32–44. Available at: https://doi.org/10.1016/j.tox.2009.07.011.

Luebker, D.J. *et al.* (2005) 'Neonatal mortality from in utero exposure to perfluorooctanesulfonate (PFOS) in Sprague–Dawley rats: dose–response, and biochemical and pharamacokinetic parameters', *Toxicology*, 215(1–2), pp. 149–169.

Nian, M. *et al.* (2019) 'Liver function biomarkers disorder is associated with exposure to perfluoroalkyl acids in adults: Isomers of C8 Health Project in China', *Environmental Research*, 172, pp. 81–88. Available at: https://doi.org/10.1016/j.envres.2019.02.013.

NTP (2019) *NTP Technical Report on the Toxicity Studies of Perfluoroalkyl Carboxylates (Perfluorohexanoic Acid, Perfluorooctanoic Acid, Perfluorononanoic Acid, and Perfluorodecanoic Acid) Administered by Gavage to Sprague Dawley (Hsd: Sprague Dawley SD) Rats (Revised)*. Toxicity Report 97. Research Triangle Park, North Carolina, USA: National Toxicology Program Public Health Service U.S. Department of Health and Human Services, p. 241. Available at: https://www.ncbi.nlm.nih.gov/books/NBK551546/pdf/Bookshelf_NBK551546.pdf (Accessed: 3 January 2024).

Ramhøj, L. *et al.* (2018) 'Perfluorohexane sulfonate (PFHxS) and a mixture of endocrine disrupters reduce thyroxine levels and cause antiandrogenic effects in rats', *Toxicological Sciences*, 163(2), pp. 579–591.

Rogers, J.M. *et al.* (2014) 'Elevated blood pressure in offspring of rats exposed to diverse chemicals during pregnancy', *toxicological sciences*, 137(2), pp. 436–446.

Sagiv, S.K. *et al.* (2018) 'Early-pregnancy plasma concentrations of perfluoroalkyl substances and birth outcomes in project viva: confounded by pregnancy hemodynamics?', *American journal of epidemiology*, 187(4), pp. 793–802.

Shearer, J.J. *et al.* (2021) 'Serum concentrations of per-and polyfluoroalkyl substances and risk of renal cell carcinoma', *JNCI: Journal of the National Cancer Institute*, 113(5), pp. 580–587.

Song, X. *et al.* (2018) 'Emissions, Transport, and Fate of Emerging Per- and Polyfluoroalkyl Substances from One of the Major Fluoropolymer Manufacturing Facilities in China', *Environmental Science & Technology*, 52(17), pp. 9694–9703. Available at: https://doi.org/10.1021/acs.est.7b06657.

Steenland, K. *et al.* (2009) 'Association of Perfluorooctanoic Acid and Perfluorooctane Sulfonate With Serum Lipids Among Adults Living Near a Chemical Plant', *American Journal of Epidemiology*, 170(10), pp. 1268–1278. Available at: https://doi.org/10.1093/aje/kwp279.

Steenland, K. and Woskie, S. (2012) 'Cohort Mortality Study of Workers Exposed to Perfluorooctanoic Acid', *American Journal of Epidemiology*, 176(10), pp. 909–917. Available at: https://doi.org/10.1093/aje/kws171.

Thomford, P.J. (2002) '104-week dietary chronic toxicity and carcinogenicity study with perfluorooctane sulfonic acid potassium salt (PFOS; T-6295) in rats. 6329-183', *Covance Laboratories Inc* [Preprint].

Timmermann, C.A.G. *et al.* (2020) 'Serum Perfluoroalkyl Substances, Vaccine Responses, and Morbidity in a Cohort of Guinea-Bissau Children', *Environmental Health Perspectives*, 128(8), p. 087002. Available at: https://doi.org/10.1289/ehp6517.

Vieira, V.M. *et al.* (2013) 'Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis', *Environmental health perspectives*, 121(3), pp. 318–323.

Wen, L.-L. *et al.* (2013) 'Association between serum perfluorinated chemicals and thyroid function in US adults: the National Health and Nutrition Examination Survey 2007–2010', *The Journal of Clinical Endocrinology & Metabolism*, 98(9), pp. E1456–E1464.

Wikström, S. *et al.* (2020) 'Maternal serum levels of perfluoroalkyl substances in early pregnancy and offspring birth weight', *Pediatric Research*, 87(6), pp. 1093–1099.

Willey, J. *et al.* (2023) *Report on the Multi-Laboratory Validation Study of PFAS by Isotope Dilution LC-MS/MS Wastewater, Surface Water, and Groundwater*. Strategic Environmental Research and Development Program (SERDP) Project ER19-1409. Available at: https://www.epa.gov/system/files/documents/2023-07/MLVS%20Aqueous%20Draft%2007252023%20508.pdf (Accessed: 31 January 2024).

Wolf, C.J. *et al.* (2010) 'Developmental Effects of Perfluorononanoic Acid in the Mouse Are Dependent on Peroxisome Proliferator-Activated Receptor-Alpha', *PPAR Research*, 2010, pp. 1–11. Available at: https://doi.org/10.1155/2010/282896.

Zhong, J. *et al.* (2016) 'Coating morphology and surface composition of acrylic terpolymers with pendant catechol, OEG and perfluoroalkyl groups in varying ratio and the effect on protein adsorption', *Colloids and Surfaces B: Biointerfaces*, 140, pp. 254–261. Available at: https://doi.org/10.1016/j.colsurfb.2015.12.051.

6. Appendix

6.1. Supplementary Tables

Table A - 1: A comparison between the BMD and NOAEL or LOAEL approaches to modeling Cancer Slope Factors (CSF).

BMD Approach	NOAEL or LOAEL Approach
Modeling extrapolates dose-response data to provide lower doses than were used in the experiments.	Limited to one of the doses used in the experiment and is dependent on study design.
Includes goodness-of-fit information on the model used, the confidence limits, and other descriptive statistics.	Does not account for variability in the estimate of the dose-response from the experimental data.
Goodness-of-fit information describes the slope of the curve.	does not account for the slope of the dose-response curve.
Can be applied if there is not a NOAEL in the experimental data.	Cannot be applied when there is no NOAEL, except through the application of an uncertainty factor

Table A - 2: The required quality control metrics for EPA Method 1633.

