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Drinking Water Health Advisory: Hexafluoropropylene Oxide (HFPO) Dimer Acid (CASRN 13252-13-6) and HFPO Dimer Acid Ammonium Salt (CASRN 62037-80-3), Also Known as "GenX Chemicals"

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Abbreviations and Acronyms

ADAF	age-dependent adjustment factor
AIX	anion exchange
AF	amorphous fluoropolymer
AFFF	aqueous film-forming foam
ANSI	American National Standards Institute
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower limit
bw or BW	body weight
CASRN	Chemical Abstracts Service Registry Number
CDC	Centers for Disease Control and Prevention
CCL	Contaminant Candidate List
CCL 5	Fifth Safe Drinking Water Act Contaminant Candidate List
cm^3	cubic centimeters
CSF	cancer slope factor
DBP	disinfection byproduct
DF	detection frequency
DHS	Department of Health Services
DOM	dissolved organic matter
DQO	data quality objective
dw	dry weight
DWI	drinking water intake
DWI-BW	body weight-adjusted drinking water intake
DWTP	drinking water treatment plant
E	human exposure
EBCT	empty bed contact time
EF	exposure factor
EFH	Exposure Factors Handbook
EGLE	Michigan Department of Environment, Great Lakes, and Energy
EPA	United States Environmental Protection Agency
Eq.	equation
FDA	United States Food and Drug Administration
FEP	fluorinated ethylene propylene
g/L	grams per liter
GAC	granular activated carbon
GenX chemicals	hexafluoropropylene oxide dimer acid and its ammonium salt
H_3O^+	hydronium
HA	Health Advisory
HECD	Health and Ecological Criteria Division
HED	human equivalent dose
HFPO	hexafluoropropylene oxide
HFPO dimer acid	2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) propanoic acid
HFPO-TA	hexafluoropropylene oxide trimer acid
HFPO-TeA	hexafluoropropylene oxide tetramer acid
HI	hazard index
HIDOH	Hawai´i State Department of Health
HNIS	Human Nutrition Information Service
HQ	hazard quotient
i	mixture component chemical

IDEM	Indiana Department of Environmental Management
iHA	interim Health Advisory
Illinois EPA	Illinois Environmental Protection Agency
ITRC	Interstate Technology and Regulatory Council
km	kilometers
L/kg bw-day	liters per kilogram body weight per day
$L/(m^2 \cdot hr)$	liters per square meter per hour
LC/MS/MS	liquid chromatography/tandem mass spectrometry
LOAEL	lowest observed adverse effect level
LOQ	limit of quantification
m/hr	meters per hour
MCLG	Maximum Contaminant Level Goal
mg/kg bw-day	milligrams per kilogram body weight per day
MQL	method quantification limit
MRL	minimum reporting limit
NCDEQ	North Carolina Department of Environmental Quality
NCDHHS	North Carolina Department of Health and Human Services
ND	not detected
NH_4^+	ammonium cation
NF	nanofiltration
ng/g	nanograms per gram
ng/kg	nanograms per kilogram
ng/L	nanograms per liter
NHANES	National Health and Nutrition Examination Survey
NOAEL	no observed adverse effect level
NOM	natural organic matter
NR	not reported
NSF	National Science Foundation
OCHP	Office of Children's Health Protection
ODH	Ohio Department of Health
OGWDW	Office of Ground Water and Drinking Water
Ohio EPA	Ohio Environmental Protection Agency
OST	Office of Science and Technology
OW	Office of Water
PAC	powdered activated carbon
PECO	populations, exposures, comparators, and outcomes
PFA	perfluoroalkoxy
PFAS	per- and polyfluoroalkyl substances
PFBS	perfluorobutane sulfonic acid
PFCA	perfluoroalkyl carboxylic acid
PFECA	perfluoroalkyl ether carboxylic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctanesulfonic acid
pg/g	picograms per gram
pg/L	picograms per liter
PHG	provisional health goal
pK_a	acid dissociation constant
POD	point of departure
POD_{HED}	point of departure human equivalent dose
POE	point-of-entry
POU	point-of-use

PPARα	peroxisome proliferator-activated receptor alpha
ppt	parts per trillion
PTFE	polytetrafluoroethylene
PWS	public water system
RfD	reference dose
RO	reverse osmosis
RPF	relative potency factor
RSC	relative source contribution
SAB	Science Advisory Board
SDWA	Safe Drinking Water Act
$t_{1/2}$	half-life
TSCATS	Toxic Substances Control Act Test Submissions
UCMR	Unregulated Contaminant Monitoring Rule
UF	uncertainty factor(s)
$\mathrm{UF_A}$	interspecies uncertainty factor
$\mathrm{UF_C}$	composite uncertainty factor
$\mathrm{UF_D}$	database uncertainty factor
$\mathrm{UF_H}$	intraspecies uncertainty factor
$\mathrm{UF_S}$	extrapolation from subchronic to chronic exposure duration uncertainty factor
µg/L	micrograms per liter
µg/kg bw-day	micrograms per kilogram body weight per day
Wisconsin DHS	Wisconsin Department of Health Services
WOS	Web of Science

Executive Summary

Hexafluoropropylene oxide (HFPO) dimer acid (2,3,3,3-tetrafluoro-2- [heptafluoropropoxy] propanoic acid) (Chemical Abstracts Service Registry Number [CASRN] 13252-13-6) and HFPO dimer acid ammonium salt (ammonium 2,3,3,3- tetrafluoro-2- [heptafluoropropoxy]propanoate) (CASRN 62037-80-3) are shorter-chain members of a group of substances known as per- and polyfluoroalkyl substances (PFAS). HFPO dimer acid and its ammonium salt are referred to as “GenX chemicals” because they are two of the main chemicals associated with the GenX processing aid technology that DuPont developed to make high-performance fluoropolymers without using perfluorooctanoic acid (PFOA) (U.S. EPA, 2021a). In water, both HFPO dimer acid and its ammonium salt dissociate to form the HFPO dimer acid anion (HFPO-) as a common analyte.

GenX chemicals are replacements for the longer-chain PFOA, which was phased out in the United States by 2015 as part of an agreement between manufacturers and the U.S. Environmental Protection Agency (EPA) under the PFOA Stewardship Program, established in 2006. GenX chemicals are used to manufacture fluoropolymers which have many industrial applications including in medical, automotive, electronics, aerospace, energy, and semiconductor industries. The Chemours Company uses GenX chemicals to produce four trademarked fluoropolymers: Teflon™ polytetrafluoroethylene (PTFE), Teflon™ perfluoroalkoxy (PFA), Teflon™ fluorinated ethylene propylene (FEP), and Teflon™ amorphous fluoropolymer (AF) (Chemours, 2022). Since GenX chemicals are substitutes for PFOA, products (e.g., some nonstick coatings) that were previously made using PFOA may now rely on GenX chemicals.

GenX chemicals have been detected around the globe in surface water, groundwater, finished drinking water, rainwater, and air emissions (U.S. EPA, 2021a). Potential sources of GenX in the environment include industrial facilities that use GenX technology for polymer production, facilities that produce fluoromonomers (as a byproduct), and contaminated water, air, soil, and biosolids. GenX chemicals may also be generated as a byproduct of other manufacturing processes including fluoromonomer production. For example, GenX chemicals have been discharged into the Cape Fear River for several decades as a byproduct of manufacturing (NCDEQ, 2017). GenX chemicals can enter the aquatic environment through industrial discharges, runoff into surface water, and leaching into groundwater from soil and landfills (U.S. EPA, 2021a). GenX chemicals are water-soluble, with solubilities of greater than 751 grams per liter (g/L) and greater than 739 g/L for HFPO dimer acid and its ammonium salt, respectively, at 20°C (U.S. EPA, 2021a). Volatilization from water surfaces is expected to be an important fate process for both HFPO dimer acid and its ammonium salt (U.S. EPA, 2021a). The limited data on human serum have detected GenX chemicals in studies of workers.

EPA is issuing a lifetime noncancer drinking water Health Advisory (HA) for GenX chemicals of 10 nanograms per liter (ng/L) or 10 parts per trillion (ppt). This is the first HA for GenX chemicals and its finalization fulfills a commitment described in EPA’s PFAS Strategic Roadmap (U.S. EPA, 2021b). The final toxicity assessment for GenX chemicals titled *Final 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”* (U.S. EPA, 2021a) serves as the basis of the toxicity information used to derive the lifetime noncancer HA for GenX chemicals. This final toxicity assessment was published after a rigorous process including draft assessment development, agency and interagency review, public comment, two independent peer reviews, and an independent review of data from two studies by the National Toxicology Program. The input values for deriving the HA include 1) the final chronic reference dose (RfD) for GenX of 0.000003 milligrams per kilogram body weight per day (mg/kg bw-day) (U.S. EPA, 2021a); 2) a 20% relative source contribution (RSC) based on EPA's Exposure Decision Tree approach in EPA's *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health* (U.S. EPA, 2000a); and 3) the drinking water intake rate of 0.0469 L/kg bw-day for lactating women, which is the sensitive population identified based on the critical study selected for the final RfD (U.S. EPA, 2021a).

The final toxicity assessment for GenX chemicals (U.S. EPA, 2021a) derived both subchronic and chronic RfDs based on the critical adverse effect of a constellation of liver lesions (i.e., cytoplasmic alteration, hepatocellular single-cell and focal necrosis, and hepatocellular apoptosis) observed in female mice in an oral reproductive/developmental toxicity study (DuPont-18405-1037, 2010; NTP, 2019). Using EPA's *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2012), EPA modeled the dose-response relationship in the range of observed data. Additionally, EPA's *Recommended Use of Body Weight*$^{3/4}$ *as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011) was used to allometrically scale a toxicologically equivalent dose from adult laboratory animals to adult humans. From benchmark dose modeling (BMD) of the DuPont-18045-1037 (2010) study, the resulting POD human equivalent dose (HED) is 0.01 mg/kg bw-day. The HED was divided by a composite UF (UFc) of 3,000 to obtain the chronic RfD of 0.000003 mg/kg bw-day or 0.003 micrograms per kilogram body weight per day (µg/kg bw-day) for GenX chemicals (U.S. EPA, 2021a).

There is insufficient toxicity information available to derive a one-day HA for GenX chemicals because U.S. EPA (2021a) does not have a final RfD for acute exposure (i.e., relevant to a 7 day or less exposure period). There is also insufficient toxicity information available to derive a ten-day HA because U.S. EPA (2021a) did not derive a final short-term exposure RfD for a 7-to-30-day exposure on which to base a ten-day HA for GenX chemicals.

For cancer toxicity, one chronic 2-year study in rats evaluating the carcinogenicity of GenX chemicals was identified (U.S. EPA, 2021a). In accordance with the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005b), EPA concluded that there is *Suggestive Evidence of Carcinogenic Potential* following oral exposure in humans for GenX chemicals based on female hepatocellular adenomas and carcinomas and male combined pancreatic acinar adenomas and carcinomas observed in the chronic 2-year study in rats (U.S. EPA, 2021a). A cancer slope factor (CSF) was not derived for GenX chemicals in the toxicity assessment. This is consistent with EPA's guidelines which state that when the available evidence is suggestive for carcinogenicity, a quantitative risk estimate is generally not derived unless there exists a well-conducted study that could facilitate an understanding of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities (U.S. EPA, 2005a). Therefore, EPA did not derive a 10^{-6} cancer risk concentration in the HA for GenX chemicals.

EPA developed two analytical methods to quantitatively monitor drinking water for targeted PFAS that include HFPO dimer acid: EPA Method 533 (U.S. EPA, 2019b), which has a quantitation limit of 3.7 ng/L for HFPO dimer acid, and EPA Method 537.1, Version 2.0 (U.S. EPA, 2020b), which has a quantitation limit for HFPO dimer acid at 4.3 ng/L. These analytical methods can both effectively and accurately monitor drinking water for HFPO dimer acid at levels below the lifetime HA of 10 ng/L. Treatment technologies, including sorption-based processes such as activated carbon and ion exchange, along with high pressure membrane processes such as reverse osmosis (RO), and nanofiltration (NF), are available and have been shown to remove HFPO dimer acid in drinking water.

1.0 Introduction and Background

The Safe Drinking Water Act (SDWA) (42 U.S.C. § § 300f - 300j-27) authorizes the U.S. Environmental Protection Agency (EPA) to develop drinking water Health Advisories (HAs).[1] HAs are national non-enforceable, non-regulatory drinking water concentration levels of a specific contaminant at or below which exposure for a specific duration is not anticipated to lead to adverse human health effects.[2] HAs are intended to provide information that tribal, state, and local government officials and managers of public water systems (PWSs) can use to determine whether actions are needed to address the presence of a contaminant in drinking water. HA documents reflect the best available science and include HA values as well as information on health effects, analytical methodologies for measuring contaminant levels, and treatment technologies for removing contaminants from drinking water. EPA's lifetime HAs identify levels to protect all Americans, including sensitive populations and life stages, from adverse health effects resulting from exposure throughout their lives to contaminants in drinking water.

In October 2021, EPA published a final toxicity assessment for two per- and polyfluoroalkyl substances (PFAS), hexafluoropropylene oxide (HFPO) dimer acid and its ammonium salt, collectively known as "GenX chemicals" (U.S. EPA, 2021a). EPA's final *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"* was an essential step to better understanding the potential human health effects of exposure to these two main GenX chemicals. The human health chronic reference dose (RfD) calculated in the toxicity assessment allows EPA to develop a lifetime HA that will help communities make informed decisions about GenX chemicals to better protect human health. The final HA for GenX chemicals satisfies a commitment described in EPA's PFAS Strategic Roadmap (U.S. EPA, 2021b).