PFAS Compound	Range of LOQs (ng/L)	% RSD	% Mean Recovery
PFOS	1 – 4	29	70 – 140
PFOA	1 – 4	27	65 – 155
HFPO-DA	2 – 8	23	70 – 135
PFBA	4 – 16	21	70 – 135
PFHxA	1 – 4	24	70 – 135
PFBS	1 – 4	23	70 – 140
PFNA	1 – 4	28	70 – 140
PFHxS	1 – 4	27	70 – 135

%RSD taken from Table 5; Aqueous LOQs taken from Table 9 in Method 1633 (EPA, 2024d).

Table A - 3: The candidate RfDs for PFOS, excerpted from the EPA Toxicity Assessment for PFOS (EPA, 2024b).

Endpoint	Reference Confidence	Strain Species Sex	POD_{HED} (mg /kg/day)	UF_A	UF_H	UF_S	UF_L	UF_D	UF_C	Candidate RfD[a] (mg/kg/day)
Immune Effects										
Decreased Serum Anti Tetanus Antibody Concentration in Children	(Budtz-Jørgensen and Grandjean, 2018) Medium	Human, male and female	2.71×10^{-6}	1	10	1	1	1	10	3×10^{-7}
	(Timmermann *et al.*, 2020) Medium		1.78×10^{-6}	1	10	1	1	1	10	2×10^{-7}
Decreased Serum Anti-Diphtheria Antibody Concentration in Children	(Budtz-Jørgensen and Grandjean, 2018) Medium	Human, male and female	1.83×10^{-6}	1	10	1	I	1	10	2×10^{-7}
	(Timmermann *et al.*, 2020) Medium		1.03×10^{-6}	1	10	1	1	1	10	1×10^{-7}
Decreased Plaque Forming Cell (PFC) Response to SRBC	(Zhong *et al.*, 2016) Medium	C57BL/6 Mice, PNW 4 F_1 males	5.32×10^{-4}	3	10	1	1	1	30	2×10^{-5}
Extramedullary Hematopoiesis in the Spleen	(NTP, 2019) High	Sprague-Dawley rats, female	2.91×10^{-4}	3	10	10	I	1	300	1×10^{-6}
Developmental Effects										
Low Birth Weight	(Sagiv *et al.*, 2018) High	Human, male and female	6.00×10^{-6}	1	10	1	1	I	10	6×10^{-7}
	(Wikström *et al.*, 2020) High		**1.13×10^{-6}**	**1**	**10**	**1**	**1**	**1**	**10**	**1×10^{-7}**
Decreased Pup Body Weight	(Luebker *et al.*, 2005) Medium	Sprague - Dawley Rats, F_1 male and female	3.96×10^{-3}	3	10	1	I	1	30	1×10^{-4}
Cardiovascular Effects										
Increased Serum Total Cholesterol	(Dong *et al.*, 2019) Medium	Human, male and female, excluding individuals prescribed cholesterol medication	**1.20×10^{-6}**	**1**	**10**	**I**	**1**	**1**	**10**	**1×10^{-7}**
	(Steenland *et al.*, 2009) Medium		1.22×10^{-6}	1	10	1	1	1	10	1×10^{-7}
Hepatic Effects										
Increased Serum ALT	(Gallo *et al.*, 2013) Medium	Human, female	7.27×10^{-6}	1	10	1	1	I	10	7×10^{-7}
	(Nian *et al.*, 2019) Medium		1.94×10^{-6}	1	10	1	1	1	10	2×10^{-7}
Individual Cell Necrosis in the Liver	(Thomford, 2002; Butenhoff *et al.*, 2012)[b] High	Sprague-Dawley rats, females	3.45×10^{-3}	3	10	1	1	1	30	1×10^{-4}

Notes: ALT = alanine transaminase; UF_A = interspecies uncertainty factor; UF_D = database uncertainty factor, UF_H = intraspecies uncertainty factor; UFs = subchronic-to-chronic extrapolation uncertainty factor, UF_L = extrapolation from a LOAEL to a NOAEL uncertainty factor; UF_C = composite uncertainty factor.
[a] RfDs were rounded to one significant figure.
[b] (Butenhoff *et al.*, 2012) and (Thomford, 2002) reported data from the same experiment.
Endpoint is bold to indicate that it was selected as the basis for RfD.

Table A - 4: The candidate CSF for PFOS excerpted from the EPA Toxicity Assessment for PFOS (EPA, 2024b).

Tumor Type	Sex	POD Type, Model	POD Internal Dose /Internal Dose Metric	POD_{HED}	Candidate CSF (BMR/POD_{HED})
Hepatocellular Adenomas	Male	$BMDL_{10}$ Multistage Degree 4 Model	25.6 mg/L normalized per day	3.28×10^{-3} mg/kg/day	30.5 (mg/kg/day)
Hepatocellular Adenomas	Female	$BMDL_{10}$ Multistage Degree 1 Model	21.8 mg/L normalized per day	2.79×10^{-3} mg/kg/day	35.8 (mg/kg/day)
Combined Hepatocellular Adenomas and Carcinomas	**Female**	**$BMDL_{10}$ Multistage Degree 1 Model**	**19.8 mg/L normalized per day**	**2.53×10^{-3} mg/kg/day**	**39.5 (mg/kg/day)**
Pancreatic Islet Cell Carcinomas	Male	$BMDL_{10}$ Multistage Degree 1 Model	26.1 mg/L normalized per day	3.34×10^{-3} mg/kg/day	29.9 (mg/kg/day)

Notes: $BMDL_{10}$ = benchmark dose level corresponding to the 95% lower confidence limit of a 10% change.
Endpoint is bold to indicate that it was selected as the basis for the cancer slope factor.

Appendix A:
Proposed PFAS Water Quality Standards Supporting Information:
Toxicological Summary Information and Derivation 15A NCAC 02L .0202 - Groundwater Quality Numerical Standards

Table A - 5: Candidate RfDs for PFOA, table excerpted from EPA Tox Assessment for PFOA (EPA, 2024c).