1.1 History under SDWA

HFPO dimer acid and its ammonium salt are not currently regulated under SDWA. GenX is a trade name for a technology that is used to make high-performance fluoropolymers without the use of perfluorooctanoic acid (PFOA). In 2008, DuPont de Nemours, Inc. (hereinafter DuPont) submitted premanufacture notices to EPA under the Toxic Substances Control Act (Title 15 of the United States Code § 2601 et seq.) for two chemicals:

- 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) propanoic acid (CASRN13252-13-6) or HFPO dimer acid
- ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) propanoate (CASRN 62037-80-3) or HFPO dimer acid ammonium salt

Both HPFO dimer acid and its ammonium salt are components of the GenX processing aid technology that DuPont developed to make high-performance fluoropolymers without using

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[1] SDWA § 1412(b)(1)(F) authorizes EPA to "publish health advisories (which are not regulations) or take other appropriate actions for contaminants not subject to any national primary drinking water regulation." www.epa.gov/sites/default/files/2020-05/documents/safe_drinking_water_act-title_xiv_of_public_health_service_act.pdf

[2] This document is not a regulation and does not impose legally binding requirements on EPA, states, tribes, or the regulated community. This document is not enforceable against any person and does not have the force and effect of law. No part of this document, nor the document as a whole, constitutes final agency action that affects the rights and obligations of any person. EPA may change any aspects of this document in the future.

PFOA (U.S. EPA, 2021a). These compounds fall into the perfluoroalkyl ether carboxylic acids (PFECAs) PFAS class or subgroup. Although not the only GenX chemicals, HFPO dimer acid and its ammonium salt are the major chemicals associated with the GenX processing aid technology (ECHA, 2015; U.S. EPA, 2021a). The lifetime HA for GenX chemicals derived in this document pertains only to the two major GenX chemicals, HFPO dimer acid and its ammonium salt, because this was the scope of the toxicity assessment for GenX chemicals (U.S. EPA, 2021a).

HFPO dimer acid and its ammonium salt were listed on the draft fifth SDWA Contaminant Candidate List (CCL 5) not as individual chemicals but as part of the PFAS group inclusive of any PFAS except for PFOA and perfluorooctanesulfonic acid (PFOS) (U.S. EPA, 2021c). The Contaminant Candidate List (CCL) is a list of contaminants that are not subject to any proposed or promulgated National Primary Drinking Water Regulations, are known or anticipated to occur in PWSs and may require regulation under SDWA.[3] EPA is currently evaluating public comments and additional information to inform the Final CCL 5 and any future regulatory actions for these chemicals under SDWA.

The 1996 amendments to SDWA require that EPA issue a new list of unregulated contaminants (once every five years) to be monitored by PWSs.[4] Under the Unregulated Contaminant Monitoring Rule (UCMR), EPA collects occurrence data for contaminants that may be present in drinking water but do not have health-based standards set under SDWA. HFPO dimer acid is one of 29 PFAS included for monitoring under the fifth Unregulated Contaminant Rule (UCMR 5) between 2023 and 2025 (U.S. EPA, 2021d). The collection of drinking water occurrence data supports EPA's future regulatory determinations and may support additional actions to protect public health (U.S. EPA, 2021d).

1.2 Current Advisories and Guidelines

Table 1 provides drinking water guideline values for GenX chemicals that have been developed by states. The state values range from 21 to > 700 parts per trillion (ppt) or nanograms per liter (ng/L). This broad range of values may in part reflect differences in the level type derived, state guidance, or use of different methods (see references for more details).

Table 1. State Guideline Values for GenX Chemicals

State[a,b]	GenX Chemical Level (ppt [ng/L])	Standard/Guidance	Type of Medium	Reference
Hawaii	160	Environmental Action Levels	Groundwater	HIDOH (2020)
Illinois	21	Health-Based Guidance Level	Drinking water; Groundwater	Illinois EPA (2022)

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[3] https://www.epa.gov/ccl/basic-information-ccl-and-regulatory-determination

[4] SDWA § 1445 (a)(1)(D)(2)(B) — "Not later than 3 years after the date of enactment of the Safe Drinking Water Act Amendments of 1996 and every 5 years thereafter, the Administrator shall issue a list pursuant to subparagraph (A) of not more than 30 unregulated contaminants to be monitored by public water systems and to be included in the national drinking water occurrence data base maintained pursuant to subsection (g)."

State[a,b]	GenX Chemical	Standard/Guidance	Type of Medium	Reference
Indiana	> 700	Action Level	Drinking water	IDEM (2022)
Michigan	370	Drinking Water Maximum Contaminant Level	Drinking water; Groundwater	EGLE (2020)
North Carolina	140	Health Goal	Drinking water	NCDHHS (2017)
Ohio	21	Action Level	Drinking water	Ohio EPA and ODH (2022)
Wisconsin	300	Recommended Enforcement Standard	Groundwater	Wisconsin DHS (2020)
	30	Recommended Preventive Action Limit	Groundwater	

Notes:

[a] The information was collected via EPA regional office outreach by EPA's Office of Science and Technology (OST) in March 2022; and from the Interstate Technology and Regulatory Council's (ITRC) *Standards and guidance values for PFAS in groundwater, drinking water, and surface water/effluent (wastewater)* PFAS Water and Soil Values Table, last updated in April 2022 (available for download here: https://pfas-1.itrcweb.org/fact-sheets/).

[b] Only states with final guidelines are included in the table. Note: EPA regions report that New Jersey and New York are developing guidelines for GenX chemicals.

Table 2 provides drinking water guideline values for GenX chemicals that have been developed by international agencies; the Interstate Technology and Regulatory Council (ITRC) only reported guideline values for GenX chemicals for the Netherlands (ITRC, 2022). The guidelines presented are indicative levels for severe pollution in drinking water (660 ppt or ng/L) and groundwater (140,000 ppt or ng/L). Other countries may be developing guidelines for GenX chemicals.

Table 2. International Guideline Values for GenX Chemicals

Country[a,b]	GenX Chemical Level (ppt [ng/L])	Standard/Guidance	Type of Medium	Reference
The Netherlands	660	Indicative Level for Severe Pollution	Drinking water	ITRC (2022)
	140,000	Indicative Level for Severe Pollution	Groundwater	

Notes:

[a] The information was collected from ITRC *Standards and guidance values for PFAS in groundwater, drinking water, and surface water/effluent (wastewater)* PFAS Water and Soil Values Table, last updated in April 2022 (available for download here: https://pfas-1.itrcweb.org/fact-sheets/).

[b] Only countries with guideline values provided in the ITRC table are included; other countries may be developing guidelines for GenX chemicals.

1.3 Uses and Sources of GenX Chemicals

GenX chemicals are used to manufacture fluoropolymers. Since GenX chemicals are substitutes for PFOA, products (e.g., some nonstick coatings, aqueous film-forming foam [AFFF]) that were previously made using PFOA may now rely on GenX chemicals. PFOA was phased out between 2006 and 2015 in the United States under an agreement between EPA and eight major PFAS companies under the PFOA Stewardship Program[5] established in 2006. According to the Chemours Company,[6] fluoropolymers have "countless" industrial applications, including in the medical, automotive, electronics, aerospace, energy, and semiconductor industries.[7] The Chemours Company uses GenX chemicals to produce four trademarked fluoropolymers: Teflon™ polytetrafluoroethylene (PTFE), Teflon™ perfluoroalkoxy (PFA), Teflon™ fluorinated ethylene propylene (FEP), and Teflon™ amorphous fluoropolymer (AF) (Chemours, 2022). GenX chemicals may also be generated as a byproduct of fluoromonomer production. There is a paucity of publicly available information on specific end-use products made with GenX chemicals.

Potential sources of GenX chemicals in the environment include industrial facilities that use GenX technology for fluoropolymer or fluoromonomer production, and contaminated water, air, soil, and biosolids. GenX chemicals have been detected around the globe, in surface water, groundwater, finished drinking water, rainwater, air, soil, and sediment as further described below and in U.S. EPA (2021a).

1.4 Environmental Fate, Occurrence in Water, and Exposure to Humans

1.4.1 Environmental Fate and Transport in the Environment

As noted in U.S. EPA (2021a), HFPO dimer acid and its ammonium salt are stable to photolysis, hydrolysis, and biodegradation. The degradation data suggest that they will be persistent (i.e., have a half-life [$t_{1/2}$] longer than six months) in air, water, soil, and sediments. Measured physical-chemical and sorption data indicate that GenX chemicals are expected to run off into surface water and to leach to groundwater from soil and landfills. Based on chemicals with similar properties (e.g., PFOA), HFPO dimer acid and its ammonium salt might undergo long-range atmospheric transport in the vapor phase and associate with particulates. They are not expected to be removed during conventional wastewater treatment or conventional drinking water treatment processes such as coagulation, flocculation, or sedimentation.

When released to the freshwater environment, HFPO dimer acid will dissociate to the HFPO carboxylate anion and hydronium cation (H_3O^+). The ammonium salt will dissolve to the HFPO carboxylate anion and the ammonium cation (NH_4^+). Both HFPO dimer acid and its ammonium salt are highly water-soluble and are expected to remain in water with low sorption to sediment or soil. Based on its high vapor pressure, the HFPO dimer acid can partition to air. The ammonium salt can also be transported in air, although the mechanism of vapor phase transport is not well understood (DuPont CCAS, 2009). In the vapor phase, the HFPO dimer acid and its

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[5] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/fact-sheet-20102015-pfoa-stewardship-program

[6] The GenX processing technology and associated chemicals are products of The Chemours Company, a spin-off of DuPont de Nemours, Inc. (Chemours, 2015).

[7] https://www.epa.gov/system/files/documents/2022-03/3.18.22-request-for-correction-letter-and-exhibits_0.pdf

ammonium salt are expected to be stable to direct photolysis and will undergo hydroxyl radical-catalyzed indirect photolysis very slowly (U.S. EPA, 2021a).

1.4.2 Occurrence in Water

GenX chemicals can enter the aquatic environment through industrial discharges, runoff into surface water, and leaching into groundwater from soil and landfills (U.S. EPA, 2021a). GenX chemicals are water-soluble, with solubilities of greater than 751 grams per liter (g/L) and greater than 739 g/L for HFPO dimer acid and its ammonium salt, respectively, at 20°C (U.S. EPA, 2021a). Volatilization from water surfaces is expected to be an important fate process for both HFPO dimer acid and its ammonium salt (U.S. EPA, 2021a). Due to the limited number of U.S. occurrence studies on GenX chemicals, this section includes studies conducted outside as well as inside the U.S. to better understand sources and occurrence patterns in water.

1.4.2.1 Drinking Water

GenX chemicals were not included in the suite of PFAS analyzed in EPA's Third Unregulated Contaminant Monitoring Rule (UCMR 3) monitoring; thus, national GenX chemicals occurrence data from drinking water facilities are not available at this time (U.S. EPA, 2017a). However, occurrence data for GenX chemicals in drinking water are available, collected using EPA methods 533 and 537.1, from studies investigating areas known to be affected by GenX chemicals in a subset of U.S. states. GenX chemicals have been detected in the finished drinking water of at least nine states (ADEM, 2020; CDPHE, 2020; KYDEP, 2019; Michigan EGLE, 2021; NCDEQ, 2021, NHDES, 2021; Ohio DOH, 2021; SCDHEC, 2020; VTDEC, 2021). In states where sampling locations were selected randomly, the percentage of total samples that had concentrations of GenX chemicals above the reporting limit is generally well below 1%. Where targeted sampling has been performed, some states have found GenX chemicals at relatively higher concentrations, whereas in other states, the total number of samples with GenX chemicals is low or there are no detections. Further, EPA is aware of four states in which state-level monitoring efforts have found GenX chemicals in at least one finished water sample at a concentration above 0.010 micrograms per liter (µg/L) (10 ng/L). For example, the Kentucky Department for Environmental Protection (KYDEP, 2019) detected HFPO dimer acid in 11 post-treatment samples from statewide drinking water treatment plants (DWTPs) (median concentration of < 1.32 ng/L and maximum concentration of 29.7 ng/L). There were 10 detections of HFPO dimer acid at DWTPs that use surface water and one detection at a DWTP that uses groundwater; all detections occurred at DWTPs that use the Ohio River and Ohio River Alluvium as sources. Many of the DWTPs tested did not utilize treatment technologies that remove PFAS at that time.

In addition to those data collected by some states, GenX chemicals have been detected in three on-site production wells and one on-site drinking water well at the Chemours Washington Works facility outside of Parkersburg, West Virginia (U.S. EPA, 2021a). EPA subsequently requested that Chemours test for GenX chemicals in both raw and finished water at four PWSs and 10 private drinking water wells in Ohio and West Virginia near the Washington Works facility. Chemours completed the additional testing in February 2018 and reported HFPO dimer acid concentrations of < 0.010–0.081 µg/L in the PWS samples before treatment and < 0.010–0.052 µg/L in the private drinking water wells before treatment (U.S. EPA, 2018). Results for all samples collected after treatment were below the reporting limit of 0.010 µg/L (10 ng/L) achievable at that time (U.S. EPA, 2018). Additionally, a study by Galloway et al. (2020) analyzed eight drinking water samples from public buildings (e.g., schools and libraries) and private wells located more than 27 kilometers (km) northeast of the Washington Works facility. HFPO dimer acid was detected in only one sample, and at a concentration below the limit of quantification (LOQ).

Three published studies evaluated the occurrence of GenX chemicals in drinking water near Cape Fear River in North Carolina (McCord et al., 2018; Pritchett et al., 2019; Sun et al., 2016). In finished drinking water collected from a DWTP downstream of a fluorochemical manufacturer, McCord et al. (2018) reported an HFPO dimer acid concentration of approximately 500 ng/L. After this sampling, the fluorochemical manufacturer diverted waste stream emissions from one of its manufacturing lines, and subsequent measured concentrations at this location were close to or below the North Carolina Department of Health and Human Services (NCDHHS) provisional health goal (PHG) of 140 ng/L. Pritchett et al. (2019) reported that according to the North Carolina Department of Environmental Quality (NCDEQ), as of April 2018, 207 out of 837 private wells (25%) within a 5-mile radius of a PFAS manufacturing facility in the Cape Fear River basin had levels of GenX chemicals exceeding the NCDHHS PHG of 140 ng/L, with a maximum measured concentration of 4,000 ng/L. Sun et al. (2016) analyzed finished drinking water from a DWTP downstream of a PFAS manufacturing site and reported HFPO dimer acid concentrations of ~475 ng/L.