Endpoint	Study, Confidence	Strain/Species Sex	POD_{HED} (mg /kg/day)	UF_A	UF_H	UF_S	UF_L	UF_D	UF_C	Candidate RfD[a] (mg/kg/day)
Immune Effects										
Decreased serum Anti tetanus Antibody concentration in children	(Budtz-Jørgensen and Grandjean, 2018) Medium	Human, male and female	**3.05×10^{-7}**	**1**	**10**	**1**	**1**	**1**	**10**	**3×10^{-8}**
	(Timmermann *et al.*, 2020) Medium		2.92×10^{-6}	1	10	1	1	1	10	3×10^{-8}
Decreased Serum Anti-diphtheria Antibody concentration in children	(Budtz-Jørgensen and Grandjean, 2018) Medium	Human, male and female	1.83×10^{-6}	1	10	1	1	1	10	3×10^{-8}
	(Timmermann *et al.*, 2020) Medium		1.03×10^{-6}	1	10	1	1	1	10	2×10^{-8}
Decreased IgM response to SRBC	(DeWitt *et al.*, 2009) Medium	Mouse, Female Study 1	2.18×10^{-3}	3	10	10	1	1	300	7×10^{-6}
Developmental Effects										
Low Birth Weight	(Sagiv *et al.*, 2018)) High	Human, male and female	1.21×10^{-6}	1	10	1	1	1	10	1×10^{-7}
	(Wikström *et al.*, 2020) High		**2.92×10^{-7}**	**1**	**10**	**1**	**1**	**1**	**10**	**3×10^{-8}**
Decreased Offspring Survival	(Song *et al.*, 2018) Medium	Kunming Mice, F_1 males and females	6.40×10^{-4}	3	10	1	1	1	30	2×10^{-5}
Delayed Time to Eye Opening	(Lau *et al.*, 2006) Medium	CD - 1 Mice, F_1 males and females	1.71×10^{-3}	3	10	1	I	1	30	6×10^{-5}
Cardiovascular Effects										
Increased Serum Total Cholesterol	(Dong *et al.*, 2019) Medium	Human, male and female, excluding individuals prescribed cholesterol medication	**2.75×10^{-7}**	**1**	**10**	**1**	**1**	**1**	**10**	**1×10^{-8}**
	(Steenland *et al.*, 2009) Medium		5.10×10^{-7}	1	10	1	1	1	10	1×10^{-8}
Hepatic Effects										
Increased Serum ALT	(Gallo *et al.*, 2013) Medium	Human, female	2.15×10^{-6}	1	10	1	1	1	10	2×10^{-7}
	(Darrow, Stein and Steenland, 2013) Medium		7.92×10^{-6}	1	10	1	1	1	10	8×10^{-7}
	(Nian *et al.*, 2019) Medium		4.51×10^{-7}	1	10	1	1	1	10	5×10^{-8}
Necrosis	(NTP, 2019) High	Sprague-Dawley rats, perinatal and postweaning, male	3.23×10^{-3}	3	10	1	1	1	30	1×10^{-4}

Notes: ALT = alanine aminotransferase; NTP = National Toxicology Program; POD_{HED} = point-of-departure human equivalence dose; RfD = reference dose; SRBC = sheep red blood cells; UF_A = interspecies uncertainty factor; UF_H = intraspecies uncertainty factor; UFs = subchronic-to-chronic extrapolation uncertainty factor, UF_L = extrapolation from a LOAEL to a NOAEL uncertainty factor; UF_D = database uncertainty factor; UF_C = composite uncertainty factor.
[a] RfDs were rounded to one significant figure.
Endpoint is bold to indicate that it was selected as the basis for RfD.

Appendix A:
Proposed PFAS Water Quality Standards Supporting Information:
Toxicological Summary Information and Derivation 15A NCAC 02L .0202 - Groundwater Quality Numerical Standards

Table A - 6: The candidate CSFs for PFOA, excepted from the EPA Tox Assessment on PFOA (EPA, 2024c).

Tumor Type	Reference, Confidence	Strain/ Species/Sex	POD Type, Model	Internal CSF[1]	CSF[2]
Renal cell carcinoma (RCC)	**(Shearer *et al.*, 2021) Medium**	**Human, male and female 55-74 years**	**CSF serum in adults (per ng/mL of serum PFOA); upper limit of the 95 % CI**	**3.52×10-3 (ng/mL)**	**0.0293 (ng/kg/day)**
Kidney cancer	(Vieira *et al.*, 2013) Medium	Human, male and female	CSF serum in adults (per ng/mL of serum PFOA); upper limit of the 95 % CI, highest	4.81×10 (ng/mL)	0.00401 (ng/kg/day)

[1]Internal CSF - Increase in cancer risk per 1 ng/mL serum increase
[2]CSF - Increase in cancer risk per 1 (ng/kg/day) increase in dose.
Endpoint is bold to indicate that it was selected as the basis for the cancer slope factor.

Table A - 7: The candidate RfDs for HFPO-DA (GenX), excepted from the EPA Tox Assessment of GenX (EPA, 2021a).

Endpoint and reference	POD_{HED}[a] (mg/kg/day)	POD Type	UF_L	UF_S	UF_A	UF_H	UF_D	UF_{TOT}	Candidate RfD (mg/kg/day)
Liver constellation of lesions in parental male mice (Dupont, 2010)	0.02	$BMDL_{10}$	1	10	3	10	10	3000	7×10^{-6}
Liver constellation of lesions in parental female mice (Dupont, 2010)	**0.01**	**$BMDL_{10}$**	**1**	**10**	**3**	**10**	**10**	**3000**	**3×10^{-6}**

UF_A = interspecies uncertainty factor; UF_H = intraspecies uncertainty factor; UFs = subchronic-to-chronic extrapolation uncertainty factor, UF_L = extrapolation from a LOAEL to a NOAEL uncertainty factor; UF_D = database uncertainty factor; UF_C = composite uncertainty factor.
Endpoint is bold to indicate that it was selected as the basis for RfD.

Appendix A:
Proposed PFAS Water Quality Standards Supporting Information:
Toxicological Summary Information and Derivation 15A NCAC 02L .0202 - Groundwater Quality Numerical Standards

Table A - 8: The candidate RfDs for PFBS, excepted from EPA HH Tx Values for PFBS (EPA, 2021b).

Endpoint/Reference	Species/Life Stage/Sex	POD_{HED} (mg/kg-d)	UF_A	UF_H	UF_S	UF_L	UF_D	UF_C	Candidate RfD (mg/kg/day)
Thyroid effects									
Total T_4 (Feng *et al.*, 2017)	Mouse/Po - female	$BMDL_{1SD}$ = 0.093	3	10	1	1	10	300	3×10^{-4}
Total T_4 PND 1(Feng *et al.*, 2017)	**Mouse/F1 - female**	**$BMDL_{1SD}$ = 0.095**	3	10	1	1	10	300	**3×10^{-4}**
Total T_4 (NTP, 2019)	Rat - female	$BMDL_{1SD}$ = 0.037	Not calculated as the biological significance of decreased T4 in adults without overt thyroid toxicity is unclear (EPA, 2021b)						
Free T_4 (NTP, 2019)	Rat - female	$BMDL_{1SD}$ = 0.027							

UF_A = interspecies uncertainty factor; UF_H = intraspecies uncertainty factor; UFs = subchronic-to-chronic extrapolation uncertainty factor, UF_L = extrapolation from a LOAEL to a NOAEL uncertainty factor; UF_D = database uncertainty factor; UF_C = composite uncertainty factor.
Endpoint is bold to indicate that it was selected as the basis for RfD.

Table A - 9: The RfD information that the ATDSR MRL and EPA RfD for PFNA are based on, excerpted from the ATSDR Toxicological Profile for Perfluoroalkyls (ATSDR, 2021).

Oral exposure	MRL (mg/kg/day)	Critical effect	POD_{HED}	UF_A	UF_H	UF_D	UF_C	Reference
Acute	*NA*	Inadequate acute - *duration* study (exposure ≤14 days)						
Intermediate	3×10^{-6}	Decreased body weight and developmental delays in mice	0.001	3	10	10	300	(Das *et al.*, 2015)
Chronic	*NA*	Inadequate chronic - duration study (exposure ≥365 *days*)						

UF_A = interspecies uncertainty factor; UF_H = intraspecies uncertainty factor; UFs = subchronic-to-chronic extrapolation uncertainty factor, UF_L = extrapolation from a LOAEL to a NOAEL uncertainty factor; UF_D = database uncertainty factor; UF_C = composite uncertainty factor.

Table A - 10: The RfD information that the ATDSR MRL and EPA RfD for PFHxS are based on, excerpted from the ATSDR Toxicological Profile for Perfluoroalkyls (ATSDR, 2021).

Oral exposure	MRL (mg/kg/day)	Critical effect	POD_{HED}	UF_A	UF_H	UF_D	UF_C	Reference
Acute	*NA*	*Inadequate acute-duration study (exposure ≤14 days)*						
Intermediate	2×10^{-5}	Thyroid follicular epithelial hypertrophy/ hyperplasia in rats	0.0047	3	10	10	300	(Butenhoff *et al.*, 2009)
Chronic	*NA*	*Inadequate chronic - duration study (exposure ≥365 days)*						

Table A - 11: The candidate RfD values based on organ/system specific effects of PFBA exposure; excerpted from the EPA IRIS Assessment of PFBA (EPA, 2022b).

System	Basis	POD	UF_A	UF_H	UF_S	UF_L	UF_D	UF_C	Candidate RfD (mg/kg/day)
Hepatic	Increased hepatocellular hypertrophy in adult male S-D rats	$BMDL_{HED}$ from (Butenhoff *et al.*, 2012)	**3**	**10**	**10**	**1**	**3**	**1000**	**1×10^{-3}**
Thyroid	Decreased total T4 in adult male S-D rats	$NOAEL_{HED}$ from (Butenhoff *et al.*, 2012)	**3**	**10**	**10**	**1**	**3**	**1000**	**1×10^{-3}**
Developmental	Developmental delays after gestational exposure in CD1 mice	$BMDL_{HED}$ from (Das *et al.*, 2015)	3	10	1	1	3	100	6×10^{-3}

UF_A = interspecies uncertainty factor; UF_H = intraspecies uncertainty factor; UFs = subchronic-to-chronic extrapolation uncertainty factor, UF_L = extrapolation from a LOAEL to a NOAEL uncertainty factor; UF_D = database uncertainty factor; UF_C = composite uncertainty factor.
Endpoint is bold to indicate that it was selected as the basis for RfD.

Table A - 12: The candidate RfD values based on organ/system specific effects of PFHxA exposure; excerpted from the EPA IRIS Assessment of PFHxA (EPA, 2023a).

System	Basis	POD	UF_A	UF_H	UF_S	UF_L	UF_D	UF_C	Candidate RfD (mg/kg/day)
Hepatic	Increased hepatocellular hypertrophy in adult male S-D rats	0.11 mg/kg/day based on $BMDL_{10ER}$ and free salt normalization (Loveless *et al.*, 2009)	3	10	3	1	3	300	4×10^{-4}
Hematopoietic	Decreased red blood cells in adult female S-D rats	0.52 mg/kg/day based on $BMDL_{1SD}$ (Klaunig *et al.*, 2015)	3	10	1	1	3	100	5×10^{-3}
Developmental (selected as RfD)	Decreased postnatal body weights in F1 SD male and female rats exposed throughout gestation and lactation	0.048 mg/kg/day based on BMDL5RD and free salt normalization (Loveless *et al.*, 2009)	**3**	**10**	**1**	**1**	**3**	**100**	**5×10^{-4}**

UF_A = interspecies uncertainty factor; UF_H = intraspecies uncertainty factor; UFs = subchronic-to-chronic extrapolation uncertainty factor, UF_L = extrapolation from a LOAEL to a NOAEL uncertainty factor; UF_D = database uncertainty factor; UF_C = composite uncertainty factor.
Endpoint is bold to indicate that it was selected as the basis for RfD.