Three European studies on GenX chemicals occurrence in drinking water were identified: two studies that analyzed drinking water samples from the vicinity of the same fluorochemical plant in the Netherlands (Brandsma et al., 2019; Gebbink et al., 2017), and a third that analyzed drinking water from areas of Belgium and the Netherlands, some of which were in the vicinity of known PFAS point sources (Vughs et al., 2019). Gebbink et al. (2017) detected HFPO dimer acid in drinking water samples from three of four sites in the vicinity of the fluorochemical plant, at concentrations of 0.25, 0.48, and 11 ng/L, respectively. All three sites at which HFPO dimer acid was detected were downstream of the plant; the high concentration of 11 ng/L was measured at the downstream site closest to the plant. HFPO dimer acid was not detected in samples from two control sites nor in a sample from a site upstream of the plant. Brandsma et al. (2019) analyzed drinking water at residential homes from six different municipalities within 50 km of the same fluorochemical plant featured in the study by Gebbink et al. (2017). The measured levels of HFPO dimer acid ranged from 1.4 to 8.1 ng/L; the highest concentration (8.1 ng/L) was measured at the sampling site that was closest to and downstream of the plant. Vughs et al. (2019) analyzed drinking water from 11 water suppliers at sites in Belgium and the Netherlands, some of which were in the vicinity of a fluoropolymer manufacturing plant. HFPO dimer acid was detected in 46% of samples, with a mean concentration of 2.9 ng/L and maximum concentration of 28 ng/L. The study reported that concentrations above 4 ng/L were measured in drinking water from suppliers that sourced surface water in the vicinity of the fluoropolymer manufacturing plant in the Netherlands. However, the study did not map the distribution of reported concentrations by geographic location or with respect to distance from the fluoropolymer manufacturing plant.

1.4.2.2 Groundwater

Petre et al. (2021) quantified the mass transfer of PFAS, including GenX chemicals, from contaminated groundwater to five tributaries of the Cape Fear River. All sampling sites were located within 5 km of a manufacturing plant known known to be a major source of PFAS contamination. HFPO dimer acid and another fluoroether (perfluoro-2-[perfluoromethoxy] propanoic acid) together accounted for 61% of the total quantified PFAS. The study authors calculated that approximately 32 kg/year of PFAS is discharged from contaminated groundwater to the five tributaries. These data indicate that the discharge of contaminated groundwater has led to long-term contamination from GenX chemicals in surface water and could lead to subsequent impacts on downstream drinking water (Petre et al., 2021).

In a European study, Vughs et al. (2019) reported that HFPO dimer acid was not detected in any of five samples of groundwater obtained from water suppliers in the Netherlands and Belgium. Some sampling locations were in the vicinity of a fluoropolymer manufacturing plant, but the study did not identify the locations of sites relative to the plant.

1.4.2.3 Surface Water

Chemours has reported that GenX chemicals have been discharged into the Cape Fear River for several decades as a byproduct of other manufacturing processes (NCDEQ, 2017). Additionally, several studies evaluated the occurrence of GenX chemicals in surface waters, with studies conducted in North America, Europe, Asia, and across multiple continents (see Appendix B, Table B-1). As noted in the final toxicity assessment for GenX chemicals (U.S. EPA, 2021a), GenX chemicals were first detected in North Carolina's Cape Fear River and its tributaries in the summer of 2012 (Pritchett et al., 2019; Strynar et al., 2015). Since that finding, U.S. studies of surface waters, some of which are source waters for PWSs, have reported results of sampling efforts from contaminated areas near the Cape Fear River (McCord et al., 2018; Sun et al., 2016) and in Ohio and West Virginia (Galloway et al., 2020).

In studies of the Cape Fear River basin by McCord et al. (2018) and Sun et al. (2018), surface water concentrations of GenX chemicals ranged from below the NCDHHS PHG of 140 ng/L to a maximum level of 4,560 ng/L. Sun et al. (2016) analyzed surface water from two sites upstream of a DWTP and one site downstream. They reported a median HFPO dimer acid concentration of 304 ng/L with a maximum of 4,560 ng/L in the source water of the plant. HFPO dimer acid levels did not exceed the quantitation limit (10 ng/L) at the two upstream locations. In source water samples collected from the Cape Fear River near a DWTP downstream of a fluorochemical manufacturer, McCord et al. (2018) reported initial HFPO dimer acid concentrations of approximately 700 ng/L. After the manufacturer diverted waste stream emissions from one of its manufacturing lines, the measured concentrations decreased to levels below the NCDHHS PHG (140 ng/L).

In Ohio and West Virginia, Galloway et al. (2020) sampled rivers and streams located upstream, downstream, and downwind to the north and northeast of the Chemours Washington Works facility outside Parkersburg, West Virginia. The downwind sampling was intended to explore potential airborne deposition. Some of the downstream sampling sites were in the vicinity of landfills. Reported levels of HFPO dimer acid in these waters ranged from non-detectable levels to a maximum of 227 ng/L. The highest HFPO dimer acid concentrations were measured downwind of the facility (i.e., to the northeast). The study observed an exponentially declining trend of HFPO dimer acid concentrations in surface water with distance from the facility in this direction and attributed its occurrence in surface water to air dispersion of emissions from the facility. The most distant site where HFPO dimer acid was detected was 24 km north of the facility.

In one study of sites located in highly industrialized commercial waterways (authors did not indicate whether sampling sites were in the vicinity of known PFAS point sources), Pan et al. (2018) detected HFPO dimer acid in 100% of samples from sites in the Delaware River (n=12), reporting median and maximum concentrations of 2.02 ng/L and 8.75 ng/L, respectively, in surface waters.

Globally, GenX chemicals occurrence has been reported in surface waters from Germany (Heydebreck et al., 2015; Pan et al., 2018), China (Heydebreck et al., 2015; Li et al., 2020a; Pan et al., 2017, 2018; Song et al., 2018), the Netherlands (Gebbink et al., 2017; Heydebreck et al., 2015; Pan et al., 2018), the United Kingdom (Pan et al., 2018), South Korea (Pan et al., 2018), and Sweden (Pan et al., 2018). HFPO dimer acid was also detected with a mean concentration of 30 picograms per liter (pg/L; 0.030 ng/L) in Artic seawater samples, suggesting long-range transport (Joerss et al., 2020).

In one study of surface water collected from industrialized areas in Europe (authors did not indicate whether sampling sites were in the vicinity of known PFAS point sources), Pan et al. (2018) reported HFPO dimer acid detections in 100% of samples from the Thames River in the United Kingdom (n=6 sites), the Rhine River in Germany and the Netherlands (n=20 sites), and the Malaren Lake in Sweden (n=10 sites). Across these three river systems, median HFPO dimer acid concentrations ranged from 0.90 to 1.38 ng/L and the highest concentration detected was 2.68 ng/L.

Heydebreck et al. (2015) detected HFPO dimer acid at 17% of sampling locations on the industrialized non-estuarine reaches of the Rhine River, with a maximum concentration of 86.08 ng/L; however, HFPO dimer acid was not detected at locations on the Elbe River.

Gebbink et al. (2017) evaluated surface water samples upstream and downstream of a fluorochemical production plant in the Netherlands and reported only one of three samples upstream of the plant with detectable HFPO dimer acid concentrations (22 ng/L; method quantification limit [MQL] = 0.2 ng/L). Downstream of the fluorochemical plant, HFPO dimer acid was detected in 100% of samples, with a mean concentration of 178 ng/L and a range of 1.7 to 812 ng/L. Vughs et al. (2019) analyzed surface water from 11 water suppliers in the Netherlands and Belgium, some of which were located in the vicinity of a fluoropolymer manufacturing plant. The authors reported HFPO dimer acid detections in 77% of surface water samples (n=13) with a mean concentration of 2.2 ng/L and a maximum of 10.2 ng/L; however, only three samples in the study had HFPO dimer acid concentrations exceeding 1 ng/L.

Of the five studies conducted in China, one study evaluated surface water samples from an industrialized region (authors did not indicate whether sampling sites were in the vicinity of known PFAS point sources) (Pan et al., 2018), one study evaluated surface water river and reservoir samples in an industrialized river basin with potential PFAS point sources (Li et al., 2020a), and three studies examined samples from sites along the Xiaoqing river at locations upstream, downstream, or in the vicinity of known PFAS sources (Heydebreck et al., 2015; Pan et al., 2017; Song et al., 2018). GenX chemicals were detected in freshwater systems sampled in all five studies, though HFPO dimer acid concentrations appeared to be positively correlated with proximity to known PFAS point sources. Song et al. (2018), Pan et al. (2017), and Heydebreck et al. (2015) sampled sites in the Xiaoqing River system, including one of its tributaries, nearby a known fluoropolymer production facility. These three studies reported maximum HFPO dimer acid concentrations of 9,350, 2,060, and 3,060 ng/L, respectively. HFPO dimer acid concentrations in samples collected upstream of the facility did not exceed 3.64 ng/L. Other Chinese freshwater systems evaluated in the other two studies (Li et al., 2020a; Pan et al., 2018) generally reported maximum concentrations similar to those from the upstream Xiaoqing River system sites (≤ 10.3 ng/L), except for one site in Tai Lake which was reported to have a maximum HPFO dimer acid concentration of 143 ng/L. Similarly, in a study that sampled an industrialized river in South Korea (authors did not report whether sampling sites were in the vicinity of known PFAS point sources), HFPO dimer acid was found in 100% of samples and the maximum concentration found was 2.49 ng/L (Pan et al., 2018).

1.4.3 Exposure in Humans

As described 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"* (U.S. EPA, 2021a), PFAS including GenX chemicals were analyzed in 2,682 urine samples of children ≥ 6 years of age collected as part of the 2013–2014 National Health and Nutrition Examination Survey (NHANES) (Calafat et al., 2019). GenX chemicals were detected (limit of detection of 0.1 µg/L) in the urine in approximately 1.2% of the population, though this limit of detection is 10-fold greater than the lifetime HA, which may lead to the low rate of urine positivity. The finding for GenX chemicals was similar to PFOA and PFOS which were only detected in paired urine samples for < 0.1% of the same population. In serum samples, PFOA and PFOS were detected in > 98% of this same study population (HFPO dimer acid was not measured), demonstrating that serum is a better biomarker than urine for PFAS.

The Chemours Company submitted a report to EPA of their analysis of HFPO dimer acid assessment in 24 human plasma samples. The results of their analysis are publicly available in a truncated study report that does not appear to be peer-reviewed or be the results of an epidemiology study. The results of their analysis found HFPO dimer acid at concentrations ranging from 1.0 ng/mL (reporting limit) to 51.2 ng/mL in plasma samples (DuPont-C30031_516655, 2017). HFPO dimer acid was not detected above the analytical reporting limit of less than 1.0 ng/mL in seven of the samples. However, it is important to note that interpretation of these results is difficult given that the publicly available information is lacking study design details, study participant characteristics, or exposure detail (e.g., "some of these workers are in areas with potential for exposure, others are not.")

Concern in the Cape Fear Watershed communities about the detection of GenX chemicals in water led to the initiation of a human exposure study in this area.[8] In blood samples from 344 Wilmington, North Carolina residents collected between November 2017 and May 2018 (including repeat sampling of 44 participants), GenX chemicals were not detected above the analytical reporting limit of 2 ng/mL in any of the blood samples collected (Kotlarz et al., 2020). It is difficult to draw conclusions about GenX exposure because discharge control of GenX chemicals from the nearby Chemours Fayetteville Works plant began in June of 2017 and by

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[8] See GenX Exposure Study website, located at https://genxstudy.ncsu.edu/

September of 2017, the facility stopped discharging process wastewater containing PFAS into the Cape Fear River. Also, it is unknown whether study participants were drinking tap water, bottled water, or filtered tap water at the time of sample collection. GenX chemicals were not detected in a study from the Cape Fear River that measured concentrations of GenX chemicals and other PFAS in the urine and serum of nearby residents who had high concentrations of GenX in their drinking water wells (Pritchett et al., 2019). The authors indicated that it was not known if residents were using the well water or bottled water, but this finding does support the shorter $t_{1/2}$ in humans for GenX chemicals in comparison to other PFAS.

2.0 Problem Formulation and Scope

2.1 Conceptual Model

A conceptual model provides useful information to characterize and communicate the potential health risks related to GenX chemicals exposure from drinking water and to outline the scope of the HA. The sources of GenX chemicals, the routes of exposure for biological receptors of concern (e.g., various human activities related to tap water ingestion such as drinking, food preparation, and consumption), the potential health effects, and exposed populations including sensitive populations and life stages are depicted in the conceptual diagram below (Figure 1).