Appendix A:
Proposed PFAS Water Quality Standards Supporting Information:
Toxicological Summary Information and Derivation 15A NCAC 02L .0202 - Groundwater Quality Numerical Standards

6.2. NC SSAB PFAS Toxicity Assessment Methodology Comparison

				EPA MCL PFAS Compounds					
Category	**IRIS Handbook method (EPA 2022)**	**PFHxA (EPA ORD CPHEA IRIS 2023)**	**PFBA (EPA ORD CPHEA IRIS 2022)**	**PFOS (EPA OW 2022)**	**PFOA (EPA OW 2022)**	**PFBS (EPA ORD CPHEA 2021)**	**HFPO-DA (EPA OW 2021)**	**PFHxS (ATSDR 2021)**	**PFNA (ATSDR 2021)**
Stated that the IRIS Handbook was followed or conducted by IRIS Program?	ORD Staff Handbook for Developing IRIS Assessments 2022	✓	✓	✓	✓	Published before handbook was drafted/published	Texet states that the draft IRIS handbook was followed, final was not published at this time	ATSDR's Guidance for the Preparation of Toxicological Profiles	
Literature Search	Using Health and Environmental Research Online (HERO) database andworkflow	✓	✓	PFOS and PFOA HERO webpage PFOS and PFOA MCLG Approaches HERO webpage		PFBS HERO webpage	GenX HERO webpage	ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology.	
	Retrieve results from each database using HERO in this order: • PubMed • Web of Science • SCOPUS • Other resources (e.g., NTP, ECHA, TSCATS)	✓	✓	Web of Science, PubMed,ToxLine, and, TSCATS	Web of Science, PubMed,ToxLine, and, TSCATS	PubMed, Web of Science, TOXLINE, and TSCATS via TOXLINE were searched by HERO	PubMed, Toxline, Web of Science (WOS), and Toxic Substances Control Act Test Submissions (TSCATS) searched by HERO	PubMed, National Library of Medicine's TOXLINE, Scientific and Technical Information Network's TOXCENTER	
	Dates of Literature Search								
Study Screening	Use the Distiller SR software to screen studies in a systematic and unbiased way	✓	✓	Used Distiller SR	Used Distiller SR	Used Distiller SR	Used Distiller SR	A two-step process was used to screen the literature search to identify relevant studies on	
Study Evaluation	IRIS study evaluation approach. (a) individual evaluation domains organized by evidence type, and (b) individual evaluation domain judgments and definitions for overall ratings (i.e., domain and overall judgments are performed on an outcome-specific basis).	✓	✓	Two or more quality assurance (QA) reviewers, working independently, assigned ratings about the reliability of study results (good, adequate, deficient (or "not reported"), or critically deficient) for different evaluation domains.		For each study in each evaluation domain, reviewers reached a consensus rating regarding the utility of the study for hazard identification, with categories of good, adequate, deficient, not reported, or critically deficient. These ratings were then combined across domains to reach an overall classification of high, medium, or low confidence or uninformative.	The twelve studies providing dose-response information were then evaluated for study quality using an approach consistent with the draft ORD Handbook for developing IRIS assessments	Expert peer-review panel	
Study Quality	Key concerns for the review of epidemiological, controlled human exposure, animal, and in vitro studies are risk of bias (RoB), which is the assessment of internal validity (factors that might affect the magnitude or direction of an effect in either direction), and sensitivity (factors that limit the ability of a study to detect a true effect; low sensitivity is a bias toward the null when an effect exists).	✓	✓	Considerations when evaluating the available studies included risk of bias, sensitivity, consistency, strength (effect magnitude) and precision, biological gradient/dose-response, coherence, and mechanistic evidence related to biological plausibility.		The evaluation process focused on assessing aspects of the study design and conduct through three broad types of evaluations: reporting quality, risk of bias, and study sensitivity.	Study quality was determined by two independent reviewers who assessed risk of bias and sensitivity for the following domains: reporting quality, risk of bias (selection or performance bias, confounding/variable control, and reporting or attrition bias), and study sensitivity (exposure methods sensitivity, and outcome measures and results display)	The properties of the body of evidence were considered are: Risk of bias, Unexplained inconsistency, indirectness, imprecision, publication bias, magnitude of effect, dose response, confouding bias, consistency	
				HAWC Quailty Tables	HAWC Quality Tables	HAWC Quality Table	HAWC Quality Table		
Data Extraction	Health Assessment Workspace Collaborative (HAWC) - interface that allows the data and decisions supporting an assessment to be managed in modules (e.g., study evaluation, summary study data, etc.) that can be publicly accessed online	✓	✓	Used HAWC and info is online		Used HAWC and info is online	Used HAWC and the info is online	Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms	
vidence Integration	Evidence Integration Judgment: one of five phrases is used: evidence demonstrates, evidence indicates (likely), evidence suggests, evidence is inadequate, or strong evidence supports no effect	✓	✓	"EPA determined that either evidence indicates or evidence demonstrates that oral PFOS exposure is associated with adverse effects"	"EPA determined that either evidence indicates or evidence demonstrates that oral PFOA exposure is associated with adverse effects"	"Taken together, the evidence indicates that the developing reproductive system, particularly in females, might be a target for PFBS toxicity"	"Taken together, the available data indicate that a PPARα MOA is plausible in the liver in response to GenX chemical exposure…"	"There is strong evidence that many of the adverse effects observed in laboratory animals involve the activation of peroxisome proliferator-activated receptor-α (PPARα), which can mediate a broad range of biological responses"	
Approach for deriving reference values	Systematic Assesment of Study Attributes to Support Derivation of Toxicity Values	✓	✓	✓	✓	✓	✓	Integration of the evidence streams for the human studies and animal studies	
	Selecting Benchmark Dose Response Values for Dose-Resoponse Modeling	✓	✓	✓	✓	✓	✓	MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach.	
	Conduct Dose-Response Modeling	✓	✓	✓	✓	✓	✓		
	Characterization of Exposure for Extrapolation to Humans	✓	✓	✓	✓	✓	✓	Discuss qualitative and quantitative differences in	
	Characterizing Uncertainty and Confidence	✓	✓	✓	✓	✓	✓	UFs simlilar to EPA's UF categories	
	Selecting Final Toxicity Values	✓	✓	✓	✓	✓	✓	MRLs are derived for acute (1–14 days),	
Assessment used to support EPA's proposed PFAS MCLs		no	no	✓	✓	✓	✓	✓	✓

6.3. Ground Water Quality Standards Calculation Sheets

This section of the Appendix contains copies of the calculation sheets that the NC DEQ Division of Water Resources used for derivation of the Groundwater Standards.

6.3.1. *PFOS 02L Numerical Standard Calculations*

North Carolina Groundwater Standard

Perfluorooctanesulfonic acid (PFOS) CASRN 1763-23-1

North Carolina Ground Water (GW) Standard = 0.7 ng/L*

GW standard based on noncancer endpoint

GWQS = [(RfD x WT x RSC) / WI] * 1000

RfD = reference dose[1]	1.0E-07	mg/kg/day	
WT = average adult human body weight[2]	70	kg	
RSC= relative source contribution	0.2	unitless value	
WI = average daily adult human water intake[3]	2	L/day	
1000 = conversion factor	1000	µg/mg	
Calculated GW Standard using noncancer endpoint	**0.00070**	**µg/L (ppb)**	**0.7 ng/L (ppt)**

GW Standard based on cancer endpoint

GWQS = [(RL x WT) / (q1* x WI)] * 1000

RL = risk level	1.0E-06		
WT = average adult human body weight[2]	70	kg	
q1* = carcinogenic potency factor (slope factor)[1]	39.5	$(mg/kg/day)^{-1}$	
WI = average daily adult human water intake[3]	2	L/day	
1000 = conversion factor	1000	ng/µg	
Calculated GW Standard using cancer endpoint	**0.0008861**	**µg/L (ppb)**	**0.89 ng/L (ppt)**

GW Standards based on published values

Taste Threshold	NA	µg/L	
Odor Threshold	NA	µg/L	
Maximum Contaminant Level (MCL)[4]	0.004	µg/L	4 ng/L (ppt)
Secondary Drinking Water Standard (SMCL)	NA	µg/L	

References

[1] U.S. EPA. (2024). Human Health Toxicity Assessment for Perfluorooctane Sulfonic Acid (PFOS) and Related Salts. Office of Water. EPA Document Number: 815R24007. https://www.epa.gov/system/files/documents/2024-04/main_final-toxicity-assessment-for-pfos_2024-04-09-refs-

[2] Average adult body weight from 15A NCAC 02L .0202 (effective date April 1, 2022).

[3] Average water consumption from 15A NCAC 02L .0202 (effective date April 1, 2022).

[4] U.S. EPA. (2024). Per- and Polyfluoroalkyl Substances (PFAS) Final PFAS National Primary Drinking Water Regulation. https://www.epa.gov/sdwa/and-polyfluoroalkyl-substances-pfas

*Rounded using conventions from EPA Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (Office of Water, EPA 822-B-00-004, October 2000)

ppb= parts per billion
ppt= parts per trillion
NA = Not available
RSC = 0.1 for nonorganics, 0.2 for organics

6.3.2. *PFOA 02L Numerical Standard Calculations*

North Carolina Groundwater Standard

Perfluorooctanoic acid (PFOA) **CASRN 335-67-1**

North Carolina Ground Water (GW) Standard = 0.001 ng/L*

GW standard based on noncancer endpoint

GWQS = [(RfD x WT x RSC) / WI] * 1000

RfD = reference dose[1]	3.0E-08	mg/kg/day	
WT = average adult human body weight[2]	70	kg	
RSC= relative source contribution	0.2	unitless value	
WI = average daily adult human water intake[3]	2	L/day	
1000 = conversion factor	1000	µg/mg	
Calculated GW Standard using noncancer endpoint	**0.00021**	**µg/L (ppb)**	**0.21 ng/L (ppt)**

GW Standard based on cancer endpoint

GWQS = [(RL x WT) / (q1* x WI)] * 1000

RL = risk level	1.0E-06		
WT = average adult human body weight[2]	70	kg	
q1* = carcinogenic potency factor (slope factor)[1]	0.0293	$(ng/kg/day)^{-1}$	
WI = average daily adult human water intake[3]	2	L/day	
1000 = conversion factor	0.001	µg/ng	
Calculated GW Standard using cancer endpoint	**0.0000012**	**µg/L (ppb)**	**0.0012 ng/L (ppt)**

GW Standards based on published values

Taste Threshold	NA	µg/L	
Odor Threshold	NA	µg/L	
Maximum Contaminant Level (MCL)[4]	0.004	µg/L	4 ng/L (ppt)
Secondary Drinking Water Standard (SMCL)	NA	µg/L	

References

[1] U.S. EPA. (2024). Human Health Toxicity Assessment for Perfluorooctanoic Acid (PFOA) and Related Salts, U.S. Environmental Protection Agency. Office of Water. EPA Document Number: 815R24006. https://www.epa.gov/system/files/documents/2024-04/main_final-toxicity-assessment-for-pfoa_2024-04-09-refs-formatted.pdf

[2] Average adult body weight from 15A NCAC 02L .0202 (effective date April 1, 2022).

[3] Average water consumption from 15A NCAC 02L .0202 (effective date April 1, 2022).

[4] U.S. EPA. (2024). Per- and Polyfluoroalkyl Substances (PFAS) Final PFAS National Primary Drinking Water Regulation. https://www.epa.gov/sdwa/and-polyfluoroalkyl-substances-pfas

*Rounded using conventions from EPA Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (Office of Water, EPA 822-B-00-004, October 2000)

ppb= parts per billion
ppt= parts per trillion
NA = Not available
RSC = 0.1 for nonorganics, 0.2 for organics

6.3.3. *HFPO-DA 02L Numerical Standard Calculations*

North Carolina Groundwater Standard

Hexafluoropropylene oxide dimer acid (HFPO-DA)	CASRN	13252-13-6

North Carolina Ground Water (GW) Standard = 0.01 µg/L

GW standard based on noncancer endpoint

GWQS = [(RfD x WT x RSC) / WI] * 1000

RfD = reference dose[1]	3.0E-06	mg/kg/day	
WT = average adult human body weight[2]	70	kg	
RSC= relative source contribution	0.2	unitless value	
WI = average daily adult human water intake[3]	2	L/day	
1000 = conversion factor	1000	µg/mg	
Calculated GW Standard with noncancer endpoint	**0.021**	**µg/L (ppb)**	**21 ng/L (ppt)**

GW Standard based on cancer endpoint

GWQS = [(RL x WT) / (q1* x WI)] * 1000

RL = risk level	1.0E-06		
WT = average adult human body weight[2]	70	kg	
q1* = carcinogenic potency factor (slope factor)	NA	$(mg/kg/day)^{-1}$	
WI = average daily adult human water intake[3]	2	L/day	
1000 = conversion factor	1000	µg/mg	
Calculated GW Standard using cancer endpoint	**NA**	**µg/L (ppb)**	

GW Standards based on published values

Taste Threshold	**NA**	**µg/L**	
Odor Threshold	**NA**	**µg/L**	
Maximum Contaminant Level (MCL)[4]	**0.01**	**µg/L**	**10 ng/L (ppt)**
Secondary Drinking Water Standard (SMCL)	**NA**	**µg/L**	

References

[1] US EPA Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3) Also Known as "GenX Chemicals". EPA Document Number: 822R-21-010.