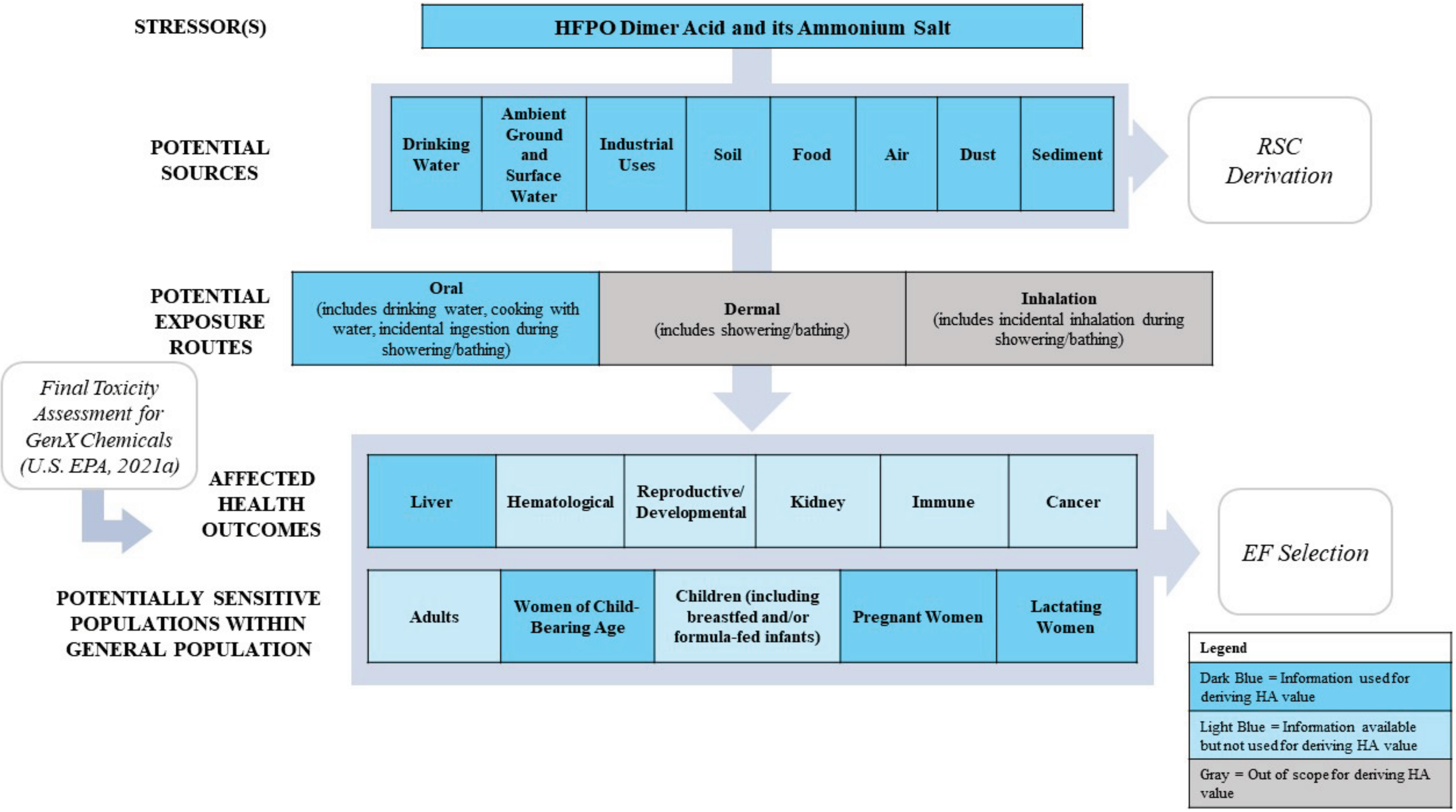

Figure 1. Conceptual Model for the Development of the Drinking Water Health Advisory for GenX Chemicals.

The conceptual model is intended to explore potential links between exposure to a contaminant or stressor and the adverse health outcomes, and to outline the information sources used to identify or derive the input values used for the HA derivation, which are the RfD, relative source contribution (RSC), and exposure factor (EF). The conceptual model also illustrates the scope of the GenX chemicals HA, which considers the following factors:

Stressors: The scope of this drinking water HA includes the two main GenX chemicals, the HFPO dimer acid and its ammonium salt, consistent with the scope of the 2021 toxicity assessment for GenX chemicals (U.S. EPA 2021a). The HFPO dimer acid and its ammonium salt are the two current commercial products of the GenX technology.

Potential Sources of Exposure: The scope of exposure sources considered for the HA derivation is limited to drinking water from public water facilities or private wells. Sources of exposure to GenX chemicals include both ground and surface waters used for drinking. To develop the RSC, information about non-drinking water sources was identified to determine the portion of the RfD attributable to drinking water. Non-drinking water sources of GenX chemicals for which studies were identified include foods, indoor dust, soil, air, and sediment. Consumer products and biosolids are other potential sources of exposure but relevant studies were not identified (see Section 3.3.1). Since GenX chemicals are replacements for PFOA, they could be present in consumer products (e.g., stain- and water-repellent textiles). Information on specific products containing GenX chemicals is not available, but they may be present in consumer products within the home, workplace, schools, and daycare centers.

Potential Exposure Routes: Oral exposure to GenX chemicals from contaminated drinking water sources (e.g., via drinking water, cooking with water, and incidental ingestion from showering) is the focus of the HA. The drinking water HA value does not apply to other exposure routes. However, information on other potential routes of exposure including dermal exposure (contact of exposed parts of the body with water containing GenX chemicals during bathing, showering, etc.) and inhalation exposure (during bathing or showering, using a humidifier or vaporizer, etc.) was considered to develop the RSC.

Affected Health Outcomes: The toxicity assessment for GenX chemicals (U.S. EPA, 2021a) considered all publicly available human, animal, and mechanistic studies of effects after exposure to GenX chemicals. The evaluation identified associations between GenX chemicals exposure and the following health outcomes: hepatic, hematological, developmental/ reproductive, renal, immune and cancer.

Potentially Sensitive Populations and Life Stages: The receptors are humans in the general population who could be exposed to GenX chemicals from tap water through ingestion at their homes and other places (e.g., workplaces, schools, daycare centers). Within the general population, there are potentially sensitive populations or life stages that may be more susceptible due to increased exposure and/or response. Potentially sensitive populations include pregnant women, women of childbearing age, and lactating women.

2.2 Analysis Plan

2.2.1 Health Advisory Guidelines

Assessment endpoints for HA guidelines or values can be developed, depending on the available data, for both short-term (one-day and ten-day) and lifetime exposure using information on the noncarcinogenic and carcinogenic toxicological endpoints of concern. Where data are available, HAs can reflect sensitive populations or life stages that may be more susceptible and/or more highly exposed.

> **One-Day HA** is protective of noncancer effects for up to 1 day of exposure and is typically based on an *in vivo* toxicity study with a duration of 7 days or less. It is typically calculated for an infant.
>
> **Ten-Day HA** is protective of noncancer effects for up to 10 days of exposure and is typically based on an *in vivo* toxicity study with a duration of 7 to 30 days. It is typically calculated for an infant.
>
> **Lifetime HA** is designed to be protective of noncancer effects over a lifetime of exposure and is typically based on a chronic *in vivo* experimental animal toxicity study and/or human epidemiological data.
>
> **10^{-6} Cancer Risk Concentration** is the concentration of a carcinogen in water at which the population is expected to have a one in a million (10^{-6}) excess cancer risk above background after exposure to the contaminant over a lifetime. It is calculated for carcinogens classified as known or likely human carcinogens (U.S. EPA, 1986, 2005b). Cancer risk concentrations are not derived for substances for which there is suggestive evidence of carcinogenic potential unless the cancer risk has been quantified.

2.2.2 Sources of Toxicity Information for Health Advisory Development

The final toxicity assessment for GenX chemicals, entitled *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"* published in October 2021 (U.S. EPA, 2021a), serves as the basis of the toxicity information and chronic RfD used to derive the lifetime noncancer HA for GenX chemicals. It also synthesizes and describes other information on GenX chemicals including physiochemical properties and toxicokinetics. This final toxicity assessment was published after a rigorous process of literature review, draft assessment development, agency and interagency review, an independent peer review, public comment, an independent expert review of data from two studies by the National Toxicology Program, and a second independent peer review.

2.2.3 Approach and Scope for Health Advisory Derivation

2.2.3.1 Approach for Deriving Noncancer HAs

The following equations (Eqs. 1–3) are used to derive the HAs.[9] Lifetime HAs and 10^{-6} cancer risk concentrations are only derived for chemicals without an existing National Primary Drinking Water Regulation.

$$\textbf{One-Day HA} = \left(\frac{\text{POD}}{\text{UF}_\text{C} * \text{DWI-BW}}\right)$$

POD is typically derived from a toxicity study of duration 7 days or less

(Eq. 1)

$$\textbf{Ten-Day HA} = \left(\frac{\text{POD}}{\text{UF}_\text{C} * \text{DWI-BW}}\right)$$

POD is typically derived from a toxicity study of duration 7–30 days

(Eq. 2)

$$\textbf{Lifetime HA} = \left(\frac{\text{RfD}}{\text{DWI-BW}}\right) * \text{RSC}$$

RfD is typically derived from a chronic study

(Eq. 3)

Where:

POD is the point of departure, typically a lowest observed adverse effect level (LOAEL), a no observed adverse effect level (NOAEL), or a benchmark dose (BMD) (lower confidence limit; BMDL) from the critical study.

UF_C is the composite UF or total UF value after multiplying individual UFs. UFs are established in accordance with EPA best practices (U.S. EPA, 2002) and consider uncertainties related to the following: variation in sensitivity among the members of the human population (i.e., inter-individual variability), extrapolation from animal data to humans (i.e., interspecies uncertainty), extrapolation from data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure), extrapolation from a LOAEL rather than from a NOAEL, and extrapolation when the database is incomplete. For GenX chemicals, the value of UF_C was determined in the final toxicity assessment (U.S. EPA, 2021a).

DWI-BW is the 90th percentile drinking water intake (DWI), adjusted for body weight (bw), for the selected population in units of liter per kilogram body weight per day (L/kg bw-day). The DWI-BW considers direct and indirect consumption of tap water (indirect water consumption encompasses water added in the preparation of foods or beverages, such as tea and coffee). For GenX chemicals, the value of this parameter is based on the critical study identified in the GenX

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[9] https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf

chemicals final toxicity assessment (U.S. EPA, 2021a), and is identified in Chapter 3 of EPA's Exposure Factors Handbook (EFH) (U.S. EPA, 2019a).

RfD is the chronic reference dose—an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure of the human population to a substance that is likely to be without an appreciable risk of deleterious effects during a lifetime. The value of this parameter was derived in the final GenX chemicals toxicity assessment and is based on the critical effect and study identified in that assessment (U.S. EPA, 2021a).

RSC is the relative source contribution—the percentage of the total oral exposure attributed to drinking water sources (U.S. EPA, 2000a) where the remainder of the exposure is allocated to other routes or sources. The RSC is calculated by examining other sources of exposure (e.g., air, food, soil) and pathways of exposure in addition to drinking water using the methodology described for calculation of an RSC described in U.S. EPA (2000a) and Section 3.3.2.

2.2.3.2 Scope of Noncancer Health Advisory Values

Adequate data are available to derive a lifetime HA for GenX chemicals. EPA's final toxicity assessment for GenX chemicals derived subchronic and chronic RfDs but not an acute or short-term RfD (U.S. EPA, 2021a). Due to the lack of an available short duration (30 day or less exposure duration) toxicity value for GenX chemicals, EPA did not develop a one-day or ten-day HA value. Specifically, EPA did not derive an RfD for durations of 7-day or less exposure period on which to base a one-day HA or an RfD for a 7-to-30-day exposure on which to base a ten-day HA for GenX chemicals in the toxicity assessment (U.S. EPA, 2021a). Information about the available acute and short-term toxicity studies for HFPO dimer acid and its ammonium salt can be found in Sections 4.1 and 4.2 and Appendix B of the toxicity assessment (U.S. EPA, 2021a).

2.2.3.3 Approach and Scope for Deriving Cancer Risk Concentrations

The following equations (Eqs. 4–5) are used to derive cancer risk concentrations.

Calculated for non-mutagenic carcinogens[10] only:

$$\mathbf{10^{-6}\ Cancer\ Risk\ Concentration} = \frac{1\text{x}10^{-6}}{\text{CSF} * \text{DWI-BW}}$$

(Eq. 4)

Calculated for mutagenic carcinogens only:

$$\mathbf{10^{-6}\ Cancer\ Risk\ Concentration} = \frac{1\text{x}10^{-6}}{\text{CSF}} * \sum_{\text{i}} \left(\frac{\text{F}_{\text{i}} * \text{ADAF}_{\text{i}}}{\text{DWI-BW}_{\text{i}}}\right)$$

(Eq. 5)

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[10] https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf

Where:

CSF is the cancer slope factor—an upper bound, approximating a 95 percent confidence limit of the increased cancer risk from a lifetime of oral exposure to a stressor. The value for this parameter is derived in the final toxicity assessment when data are available.

$DWI\text{-}BW_i$ is the 90th percentile bw-adjusted DWI in units of L/kg bw-day for each age group (i), considered when calculating cancer risk concentrations for mutagenic carcinogens.

$ADAF_i$ is the age-dependent adjustment factor for each age group (i), used when calculating cancer risk concentrations for carcinogens that act via a mutagenic mode of action (U.S. EPA, 2005a,b).

F_i is the fraction of life spent in each age group (i), used when calculating cancer risk concentrations for mutagens (U.S. EPA, 2005a).

2.2.3.4 Scope of Cancer Risk Concentration Derivation

For cancer toxicity, EPA's toxicity assessment for GenX chemicals (U.S. EPA, 2021a) evaluated the weight of the evidence for cancer among the available cancer studies for GenX chemicals exposure per EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005b). Based on the evaluation of the limited (i.e., one study) data for GenX chemicals, EPA concluded that there is *Suggestive Evidence of Carcinogenic Potential* of oral exposure to GenX chemicals in humans. EPA's conclusion is based on the findings of female hepatocellular adenomas and hepatocellular carcinomas and male combined pancreatic acinar adenomas and carcinomas observed in the chronic 2-year study in rats (for more information see U.S. EPA [2021a]). The single cancer bioassay for HFPO dimer acid ammonium salt showed increased incidence of liver tumors (females) and combined pancreatic acinar adenomas and carcinomas (males) in rats at the high doses only. A CSF was not derived in the toxicity assessment for GenX chemicals (U.S. EPA, 2021a). This is consistent with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) which state that when the available evidence is suggestive for carcinogenicity, a quantitative risk estimate is generally not derived unless there exists a well-conducted study that could facilitate an understanding of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities (U.S. EPA, 2005a). In the toxicity assessment for GenX chemicals, EPA concluded that the available human and animal studies are not sufficient to establish a reasonable understanding of the magnitude and uncertainty of potential risks for exposure to GenX chemicals and tumor incidence, and therefore do not justify a quantitative cancer assessment (U.S. EPA, 2021a). Consistent with EPA's guidelines, a CSF was not derived in the toxicity assessment for GenX chemicals (U.S. EPA, 2021a). Therefore, EPA did not derive a 10^{-6} cancer risk concentration in this HA for GenX chemicals.

2.2.4 Exposure Factors for Deriving Health Advisory

2.2.4.1 Exposure Factor Selection

An EF, such as body weight-adjusted drinking water intake (DWI-BW), is one of the input values for deriving a drinking water HA. EFs are factors related to human activity patterns, behavior, and characteristics that help determine an individual's exposure to a contaminant. EPA's EFH[11] is a resource for conducting exposure assessments and provides EFs based on

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[11] EPA's EFH is available at https://www.epa.gov/expobox/about-exposure-factors-handbook

information from publicly available, peer-reviewed studies. Chapter 3 of the EFH presents EFs in the form of DWIs and DWI-BWs for various populations or life stages within the general population (U.S. EPA, 2019a). The use of EFs in HA calculations is intended to protect sensitive populations and life stages within the general population from adverse effects resulting from exposure to a contaminant.

When developing HAs, the goal is to protect all ages of the general population including potentially sensitive populations or life stages such as children. The approach to select the EF for the drinking water HA includes a step to identify sensitive population(s) or life stage(s) (i.e., populations or life stages that may be more susceptible or sensitive to a chemical exposure) by considering the available data for the contaminant. Although data gaps can make it difficult to identify the most sensitive population (e.g., not all windows of exposure or health outcomes have been assessed in studies of GenX chemicals), the critical effect and POD that form the basis for the RfD can provide some information about sensitive populations because the critical effect is typically observed at the lowest tested dose among the available data. Evaluation of the critical study, including the exposure interval, may identify a particularly sensitive population or life stage (e.g., pregnant women, formula-fed infants, lactating women). In such cases, EPA can select the corresponding DWI-BW for that sensitive population or life stage from the EFH (U.S. EPA, 2019a) to derive the HA. When multiple populations or life stages are identified based on the critical effect or other health effects data (from animal or human studies), EPA selects the population or life stage with the greatest DWI-BW because it is the most health protective. For deriving lifetime HAs, the RSC corresponding to the sensitive life stage is also determined (see Section 3.3), and the most health-protective RSC is selected when data are available for multiple sensitive populations or life stages. In the absence of information indicating a sensitive population or life stage, the DWI-BW corresponding to all ages of the general population may be selected.

To derive a chronic HA, EPA typically uses DWI normalized to body weight (i.e., DWI-BW in L of water consumed/kg bw-day) for all ages of the general population or for a sensitive population or life stage, when identified. The Joint Institute for Food Safety and Applied Nutrition's Food Commodity Intake Database (FCID) Consumption Calculator Tool[12] includes the EFs from EPA's EFH and can also be used to estimate DWI-BW for specific populations or life stages across a designated age range. EPA uses the 90th percentile DWI-BW to ensure that the HA is protective of the general population as well as sensitive populations or life stages (U.S. EPA, 2000a, 2016a). In 2019, EPA updated its EFs for DWI and DWI-BW based on newly available science (U.S. EPA, 2019a).

Table 3 shows EPA EFs for some sensitive populations or life stages. Other populations or life stages may also be considered depending on the available information regarding sensitivity to health effects after exposure to a contaminant.

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[12] Joint Institute for Food Safety and Applied Nutrition's FCID, Commodity Consumption Calculator is available at https://fcid.foodrisk.org/percentiles

Table 3. EPA Exposure Factors for Drinking Water Intake

Population or Life Stage	DWI-BW (L/kg bw-day)	Description of Exposure Metric	Source
General population (all ages)	0.0338	90th percentile direct and indirect consumption of community water, consumer-only two-day average, all ages.	2019 Exposure Factors Handbook Chapter 3, Table 3-21, NHANES 2005–2010 (U.S. EPA, 2019a)
Children	0.143	90th percentile direct and indirect consumption of community water, consumer-only two-day average, birth to < 1 year.	2019 Exposure Factors Handbook Chapter 3, Table 3-21, NHANES 2005–2010 (U.S. EPA, 2019a)
Formula-fed infants	0.249	90th percentile direct and indirect consumption of community water, formula-consumers only, 1 to < 3 months. Includes water used to reconstitute formula plus all other community water ingested.	Kahn et al. (2013), Estimates of Water Ingestion in Formula by Infants and Children Based on CSFII 1994–1996 and 1998[a,b]
Pregnant women	0.0333	90th percentile direct and indirect consumption of community water, consumer-only two-day average.	2019 Exposure Factors Handbook Chapter 3, Table 3-63, NHANES 2005–2010 (U.S. EPA, 2019a)
Women of childbearing age	0.0354	90th percentile direct and indirect consumption of community water, consumer-only two-day average, 13 to < 50 years.	2019 Exposure Factors Handbook Chapter 3, Table 3-63, NHANES 2005–2010 (U.S. EPA, 2019a)
Lactating women	0.0469	90th percentile direct and indirect consumption of community water, consumer-only two-day average.	2019 Exposure Factors Handbook Chapter 3, Table 3-63, NHANES 2005–2010[c] (U.S. EPA, 2019a)

Notes: CSFII = continuing survey of food intake by individuals; L/kg bw-day = liter per kilogram body weight per day.

[a] The sample size does not meet the minimum reporting requirements as described in the Third Report on Nutrition Monitoring in the United States (LSRO, 1995).

[b] Chapter 3.2.3 in U.S. EPA (2019a) cites Kahn et al. (2013) as the source of drinking water ingestion rates for formula-fed infants. While U.S. EPA (2019a) provides the 95th percentile total direct and indirect water intake values, Office of Water/Office of Science and Technology (OW/OST) policy is to utilize the 90th percentile DWI-BW. OW/OST was able to identify the 90th percentile DWI-BW in Kahn et al. (2013) and report the value in this table.

[c] Estimates are less statistically reliable based on guidance published in the Joint Policy on Variance Estimation and Statistical Reporting Standards on NHANES III and CSFII Reports: Human Nutrition Information Service (HNIS)/National Center for Health Statistics (NCHS) Analytical Working Group Recommendations (NCHS, 1993).

2.2.4.2 Determining Proportion of RfD Attributable to Drinking Water

To account for aggregate risk from exposures and exposure pathways other than oral ingestion of drinking water, EPA applies an RSC when calculating HAs to ensure that total human exposure to a contaminant does not exceed the daily exposure associated with the RfD. The RSC represents the proportion of an individual's total exposure to a contaminant that is attributed to drinking water ingestion (directly or indirectly in beverages like coffee, tea, or soup, as well as from transfer to dietary items prepared with drinking water) relative to other exposure pathways. The remainder of the exposure equal to the RfD is allocated to other potential exposure sources (U.S. EPA, 2000a). The purpose of the RSC is to ensure that the level of a contaminant (e.g., HA value), when combined with other identified sources of exposure common to the population of concern, will not result in exposures that exceed the RfD (U.S. EPA, 2000a).

To determine the RSC, EPA follows the Exposure Decision Tree for Defining Proposed RfD (or POD/UF) Apportionment in EPA's guidance, *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health* (U.S. EPA, 2000a). EPA considers whether there are significant known or potential uses/sources other than drinking water, the adequacy of data and strength of evidence available for each relevant exposure medium and pathway, and whether adequate information on each source is available to quantitatively characterize the exposure profile. The RSC is developed to reflect the exposure to the general population or a sensitive population within the general population.

Per EPA's guidance, in the absence of adequate data to quantitatively characterize exposure to a contaminant, EPA typically recommends an RSC of 20%. When scientific data demonstrating that sources and routes of exposure other than drinking water are not anticipated for a specific pollutant, the RSC can be raised as high as 80% based on the available data, thereby allocating the remaining 20% to other potential exposure sources (U.S. EPA, 2000a).

To inform the RSC determination, available information on all exposure sources and routes for GenX chemicals was identified using the literature search and screening method described in Appendix A. To identify information on GenX chemicals exposure routes and sources to inform RSC determination, EPA considered primary literature published between 2003–2020 and collected by EPA ORD as part of an effort to evaluate evidence for pathways of human exposure to eight PFAS, including GenX chemicals. To consider more recently published information on exposure to GenX chemicals, EPA incorporated the results of a date-unlimited gray literature search that was conducted in February 2022 as well as an ad hoc process to identify relevant and more recently published peer-reviewed scientific literature. The literature resulting from the search and screening process included only final (not draft) documents and articles that were then reviewed to inform the RSC for GenX chemicals.

3.0 Health Advisory Input Values

3.1 Toxicity Assessment Values

Table 4 summarizes the peer-reviewed chronic noncancer toxicity values for HFPO dimer acid and its ammonium salt from EPA's *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"* (U.S. EPA, 2021a).

Table 4. Chronic Noncancer Toxicity Information for GenX Chemicals for Deriving the Lifetime HA

Health Assessment	GenX Chemicals Exposure in Critical Study	RfD (mg/kg bw-day)	Critical Effect	Principal Study
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" (U.S. EPA, 2021a)	Pre-mating day 14 through lactation day 21	3×10^{-6}	Constellation of liver lesions (defined by the National Toxicology Program Pathology Working Group to include cytoplasmic alteration, hepatocellular single cell and focal necrosis, and hepatocellular apoptosis) in parental females	Oral reproductive and developmental toxicity study (Dupont 18405-1037, 2010)

Note: mg/kg bw-day = milligram per kilogram body weight per day.

As noted in EPA's toxicity assessment for GenX chemicals (U.S. EPA, 2021a), HFPO dimer acid and its ammonium salt, chronic and reproductive and developmental oral animal toxicity studies are available in rats and mice. Repeated-dose toxicity data are available for oral exposure. The available studies report liver toxicity (e.g., increased relative liver weight, hepatocellular hypertrophy, apoptosis, and single-cell/focal necrosis), kidney toxicity (e.g., increased relative kidney weight), immune effects (e.g., antibody suppression), hematological effects (e.g., decreased red blood cell count, hemoglobin, and hematocrit), reproductive/developmental effects (e.g., increased early deliveries, placental lesions, changes in maternal gestational weight gain, and delays in genital development in offspring), and cancer (e.g., liver and pancreatic tumors) after exposure to GenX chemicals. The available toxicity study findings demonstrate that the liver is particularly sensitive to HFPO dimer acid and HFPO dimer acid ammonium salt exposure.

The critical study selected for deriving the noncancer subchronic and chronic RfDs for HFPO dimer acid and/or its ammonium salt was the oral reproductive/developmental toxicity study in mice that reported a NOAEL of 0.1 milligrams per kilogram body weight per day (mg/kg bw-day) based on liver effects (a constellation of lesions, including cytoplasmic alteration, hepatocellular single-cell and focal necrosis, and hepatocellular apoptosis) in females (DuPont-18405-1037, 2010; NTP, 2019). This endpoint was selected because the available health effects studies indicate that the liver is the most sensitive target of toxicity from exposure to GenX chemicals. Liver effects were observed in both male and female mice and rats after different doses and durations of exposures. These adverse liver effects occurred at the lowest doses and shortest durations of exposure to GenX chemicals among the available data (U.S. EPA, 2021). Importantly, EPA determined that the liver lesions observed in the rodent are relevant to human health (see U.S. EPA [2021a] for more information). Using EPA's *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2012), EPA modeled the dose-response relationship in the range of observed data. Additionally, EPA's *Recommended Use of Body Weight*$^{3/4}$ *as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011) was used to allometrically scale a toxicologically equivalent dose of orally administered agents from adult laboratory animals to adult humans. Allometric scaling addresses some aspects of cross-species extrapolation of toxicokinetic and toxicodynamic processes (i.e., interspecies UFs). From BMD modeling of the DuPont-18045-1037 study, the resulting POD_{HED} is 0.01 mg/kg bw-day. For the chronic RfD, a composite UF of 3,000 was applied based on a 10X for intraspecies variability (UF_H), 3X for interspecies differences (UF_A), 10X for extrapolation from a subchronic to a chronic dosing duration (UF_S), and 10X for database deficiencies (UF_D) to yield a chronic RfD of 0.000003 mg/kg bw-day or 0.003 micrograms per kilogram body weight per day (µg/kg bw-day) (see U.S. EPA [2021a] for more details).

3.2 Exposure Factors

To identify potentially sensitive populations or life stages, EPA considered the sensitive life stage of exposure associated with the critical effect on which the chronic RfD was based. In the critical study selected in the toxicity assessment for GenX chemicals, parental female mice (approximately 10 weeks old at the start of the study) were dosed daily for 2 weeks prior to pairing, throughout gestation, and through to lactation day 20 for a total dosing duration of 53 to 65 days (Dupont 18405-1037, 2010). Therefore, exposure to GenX chemicals in the critical study corresponds to three potentially sensitive adult female life stages, women of childbearing age, pregnancy, and lactation (Table 5). For the calculation of the chronic HA for HFPO dimer acid and its ammonium salt, EPA interpreted the observation of adverse liver effects in parental females after exposure during pre-mating, pregnancy, and lactation as indicative of potentially sensitive populations relevant to the chronic exposure scenario. The available data do not permit a more precise identification of the most sensitive or critical window for GenX chemicals and the adverse liver effects because studies. However, after 10–16 days of dosing during the gestation period in mice, Blake et al. (2020) reported no significant changes in the observation of maternal liver necrosis or liver serum enzymes changes (i.e., alkaline phosphatase, alanine aminotransferase) in the 2 mg/kg bw-day dose group suggesting gestational dosing alone may be insufficient to produce adverse liver effects. These studies suggest the potential for critical windows of exposure across three potentially sensitive life stages: pre-conception or young adulthood, pregnancy, and lactation.