[2] Average adult body weight from 15A NCAC 02L .0202 (effective date April 1, 2022).

[3] Average water consumption from 15A NCAC 02L .0202 (effective date April 1, 2022).

[4] U.S. EPA. (2024). Per- and Polyfluoroalkyl Substances (PFAS) Final PFAS National Primary Drinking Water Regulation. https://www.epa.gov/sdwa/and-polyfluoroalkyl-substances-pfas

ppb= parts per billion
ppt= parts per trillion
NA = Not available
RSC = 0.1 for nonorganics, 0.2 for organics

6.3.4. *PFBS 02L Numerical Standard Calculations*

North Carolina Groundwater Standard

Perfluorobutane sulfonic acid (PFBS) — **CASRN 375-73-5**

North Carolina Ground Water (GW) Standard = 2 µg/L*

GW standard based on noncancer endpoint

GWQS = [(RfD x WT x RSC) / WI] * 1000

RfD = reference dose[1]	3.0E-04	mg/kg/day	
WT = average adult human body weight[2]	70	kg	
RSC= relative source contribution	0.2	unitless value	
WI = average daily adult human water intake[3]	2	L/day	
1000 = conversion factor	1000	µg/mg	
Calculated GW Standard using noncancer endpoint	**2.1**	**µg/L (ppb)**	**2100 ng/L (ppt)**

GW Standard based on cancer endpoint

GWQS = [(RL x WT) / (q1* x WI)] * 1000

RL = risk level	1.0E-06	
WT = average adult human body weight[2]	70	kg
q1* = carcinogenic potency factor (slope factor)	NA	$(mg/kg/day)^{-1}$
WI = average daily adult human water intake[3]	2	L/day
1000 = conversion factor	1000	µg/mg
Calculated GW Standard using cancer endpoint	**NA**	**µg/L (ppb)**

GW Standards based on published values

Taste Threshold	NA	µg/L
Odor Threshold	NA	µg/L
Maximum Contaminant Level (MCL)[4]	NA	µg/L
Secondary Drinking Water Standard (SMCL)	NA	µg/L

References

[1] U.S. EPA. (2021). Human Health Toxicity Values for Perfluorobutane Sulfonic Acid (CASRN 375-73-5) and Related Compound Potassium Perfluorobutane Sulfonate (CASRN 29420-49-3). U.S. Environmental Protection Agency, Office of Research and Development (ORD) Center for Public Health and Environmental Assessment (CPHEA).

[2] Average adult body weight from 15A NCAC 02L .0202 (effective date April 1, 2022).

[3] Average water consumption from 15A NCAC 02L .0202 (effective date April 1, 2022).

[4] U.S. EPA established a unitless Hazard Index approach to regulate for mixtures containing two or more of PFHxS, PFNA, HFPO-DA, and PFBS. No individual MCL has been established for PFBS; U.S. EPA. (2024). Per- and Polyfluoroalkyl Substances (PFAS) Final PFAS National Primary Drinking Water Regulation. https://www.epa.gov/sdwa/and-polyfluoroalkyl-substances-pfas

*Rounded using conventions from EPA Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (Office of Water, EPA 822-B-00-004, October 2000)

ppb= parts per billion
ppt= parts per trillion
NA = Not available
RSC = 0.1 for nonorganics, 0.2 for organics

6.3.5. *PFNA 02L Numerical Standard Calculations*

North Carolina Groundwater Standard

Perfluorononanoic acid (PFNA) CASRN 375-95-1

North Carolina Ground Water (GW) Standard = 0.01 µg/L

GW standard based on noncancer endpoint

GWQS = [(RfD x WT x RSC) / WI] * 1000

RfD = reference dose[1]	3.0E-06	mg/kg/day	
WT = average adult human body weight[2]	70	kg	
RSC= relative source contribution	0.2	unitless value	
WI = average daily adult human water intake[3]	2	L/day	
1000 = conversion factor	1000	µg/mg	
Calculated GW Standard using noncancer endpoint	**0.021**	**µg/L (ppb)**	**21 ng/L (ppt)**

GW Standard based on cancer endpoint

GWQS = [(RL x WT) / (q1* x WI)] * 1000

RL = risk level	1.0E-06		
WT = average adult human body weight[2]	70	kg	
q1* = carcinogenic potency factor (slope factor)	NA	$(mg/kg/day)^{-1}$	
WI = average daily adult human water intake[3]	2	L/day	
1000 = conversion factor	1000	µg/mg	
Calculated GW Standard using cancer endpoint	**NA**	**µg/L (ppb)**	

GW Standards based on published values

Taste Threshold	NA	µg/L	
Odor Threshold	NA	µg/L	
Maximum Contaminant Level (MCL)[4]	0.01	µg/L	10 ng/L (ppt)
Secondary Drinking Water Standard (SMCL)	NA	µg/L	

References

[1] Agency for Toxic Substances and Disease Registry (ATSDR). 2021. Toxicological profile for Perfluoroalkyls. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. DOI: 10.15620/cdc:59198
[2] Average adult body weight from 15A NCAC 02L .0202 (effective date April 1, 2022).
[3] Average water consumption from 15A NCAC 02L .0202 (effective date April 1, 2022).
[4] U.S. EPA. (2024). Per- and Polyfluoroalkyl Substances (PFAS) Final PFAS National Primary Drinking Water Regulation. https://www.epa.gov/sdwa/and-polyfluoroalkyl-substances-pfas

ppb= parts per billion
ppt= parts per trillion
NA = Not available
RSC = 0.1 for nonorganics, 0.2 for organics

6.3.6. *PFHxS 02L Numerical Standard Calculations*

North Carolina Groundwater Standard

Perfluorohexane sulfonate (PFHxS)			CASRN 355-46-4
North Carolina Ground Water (GW) Standard =	**0.01 µg/L***		
GW standard based on noncancer endpoint			
GWQS = [(RfD x WT x RSC) / WI] * 1000			
RfD = reference dose[1]	2.0E-06	mg/kg/day	
WT = average adult human body weight[2]	70	kg	
RSC= relative source contribution	0.2	unitless value	
WI = average daily adult human water intake[3]	2	L/day	
1000 = conversion factor	1000	µg/mg	
Calculated GW Standard using noncancer endpoint	0.01	µg/L (ppb)	14 ng/L (ppt)
GW Standard based on cancer endpoint			
GWQS = [(RL x WT) / (q1* x WI)] * 1000			
RL = risk level	1.0E-06		
WT = average adult human body weight[2]	70	kg	
q1* = carcinogenic potency factor (slope factor)	NA	$(mg/kg/day)^{-1}$	
WI = average daily adult human water intake[3]	2	L/day	
1000 = conversion factor	1000	µg/mg	
Calculated GW Standard using cancer endpoint	NA	µg/L (ppb)	
GW Standards based on published values			
Taste Threshold	NA	µg/L	
Odor Threshold	NA	µg/L	
Maximum Contaminant Level (MCL)[4]	0.01	µg/L	10 ng/L (ppt)
Secondary Drinking Water Standard (SMCL)	NA	µg/L	

References

[1] Agency for Toxic Substances and Disease Registry (ATSDR). 2021. Toxicological profile for Perfluoroalkyls. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. DOI: 10.15620/cdc:59198

[2] Average adult body weight from 15A NCAC 02L .0202 (effective date April 1, 2022).

[3] Average water consumption from 15A NCAC 02L .0202 (effective date April 1, 2022).

[4] U.S. EPA. (2024). Per- and Polyfluoroalkyl Substances (PFAS) Final PFAS National Primary Drinking Water Regulation. https://www.epa.gov/sdwa/and-polyfluoroalkyl-substances-pfas

*Rounded using conventions from EPA Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (Office of Water, EPA 822-B-00-004, October 2000)

ppb= parts per billion
ppt= parts per trillion
NA = Not available
RSC = 0.1 for nonorganics, 0.2 for organics

6.3.7. *PFBA 02L Numerical Standard Calculations*

North Carolina Groundwater Standard

Perfluorobutanoic Acid (PFBA) CASRN 375-22-4

North Carolina Ground Water (GW) Standard = 7 µg/L*

GW standard based on noncancer endpoint

GWQS = [(RfD x WT x RSC) / WI] * 1000

RfD = reference dose[1]	1.0E-03	mg/kg/day	
WT = average adult human body weight[2]	70	kg	
RSC= relative source contribution	0.2	unitless value	
WI = average daily adult human water intake[3]	2	L/day	
1000 = conversion factor	1000	µg/mg	
Calculated GW Standard using noncancer endpoint	**7**	**µg/L (ppb)**	**7000 ng/L (ppt)**

GW Standard based on cancer endpoint

GWQS = [(RL x WT) / (q1* x WI)] * 1000

RL = risk level	1.0E-06	
WT = average adult human body weight[2]	70	kg
q1* = carcinogenic potency factor (slope factor)	NA	$(mg/kg/day)^{-1}$
WI = average daily adult human water intake[3]	2	L/day
1000 = conversion factor	1000	µg/mg
Calculated GW Standard using cancer endpoint	**NA**	**µg/L (ppb)**

GW Standards based on published values

Taste Threshold	NA	µg/L
Odor Threshold	NA	µg/L
Maximum Contaminant Level (MCL)	NA	µg/L
Secondary Drinking Water Standard (SMCL)	NA	µg/L

References

[1] U.S. EPA. (2022). Integrated Risk Information System (IRIS) Toxicological Review of Perfluorobutanoic Acid (PFBA, CASRN 37522-4) and Related Salts. Office of Research and Development. EPA/635/R-22/277Fa. https://iris.epa.gov/static/pdfs/0701tr.pdf

[2] Average adult body weight from 15A NCAC 02L .0202 (effective date April 1, 2022).

[3] Average water consumption from 15A NCAC 02L .0202 (effective date April 1, 2022).

*Rounded using conventions from EPA Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (Office of Water, EPA 822-B-00-004, October 2000)

ppb= parts per billion
ppt= parts per trillion
NA = Not available
RSC = 0.1 for nonorganics, 0.2 for organics

6.3.8. *PFHxA 02L Numerical Standard Calculations*

North Carolina Groundwater Standard

Perfluorohexanoic Acid (PFHxA) CASRN 307-24-4

North Carolina Ground Water (GW) Standard = 4 µg/L*

GW standard based on noncancer endpoint

GWQS = [(RfD x WT x RSC) / WI] * 1000

RfD = reference dose[1]	5.0E-04	mg/kg/day	
WT = average adult human body weight[2]	70	kg	
RSC= relative source contribution	0.2	unitless value	
WI = average daily adult human water intake[3]	2	L/day	
1000 = conversion factor	1000	µg/mg	
Calculated GW Standard using noncancer endpoint	**3.5**	**µg/L (ppb)**	**3500 ng/L (ppt)**

GW Standard based on cancer endpoint

GWQS = [(RL x WT) / (q1* x WI)] * 1000

RL = risk level	1.0E-06	
WT = average adult human body weight[2]	70	kg
q1* = carcinogenic potency factor (slope factor)	NA	$(mg/kg/day)^{-1}$
WI = average daily adult human water intake[3]	2	L/day
1000 = conversion factor	1000	µg/mg
Calculated GW Standard using cancer endpoint	**NA**	**µg/L (ppb)**

GW Standards based on published values

Taste Threshold	**NA**	**µg/L**
Odor Threshold	**NA**	**µg/L**
Maximum Contaminant Level (MCL)	**NA**	**µg/L**
Secondary Drinking Water Standard (SMCL)	**NA**	**µg/L**

References

[1] U.S. EPA. (2023). Integrated Risk Information System (IRIS) Toxicological Review of Perfluorohexanoic Acid (PFHxA) and Related Salts. National Center for Environmental Assessment, Office of Research and Development. https://iris.epa.gov/static/pdfs/0704tr.pdf

[2] Average adult body weight from 15A NCAC 02L .0202 (effective date April 1, 2022).

[3] Average water consumption from 15A NCAC 02L .0202 (effective date April 1, 2022).

*Rounded using conventions from EPA Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (Office of Water, EPA 822-B-00-004, October 2000)

ppb= parts per billion
ppt= parts per trillion
NA = Not available
RSC = 0.1 for nonorganics, 0.2 for organics