Given the available information, EPA identified three potentially sensitive life stages for GenX chemicals exposure—women of childbearing age (13 to < 50 years), pregnant women, and lactating women (Table 5). The Eq. used to calculate a drinking water lifetime HA (Eq. 3; also see Section 2.2.3) calculates the concentration of a contaminant in water based on the DWI for the sensitive population identified from the available studies (Chapter 3 in U.S. EPA, 2019a). Since all three life stages may represent critical windows of exposure to GenX chemicals and the DWI is higher for lactating women than for women of childbearing age or pregnant women, the DWI for lactating women was selected and is anticipated to be protective of the other two sensitive life stages.

Table 5. EPA Exposure Factors for Drinking Water Intake for Different Candidate Sensitive Populations Based on the Critical Effect and Study

Population	DWI-BW (L/kg bw-day)	Description of Exposure Metric	Source
Women of childbearing age	0.0354	90th percentile direct and indirect consumption of community water, consumer-only two-day average, 13 to < 50 years.	2019 Exposure Factors Handbook Chapter 3, Table 3-63, NHANES 2005–2010 (U.S. EPA, 2019a)
Pregnant women	0.0333	90th percentile direct and indirect consumption of community water, consumer-only two-day average.	2019 Exposure Factors Handbook Chapter 3, Table 3-63, NHANES 2005–2010 (U.S. EPA, 2019a)
Lactating women	**0.0469**	90th percentile direct and indirect consumption of community water, consumer-only two-day average.	2019 Exposure Factors Handbook Chapter 3, Table 3-63, NHANES 2005–2010[a] (U.S. EPA, 2019a)

Notes: L/kg bw-day = liters of water consumed per kilogram body weight per day. The DWI-BW used to calculate the GenX chemicals' lifetime HA is in bold.

[a] Estimates are less statistically reliable based on guidance published in the Joint Policy on Variance Estimation and Statistical Reporting Standards on NHANES III and CSFII Reports: HNIS/ NCHS Analytical Working Group Recommendations (NCHS, 1993).

3.3 Relative Source Contribution

As stated in the analysis plan, EPA collected and evaluated information about GenX chemicals exposure routes and sources to inform RSC determination. Results from the literature search are described below.

3.3.1 Non-Drinking Water Sources and Routes

EPA presents information below from studies performed in the United States as well as studies published globally for this emerging contaminant to be as comprehensive as possible, given that the overall information is limited. While the studies from non-U.S. countries inform an understanding of global exposure sources and trends, the RSC determination is based on the available data for the Unites States.

3.3.1.1 Dietary Sources

HFPO dimer acid was included in a suite of individual PFAS selected as part of PFAS-targeted reexaminations of samples collected for the U.S. Food and Drug Administration's (FDA's) Total Diet Study (U.S. FDA, 2020a,b, 2021a,b, 2022a,b); however, it was not detected in any of the food samples tested. It should be noted that FDA indicated that the sample sizes were limited and that the results should not be used to draw definitive conclusions about PFAS levels or presence in the general food supply (U.S. FDA, 2022c). HFPO dimer acid was not detected in cow milk samples collected from a farm with groundwater known to be contaminated with PFAS;

however, it was detected in produce (collard greens, cabbage) collected from an area near a PFAS production plant in FDA studies of the potential exposure to the U.S. population to PFAS (U.S. FDA 2018, 2021c). GenX chemicals were detected at low levels in 14% of vegetable garden crops (endive, beets, celery, lettuce, and tomatoes) grown near a PFAS manufacturing facility in the Netherlands (Mengelers et al., 2018; NCDEQ, 2018c).

Feng et al. (2021) measured HFPO dimer acid in food samples collected from up to ten home gardens or farms in villages within 15 km of a large fluoropolymer facility located on the Dongzhulong River in Shandong Province, China. The authors detected HFPO dimer acid in wheat (mean concentration: 5.53 nanograms per gram dry weight [ng/g dw]; range: 2.27–9.19 ng/g dw; detection frequency [DF] 100%), maize (mean concentration: 1.17 ng/g dw; range: not detected (ND)–1.94 ng/g dw; DF 80%), and vegetable samples (mean concentration: 20.1 ng/g dw; range: ND–67.2 ng/g dw; DF 82%). In fish collected at two sites along the Dongzhulong River, HFPO dimer acid was detected at concentrations of 43.9 and 3.23 ng/g dw at sites approximately 3 km and 15 km downstream of the fluoropolymer facility, respectively. HFPO dimer acid was not found in eggs (home-produced and store-bought), store-bought meat or seafood, or milk from domestic goats (Feng et al., 2021). Except for the fish sampled at two sites, the study did not report HFPO dimer acid concentrations in food according to sampling location or proximity to the fluoropolymer facility.

GenX chemicals were not target chemicals in EPA's National Lake Fish Tissue Study or EPA's 2015 Great Lakes Human Health Fish Fillet Tissue Study and they were not target chemicals in EPA's 2008–2009 or 2013–2014 National Rivers and Streams Assessment studies (Stahl et al., 2014; U.S. EPA, 2009a, 2020a, 2021e). GenX chemicals were detected in a redear sunfish fillet composite sample collected from a privately-owned lake near a PFAS manufacturing facility in North Carolina at a concentration of 270 nanograms per kilogram (ng/kg) (wet weight tissue) (U.S. EPA, 2021a; NCDEQ, 2018c). GenX chemicals were not included in the National Oceanic and Atmospheric Administration's National Centers for Coastal Ocean Science, National Status and Trends Data (NOAA, 2022). Li et al. (2021) found HFPO dimer acid in fish collected from a Xiaoqing River estuary impacted by PFAS discharge from fluoropolymer manufacturing industry, at concentrations ranging from ND to 3.47 ng/g dw (mean concentration: 0.93 ng/g dw).

3.3.1.2 Consumer Products

Although no specific studies on the occurrence of GenX chemicals in consumer products were identified, DuPont began transitioning to GenX processing aid technology in 2009 to work toward eliminating long-chain PFAS as part of the company's commitment under the 2010/2015 PFOA Stewardship Program (U.S. EPA, 2021a). It is unknown if GenX chemicals in consumer products have increased as a result of this transition.

3.3.1.3 Indoor Dust

Feng et al. (2021) detected HFPO dimer acid in indoor dust samples taken from homes from 10 villages within 15 km of a large fluoropolymer facility in Shandong Province, China, at concentrations ranging from ND to 841 ng/g (mean concentration 159 ng/g; DF 72%). Contaminated dust was found in homes as far as 15 km from the fluoropolymer facility and HFPO dimer acid concentrations were highest in homes nearest to the facility. Although only one study on the occurrence of GenX chemicals in indoor dust was identified, PFAS have been detected in indoor dust and on window films (ATSDR, 2021).

3.3.1.4 Air

PFAS have been released to air from wastewater treatment plants, waste incinerators, and landfills (U.S. EPA, 2016a). GenX chemicals could be transported in the vapor phase or with particulates (U.S. EPA, 2021a). When released to air or volatilized from water, GenX chemicals are stable and short- and long-range transport has occurred (D'Ambro et al., 2021; Galloway et al., 2020). Galloway et al. (2021) analyzed HFPO dimer acid concentrations in soil samples downwind of and surface water samples upstream of the Chemours Washington Works facility outside of Parkersburg, West Virginia, and results suggest atmospheric transport of HFPO dimer acid emissions. Additionally, a study that modeled the atmospheric transport of a PFAS mixture containing GenX chemicals from a fluoropolymer manufacturing facility in North Carolina (D'Ambro et al., 2021) predicted that only 2.5% of total GenX (consisting of HFPO dimer acid and HFPO dimer acid fluoride) would be deposited within 150 km of the facility (U.S. EPA, 2021a).

HFPO dimer acid and its ammonium salt are persistent in air (half-lives longer than 6 months), and they are not readily broken down by biodegradation, direct photolysis, or hydrolysis (U.S. EPA, 2021a). In the vapor phase, HFPO dimer acid and its ammonium salt are expected to undergo hydroxyl radical-catalyzed indirect photolysis slowly, with a predicted average hydroxylation rate of 8.50×10^{-13} cubic centimeters (cm^3)/molecule - second (U.S. EPA, 2021a, 2022a,b). Based on a measured vapor pressure of 2.7 mm Hg at 20°C for HFPO dimer acid, volatilization is expected to be an important fate process for this chemical (U.S. EPA, 2021a). EPA's Toxics Release Inventory reported release data for HFPO dimer acid and its ammonium salt in 2020 (U.S. EPA, 2022c). GenX chemicals are not listed as hazardous air pollutants (U.S. EPA, 2022d).

GenX chemicals have been identified in air emissions. NCDEQ estimates for the Chemours Fayetteville Works plant, located in the North Carolina Cape Fear watershed, indicate that annual emissions of GenX chemicals could have exceeded 2,700 pounds per year during the reporting period (2017–2018) (NCDEQ, 2018a). Rainwater samples collected within a seven-mile radius of this facility were reported to have detectable levels of GenX chemicals (NCDEQ, 2018b), with the highest concentration of 810 ng/L found in a rainwater sample collected five miles from the facility. The three samples collected seven miles from the plant had GenX chemicals concentrations ranging from 45.3 to 60.3 ng/L (NCDEQ, 2018b).

3.3.1.5 Soil

When HFPO dimer acid and its ammonium salt are deposited on or applied to soil, they are expected to run off into surface waters or rapidly leach to groundwater (U.S. EPA, 2021a). PFAS can also be taken up from contaminated soil by plants (ATSDR, 2021). No specific studies on the occurrence of GenX chemicals in biosolids were identified.

Two studies reported GenX chemicals concentrations in soil. In the United States, Galloway et al. (2020) analyzed 13 soil samples for HFPO dimer acid at locations in Ohio and West Virginia that were upstream and downwind of the Chemours Washington Works facility in order to evaluate HFPO dimer acid contamination due to atmospheric deposition. HFPO dimer acid was detected in 5 out of 13 samples, with a maximum concentration of 8.14 ng/g dw. In China, Li et al. (2020a) collected and analyzed residential soil samples throughout the country from 31 provincial-level administrative regions (consisting of 26 provinces, 4 municipalities, and 1 special administrative region). HFPO dimer acid was detected in 40.5% of soil samples at concentrations up to 967 picograms per gram (pg/g) dw and a mean level of 19.1 pg/g dw. PFOA was detected in these soils more frequently (96.6%) and at higher mean levels (354 pg/g dw), leading the authors to conclude that HFPO dimer acid consumption was still limited at the national scale of China, despite its use as a PFOA replacement.

One study measured concentrations of GenX chemicals in and/or on grass and leaves collected from sites various distances from a fluoropolymer manufacturing plant in the Netherlands (Brandsma et al., 2019). GenX chemicals concentrations ranged from 86 ng/g in leaves from a site closest to the plant to ND furthest from the plant. A similar pattern was observed for grass samples, except the maximum GenX chemicals concentration was lower (27 ng/g). The study authors note that it hadn't rained for five days prior to sample collection.

Semerád et al. (2020) investigated occurrence of HFPO dimer acid in sewage sludge from 43 facilities in the Czech Republic. HFPO dimer acid was detected in 7 of 43 samples at concentrations ranging from 0.3 to 1.2 ng/g dw. The authors raised concerns about the agriculture use of sludge containing PFAS for growing crops.

3.3.1.6 Sediment

HFPO dimer acid and its ammonium salt are expected to remain in water and exhibit low partitioning to sediment (U.S. EPA, 2021a). One study evaluated the occurrence of GenX chemicals in sediments from the North and Baltic Seas in Europe, and reported that HFPO dimer acid was not detected in any of the 24 sediment samples taken in the North and Baltic Seas in the vicinity of Germany (Joerss et al. (2019). An additional four studies analyzed sediments in China (Li et al., 2020b, 2021; Song et al., 2018; Wang et al., 2019a). Of the four studies, Wang et al. (2019a) analyzed sediment from the South China Sea coastal region in the area of the highly industrialized Pearl River Delta and reported that HFPO dimer acid was below the LOQ in all 53 samples. Li et al. (2020b) analyzed 20 sediment samples from eight rivers and three reservoirs in the Hai River Basin in the vicinity of several industrialized areas. HFPO dimer acid was reportedly detected at minimal levels, but the authors did not report actual concentrations. Song et al. (2018) analyzed concentrations of HFPO dimer acid in 24 sediment samples from the Xiaoqing River in the vicinity of a fluoropolymer production facility. The study reported a maximum HFPO dimer acid concentration in sediment of 22.3 ng/g dw, with median and mean levels below the LOQ. Li et al. (2021) also analyzed sediment samples from five sites of the Xiaoqing River estuary, and reported a mean HFPO dimer acid concentration of 0.23 ng/g dw.

3.3.2 RSC Determination

In summary, based on the physical properties, detected levels, and limited available exposure information for GenX chemicals, multiple non-drinking water sources (foods, indoor dust, air, soil, and sediment) are potential exposure sources. Following the Exposure Decision Tree in EPA's *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health* (U.S. EPA, 2000a), potential sources other than drinking water ingestion were identified

(Box 8A in the Decision Tree). However, the available information is limited. The available information does not allow for the quantitative characterization of the relative levels of exposure among these different sources (Box 8B in the Decision Tree).

EPA also considered the exposure information specifically for the identified sensitive population (lactating women). However, the literature search did not identify non-drinking water exposure information specific to lactating women that could be used quantitatively to derive the RSC. Since neither the available data for the general population (all ages) nor the sensitive population enabled quantitative characterization of relative exposure sources and routes, EPA applied the default RSC of 0.2 (see Section 2.2.4.2 above; EPA, 2000a), which means that 20% of the exposure equal to the RfD is allocated to drinking water and the remaining 80% is reserved for other potential exposure sources such as food, indoor dust, soil, and sediment.

4.0 Lifetime Noncancer Health Advisory Derivation

The lifetime HA for HFPO dimer acid and its ammonium salt is calculated as follows:

$$\textbf{Lifetime HA} = \left(\frac{\text{RfD}}{\text{DWI-BW}}\right) * \text{RSC} \tag{Eq. 3}$$

$$\textbf{Lifetime HA} = \left(\frac{0.000003\ \frac{\text{mg}}{\text{kg bw} - \text{day}}}{0.0469\ \frac{\text{L}}{\text{kg bw} - \text{day}}}\right) * 0.2$$

$$\textbf{Lifetime HA} = 0.00001\ \frac{\text{mg}}{\text{L}}$$

$$= 0.01\ \frac{\mu\text{g}}{\text{L}}$$

$$= 10\ \frac{\text{ng}}{\text{L}}$$

EPA is issuing a lifetime noncancer drinking water HA for GenX chemicals of 10 ng/L (ppt). The lifetime health advisory for GenX chemicals used a chronic RfD from the final EPA toxicity assessment (U.S. EPA, 2021a) based on the critical effect of adverse liver effects in adults (parental females) from a subchronic study (53–64 day exposure, depending on the time of conception). In the assessment, a 10X UF for subchronic to chronic exposure was used to derive the chronic RfD (U.S. EPA, 2021a). Because the critical effect identified for GenX chemicals is not a developmental effect and the chronic RfD was used to develop the lifetime HA, the GenX chemicals health advisory is more appropriate for the chronic exposure scenarios than shorter duration exposure scenarios. However, application of the GenX chemicals health advisory to a shorter-term risk assessment scenario would provide a conservative, health protective approach in the absence of other information.

5.0 Analytical Methods

EPA developed two liquid chromatography/tandem mass spectrometry (LC/MS/MS) analytical methods to quantitatively monitor drinking water for targeted PFAS that include HFPO dimer acid: EPA Method 533 (U.S. EPA, 2019b) and EPA Method 537.1, Version 2.0 (U.S. EPA, 2020b). The methods discussed below can be used to accurately and reasonably quantitate HFPO dimer acid at single digit ng/L levels that are nearly three times lower than the HFPO dimer acid lifetime HA of 10 ng/L.

EPA Method 533 monitors for 25 select PFAS with published measurement accuracy and precision data for HFPO dimer acid in reagent water, finished groundwater, and finished surface water and a single laboratory-derived minimum reporting level or approximate quantitation limit for HFPO dimer acid at 3.7 ng/L (0.0037 µg/L). For further details about the procedures for this analytical method, please see *Method 533: Determination of Per- and Polyfluoroalkyl Substances in Drinking Water by Isotope Dilution Anion Exchange Solid Phase Extraction and Liquid Chromatography/Tandem Mass Spectrometry* (U.S. EPA, 2019b).

EPA Method 537.1 (an update to EPA Method 537 [EPA, 2009c]) monitors for 18 select PFAS with published measurement accuracy and precision data for HFPO dimer acid in reagent water, finished groundwater, and finished surface water and a single laboratory-derived minimum reporting level or approximate quantitation limit for HFPO dimer acid at 4.3 ng/L (0.0043 µg/L). For further details about the procedures for this analytical method, please see *Method 537.1, Version 2.0, Determination of Selected Per- and Polyfluorinated Alkyl Substances in Drinking Water by Solid Phase Extraction and Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS)* (U.S. EPA, 2020b).

Drinking water analytical laboratories have different performance capabilities dependent upon their instrumentation (manufacturer, age, usage, routine maintenance, operating configuration, etc.) and analyst experience. Some laboratories will effectively generate accurate, precise, quantifiable results at lower concentrations than others. Organizations leading efforts that include the collection of data need to establish data quality objectives (DQOs) to meet the needs of their program. These DQOs should consider establishing reasonable quantitation limits that laboratories can routinely meet, without recurring quality control (QC) failures that will necessitate repeating sample analyses, increase costs, and potentially reduce laboratory capacity. Establishing a quantitation limit that is too high may result in important lower-concentration results being overlooked.

EPA's approach to establishing DQOs within the UCMR program serves as an example. EPA established minimum reporting limits (MRLs) for UCMR 5,[13] and requires laboratories approved to analyze UCMR samples to demonstrate that they can make quality measurements at or below the established MRLs. EPA calculated the UCMR 5 MRLs using quantitation-limit data from multiple laboratories participating in an MRL-setting study. The laboratories' quantitation limits represent their lowest concentration for which future recovery is expected, with 99% confidence, to be between 50 and 150%. The UCMR 5-derived and promulgated MRL for HFPO dimer acid is 0.005 µg/L (5 ng/L).

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[13] Information about UCMR 5 is available at https://www.epa.gov/dwucmr/fifth-unregulated-contaminant-monitoring-rule

6.0 Treatment Technologies

This section summarizes available drinking water treatment technologies that have been demonstrated to remove GenX chemicals. This section is not meant to provide specific guidance for operation or design criteria. Sorption based treatment processes including granular activated carbon (GAC), anion exchange (AIX), and powdered activated carbon (PAC) as well as high pressure membranes such as nanofiltration (NF) and reverse osmosis (RO) have been shown to successfully remove GenX chemicals from drinking water to below the 5 ppt EPA UCMR5 reporting limit (Heidari et al., 2021). Care should be taken when introducing one of these processes into a well-functioning treatment train, as there can be unintended consequences related to interactions with other treatment types and for systems unfamiliar with proper operation and potential hazards. These treatment processes may have additional benefits on finished water quality by removing other contaminants and disinfection by-product (DBP) precursors. General information about these processes and treatment performance data summaries may be found in the Drinking Water Treatability Database.[14]

Non-treatment means of managing GenX chemicals such as changing source waters, consolidation, or source water protection are also viable options for reducing GenX chemical concentrations in finished drinking water. One available resource for protecting source water from PFAS, including GenX chemicals, is the PFAS-Source water Protection Guide and Toolkit,[15] which shares effective strategies for addressing PFAS contamination risk in source waters.

Conventional water treatment methods such as coagulation, flocculation, sedimentation, and biologically active carbon filtration (where the column is operated for extended periods of time) are ineffective at removing GenX chemicals (Sun et al., 2016). Ozonation has increased concentrations of some GenX chemicals at full-scale DWTPs, possibly due to precursor compound oxidation (Sun et al. 2016). Medium pressure ultra-violet lamps and chlorination can possibly decrease concentrations of GenX compounds but only to a very limited extent and the observed results could be due to temporal and spatial fluctuations within the DWTPs monitored (Sun et al., 2016). These processes are generally not considered as viable GenX chemicals, or more broadly PFECA, treatment options. Boiling water will concentrate GenX chemicals and should not be considered as an emergency action.

6.1 Sorption Technologies

Sorption is where substances present in liquids are removed by accumulation on a solid phase (Crittenden et al., 2012). There are two main sorption technologies that are in use for PFAS removal and have been demonstrated to remove GenX: activated carbon and ion exchange. Activated carbon comes in two key forms distinguished by size, PAC and GAC.

There are select considerations that are similar across all sorption technologies. Common key criteria include influent water quality and desired effluent quality. Influent water quality can greatly impact the ability of sorption technologies to treat drinking water. Desired effluent quality can drive both operational and capital expenditures. Pilot scale testing is highly recommended to ensure the design effectiveness will be maximized for given source waters.

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[14] More information regarding treatment processes is available at https://tdb.epa.gov/tdb/findtreatmentprocess

[15] The PFAS Source Water Protection Guide and Toolkit are available for download at https://www.asdwa.org/pfas/

EPA's ICR Manual for Bench- and Pilot-Scale Treatment Studies (U.S. EPA, 1996) contains guidance on conducting pilot studies for contactors which are used for GAC and ion exchange.

Sorption technologies are largely reversible: PFAS can detach from sorbents and re-enter the drinking water under certain conditions. In addition, direct competition with stronger sorbing constituents can lead to effluent PFOS concentrations temporarily exceeding influent concentration (known as chromatographic peaking). An implication for treatment plants is that the effluent GenX chemicals concentrations can temporarily exceed influent concentrations. Competitive sorption is especially important in co-removal systems where other PFAS are present. When GenX was co-removed with PFOA, the total GenX quantity removed decreased significantly. After an initial loading period absorbed GenX desorbed and then was replaced by PFOA (Wang et al. 2019b). Competitive sorption may be controlled by changing or regeneration of the sorptive media at appropriate intervals.

The majority of studies found that natural or dissolved organic matter (NOM/DOM) interferes with PFAS sorption, in general, and its presence dramatically lowers treatment efficacy (McNamara et al., 2018; Pramanik et al., 2015; Yu et al., 2012). The lowered treatment effectiveness was found to be less pronounced for GenX chemicals than for perfluoroalkyl carboxylic acid (PFCA) C7 and above for GAC (Park et al., 2020).

GAC can typically be regenerated when treatment performance reaches an unacceptable level.. Regeneration can be on or off site. On-site regeneration typically requires a higher spatial footprint and capital outlay. Given water quality and other considerations, regenerated media can become totally exhausted or "poisoned" with other contaminants not removed during regeneration and must be replaced. However, for GAC, the loss of approximately 10 percent of the media due to abrasion withing the reactivation process can result in a somewhat steady state for performance as new GAC is added each time to replace the lost GAC. Most AIX resins in current use for PFAS are single use resins and not designed to be regenerated.

6.1.1 Activated Carbon

Activated carbon is a highly porous media with high internal surface areas (U.S. EPA, 2017b). Activated carbon can be made from a variety of materials. Designs that work with a carbon made from one source material activated in a specific way may not be optimized for other carbon types. It is normally used in either a granular or powdered form for water treatment. Installing activated carbon as a treatment method may have ancillary benefits on finished water quality, particularly with disinfectant byproduct control as well as taste and odor.

With activated carbon, more non-polar and larger compounds tend to be more easily removed than smaller more polar compounds. Adsorption of acids and bases on activated carbon is dependent on the pH. Adsorption of neutral forms, as opposed to anionic forms, are generally stronger so lowering the pH increases GenX chemical sorption. However, the acid dissociation constant (pK_a) of HFPO dimer acid is 2.84 and lowering the pH is not practical for drinking water applications (Park et al. 2020; U.S. EPA 2021a). GenX forms a fast, weak electrostatic bond with adsorbents and can be substituted by PFOA or other long-chain PFAS which adsorb preferentially on activated carbon due in part to their higher hydrophobicity (Heidari et al., 2021; Wang et al., 2019b). These differences in physical chemical properties are consistent with the faster adsorption kinetics but less tight binding of GenX than PFOA and result in GenX chemicals partitioning more quickly onto activated carbon.

Based on findings with emerging PFCA PFOA replacements, cations such as aluminum, calcium, and sodium increase PFAS sorption to activated carbons (Pereira et al., 2018) at low pH. Anions such as fluorine, chlorine, nitrate, sulfate, and phosphate have not yet been shown to correlate with GenX removal despite expectations that these anions would inhibit GenX treatment (Wu et al., 2020).

Activated carbon has a maximum sorbent capacity and must be replaced or regenerated. For carbon regenerated off-site, several organizations recommend that spent carbon should be segregated and traceable from the time it leaves the drinking water facility through all steps at the reactivation facility, and then returned to the same site (National Science Foundation [NSF]/American National Standards Institute [ANSI] Standard 61 [NSF/ANSI, 2021]).

Before adding activated carbon to an existing treatment train, there are effects which should be considered. For instance, activated carbon may change system pH or, release leachable metals (particularly arsenic and antimony) when new carbon media is first used without acid washing, and may require disinfection. Activated carbon may also cause unintended consequences with disinfection efficacy depending on process placement. Activated carbon can also shift the bromide-to-total organic carbon ratio and increase brominated (Br)-DBP concentrations as well as concentrations relative to chlorinated DBPs (Krasner et al., 2016). Despite increased Br-DBP, studies have indicated a decreased overall DBP risk (Wang et al., 2019c).

6.1.1.1 Powdered Activated Carbon

PAC is the same material as GAC but has a smaller particle size and is applied differently. PAC is typically dosed intermittently although it can be employed continuously. PAC dosage and type, along with dosing location, contact time, and water quality, often influence process cost as well as treatment efficiency (Heidari et al., 2021). Sometimes PAC is combined with other processes, particularly floc blanket reactors and membrane filters (low or high pressure), although this is not necessary. For more information on employing PAC, please see the Drinking Water Treatability Database.[16]

With GenX, PAC was found to achieve equilibrium more quickly than GAC however, total removal capacity was similar (Wang et al., 2019b), although the steady state PAC application cannot match the benefits of column operation of GAC in terms of percent removal. Significant increases in GenX chemicals treatment efficiencies have been observed with smaller PAC particle sizes (Wang et al., 2019b). Compared to GAC, competing species such as PFOA displace GenX chemicals more rapidly on PAC (Wang et al. 2019b) which is consistent with GenX being less tightly bound and more mobile than PFOA. For PFAS, information to date indicates that increasing PAC dose increases removal to a point and then starts to decrease. Jar testing is used to empirically determine the optimal PAC dosage; doses between 45–100 mg/L are generally suitable for GenX Chemicals (Dudley, 2012; Hopkins et al., 2018; Sun et al., 2016). These doses are high and drinking water utilities would have difficulty in maintaining them for extended periods of time. Standardized jar testing procedures have been published

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[16] https://tdb.epa.gov/tdb/treatmentprocess?treatmentProcessId=2109700949

(ASTM, 2019; AWWA, 2011). The AWWA published standard for PAC is ANSI/AWWA B600-16 (AWWA, 2016).

Other key operational parameters determining PAC efficiency include contact time and loading rate. Contact time in most plants is generally between 30 minutes and 2 hours. Sun et al. (2016) found that the full PAC capacity for GenX chemicals is unlikely to be used in this time. While PAC can be regenerated it rarely makes sense to do so because of the associated costs, presence of coagulants and particulates in the sludge, and degraded removal capacities post-reactivation (Clifford et al., 1983).

PAC poses additional safety considerations including depleting oxygen in confined or partially enclosed areas, fire hazards including spontaneous combustion when stored with hydrocarbons or oxidants, and inhalation hazards. PAC is also a good electrical conductor and can create dangerous conditions when it accumulates (AWWA, 2016).

6.1.1.2 Granulated Activated Carbon

As a result of GenX chemicals being only moderately absorbable, GAC contactors are normally placed as a post-filter step. Key design criteria include empty bed contact time (EBCT), superficial velocity, and carbon type. Typical EBCTs for GenX chemicals removal are 10–20 minutes and superficial linear velocities are normally 5–15 meters per hour (m/hr). Normal height-to-diameter ratios are around 1.5 to 2.0; lower ratios can run into problems with too shallow beds and require more space, and higher ratios induce greater pressure drops. AWWA has published a GAC standard (ANSI/AWWA B604-18; AWWA, 2018a); there is also an AWWA published standard for GAC reactivation (ANSI/AWWA B605-18; AWWA, 2018b).

6.1.2 Ion Exchange

Ion exchange involves the exchange of an ion in the aqueous phase for an ion on the exchange resin. Once the resin has exchanged all its ions for contaminants, it can either be disposed (single use) or regenerated (i.e., restoring its ions for further use).

Resins are either cationic or anionic; cationic resins remove positively charged ions such as sodium or calcium and anionic resins remove negatively charged ions such as sulfates and nitrates. Cationic exchange resins do not remove GenX chemicals. The pK_a of HPFO-DA is 2.84; this means that in drinking water applications GenX chemicals will predominately exist in an anionic form and are strong acids (U.S. EPA, 2021a). Based on the pK_a strongly basic anionic exchange resins will be the most relevant. Key design parameters for GAC are also key design parameters for AIX, although there are slight differences in operation. AIX typically uses 2-to-5-minute EBCTs, allowing for lower capital costs and a smaller footprint; generally smaller height-to-diameter ratios are used in exchange columns compared to GAC. Columns used in pilot studies and scaled directly to full-scale if loading rates and EBCTs are kept constant (Crittenden 2012). For more information about AIX, please see Dixit et al. (2021), Tarleton (2014), or Tanaka (2015), Crittenden et al. (2012), or the EPA Drinking Water Treatability Database (2022).

Strong base acrylate resins contaminated with HFPO dimer acid have been greater than 95% regenerated with a 10% sodium chloride solution (Dixit et al., 2020). Sodium hydroxide may be added to the sodium chloride solution to combat organic fouling; this is referred to as 'brine squeeze' and helps in solubilizing NOM and unplugging pores (Dixit et al., 2021). Once PFAS-contaminated spent brine is recovered, it must be treated or disposed. Resin regeneration may not be practical for water utilities from safety and/or cost perspectives (Liu and Sun, 2021).

Before adding AIX to an existing treatment train, there are effects which should be considered. For instance, AIX can increase water corrosivity which may increase heavy metals through leaching, can release organic leachables such as the amines from which they are made, and will increase concentrations of the counter-ion used (typically chloride).

6.2 High Pressure Membranes

NF and RO are high-pressure processes where water is forced through a membrane. The water that transverses the membrane is known as permeate or produce water, and has few solutes left in it; the remaining water is known as concentrate, brine, retentate, or reject water and forms a waste stream with concentrated solutes. NF has a less dense active layer than RO, which enables lower operating pressures but also makes it less effective at removing contaminants. NF and RO tend to take up less space than sorption separation technologies. However, both NF and RO also tend to have higher operating expenses, use a significant amount of energy, and generate concentrate waste streams which require disposal. Generally, NF and RO require pre- and posttreatment processes. Higher expenses typically associated with NF and RO are only rarely competitive from an economic perspective for removing a specific contaminant; however, for waters requiring significant treatment and where concentrate disposal options are reasonably available, NF and RO may be the best option.

PFAS removal fluxes are generally 1–50 liters per square meter per hour (L/[m^2·hr]) at 5–85 bar operating pressure (Mastropietro et al., 2021). Temperature can dramatically impact flux; it is common to normalize flux to a specific reference temperature for operational purposes (U.S. EPA, 2005c). It is also common to normalize flux to pressure ratios to identify productivity changes attributable to fouling (U.S. EPA, 2005c). It is important to note that outside-in and inside-out systems operating at the same flux produce differing quantities of finished water so membrane systems with differing configurations cannot be directly compared based on flux. Total flow per module and cost per module are more important decision support indicators for capital planning. Unlike low pressure membranes, NF and RO systems are not manufactured as proprietary equipment and membranes from one manufacturer are typically interchangeable with those from others (U.S. EPA, 2005c).

High-pressure membranes may have important unintended effects when added onto a well-functioning treatment train. For instance, high-pressure membranes may remove beneficial minerals and increase corrosivity. Increased water corrosivity may increase heavy metals such as iron, lead, and copper through leaching. For more information, see AWWA (2007).

6.3 Point-of-Use Devices for Individual Household PFAS Removal

Although the focus of this treatment technologies section is the different available options for removal of PFOA at DWPs, centralized treatment technologies can also often be used in a decentralized fashion as point-of-entry (POE) (where the distribution system meets a service connection) or point-of-use (POU) (at a specific tap or application) treatment in cases where centralized treatment is impractical or individual consumers wish to further reduce their individual household risks. Many home drinking water treatment units are certified by independent third-party accreditation organizations against ANSI standards to verify contaminant removal claims. NSF International has developed protocols for NSF/ANSI Standards 53 (sorption) and 58 (RO) that establish minimum requirements for materials, design, and construction, and performance of point-of-use systems. Previously, NSF P473 was designed to certify PFOA reduction technologies below EPA's 2016 HA of 70 ppt for PFOA; in 2019, these standards were retired and folded into NSF/ANSI 53 and 58. When properly maintained, these certified systems may reduce other PFAS, including GenX chemicals, although removal should not be automatically inferred for PFAS not specified within the protocol. It has been reported that home under-the-sink RO filters effectively removed GenX chemicals in Cape Fear, North Carolina (Hopkins et al., 2018). GenX specific certification procedures may be developed by standards organizations, such as NSF and the Water Quality Association. Individuals or systems interested in POU or POE treatment should check with standards organizations for the most recent certification procedures.

6.4 Treatment Technologies Summary

Non-treatment management options, such as changing source waters, source water protection, or consolidation, are viable strategies for reducing GenX chemicals concentrations in finished drinking water. Should treatment be necessary, activated carbon, AIX, NF, or RO have been shown to successfully remove HFPO dimer acid from drinking water to below the 4 ppt reporting limit for UCMR 5. These processes are the best means for removing GenX chemicals from drinking water and can be used in central treatment plants or in POU/POE applications. Some treatment processes have been shown to increase GenX chemicals concentrations, most likely through precursor oxidation. These treatment technologies often require pre- as well as posttreatment and may help remove other unwanted contaminants along with DBP precursors. Each technology may also introduce unintended consequences to an existing treatment train. Additionally, these treatment processes are separation technologies and produce waste streams with GenX chemicals on or in them. Boiling water will concentrate GenX chemicals and should not be considered as an emergency action.

7.0 Consideration of Noncancer Health Risks from PFAS Mixtures

EPA recently released a *Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances (PFAS)* (U.S. EPA, 2021f) that is currently undergoing Science Advisory Board (SAB) review. That draft document describes a flexible, data-driven framework that facilitates practical component-based mixtures evaluation of two or more PFAS based on current, available EPA chemical mixtures approaches and methods (U.S. EPA, 2000b). Examples are presented for three approaches—Hazard Index (HI), Relative Potency Factor (RPF), and Mixture BMD—to demonstrate application to PFAS mixtures. To use these approaches, specific input values and information for each PFAS are needed or can be developed. These approaches may help to inform PFAS evaluation(s) by federal, state, and tribal partners, as well as public health experts, drinking water utility personnel, and other stakeholders interested in assessing the potential noncancer human health hazards and risks associated with PFAS mixtures.

The HI approach, for example, could be used to assess the potential noncancer risk of a mixture of four component PFAS for which HAs, either final or interim (iHA), are available from EPA

(PFOA, PFOS, GenX chemicals, and perfluorobutane sulfonic acid [PFBS]). In the HI approach described in the draft framework (U.S. EPA 2021f), a hazard quotient (HQ) is calculated as the ratio of human exposure (E) to a human health-based toxicity value (e.g., reference value [RfV]) for each mixture component chemical (i) (U.S. EPA, 1986). The HI is dimensionless, so in the HI formula, E and the RfV must be in the same units (Eq. 6). In the context of PFAS in drinking water, a mixture PFAS HI can be calculated when health-based water concentrations (e.g., HAs, Maximum Contaminant Level Goals [MCLGs]) for a set of PFAS are available or can be calculated. In this example, HQs are calculated by dividing the measured component PFAS concentration in water (e.g., expressed as ng/L) by the relevant HA (e.g., expressed as ng/L) (Eqs. 7, 8). The component chemical HQs are then summed across the PFAS mixture to yield the mixture PFAS HIs based on interim and final HAs.

$$\mathrm{HI} = \sum_{i=1}^{n} \mathrm{HQ}_i = \sum_{i=1}^{n} \frac{E_i}{\mathrm{RfV}_i}$$

(Eq. 6)

$$\mathrm{HI} = \mathrm{HQ}_{\mathrm{PFOA}} + \mathrm{HQ}_{\mathrm{PFOS}} + \mathrm{HQ}_{\mathrm{GenX}} + \mathrm{HQ}_{\mathrm{PFBS}}$$

(Eq. 7)

$$\mathrm{HI} = \left(\frac{[\mathrm{PFOA}_{\mathrm{water}}]}{[\mathrm{PFOA}_{\mathrm{iHA}}]}\right) + \left(\frac{[\mathrm{PFOS}_{\mathrm{water}}]}{[\mathrm{PFOS}_{\mathrm{iHA}}]}\right) + \left(\frac{[\mathrm{GenX}_{\mathrm{water}}]}{[\mathrm{GenX}_{\mathrm{HA}}]}\right) + \left(\frac{[\mathrm{PFBS}_{\mathrm{water}}]}{[\mathrm{PFBS}_{\mathrm{HA}}]}\right)$$

(Eq. 8)

Where:

HI = hazard index
n = the number of component (i) PFAS
HQ_i = hazard quotient for component (i) PFAS
E_i = human exposure for component (i) PFAS
RfV = human health-based toxicity value for component (i) PFAS
HQ_{PFAS} = hazard quotient for a given PFAS
$[PFAS_{water}]$ = concentration of a given PFAS in water
$[PFAS_{HA}]$ = HA value, interim or final, for a given PFAS

In cases when the mixture PFAS HI is greater than 1, this indicates an exceedance of the health protective level and indicates potential human health risk for noncancer effects from the PFAS mixture in water. When component health-based water concentrations (in this case, HAs) are below the analytical method detection limit, as is the case for PFOA and PFOS, such individual component HQs exceed 1, meaning that any detectable level of those component PFAS will result in an HI greater than 1 for the whole mixture. Further analysis could provide a refined assessment of the potential for health effects associated with the individual PFAS and their contributions to the potential joint toxicity associated with the mixture. For more details of the approach and illustrative examples of the RPF approach and Mixture BMD approaches please see U.S. EPA (2021f).

8.0 Health Advisory Characterization

EPA is issuing a lifetime noncancer drinking water HA for GenX chemicals of 10 ng/L or 10 ppt based on the best available science. This is the first HA for GenX chemicals. The input values for the HA are: 1) the final chronic RfD for GenX chemicals from the toxicity assessment (U.S. EPA, 2021a); 2) the RSC based on exposure information collected from a literature search and following EPA's Exposure Decision Tree (U.S. EPA, 2000a) and presented herein; and 3) the DWI-BW, described herein, selected for the sensitive population or life stage. The final toxicity assessment for GenX chemicals was developed from a systematic review of the available scientific information on health effects (U.S. EPA, 2021a) and reflects response to public comment, two expert peer reviews, and recommendations from an independent evaluation by the National Toxicology Program's Pathology Working Group of two liver toxicity studies.

Uncertainties in the lifetime noncancer HA value are due in part to the relatively small database of health effects information, based on animal studies, for GenX chemicals (U.S. EPA, 2021a). There were no human epidemiology studies identified during the literature search conducted as part of the toxicity assessment (U.S. EPA, 2021a). The mechanistic information for GenX chemicals was reviewed as part of the toxicity assessment (see Section 6 of EPA, 2021a). Multiple potential modes of action have been identified for effects of GenX chemicals exposure on the liver (the critical effect), including peroxisome proliferator-activated receptor alpha (PPARα) activation and cytotoxicity. Mechanisms and modes of action have not been elucidated for the other health outcomes associated with GenX chemicals exposure (e.g., developmental/reproductive effects). However, the current data gaps in the GenX chemicals health effects information were accounted for in the derivation of the final RfD by applying relevant UFs including a 10X UF_D.

Regarding EPA's RSC selection, uncertainties exist due to the current lack of information to allow for a quantitative exposure characterization among exposure sources including for lactating women, the sensitive population selected for deriving the HA. There is also uncertainty in the EF that EPA selected since it is possible that additional toxicity information may reveal more sensitive populations or life stages for GenX chemicals. This final HA is based on a recent toxicity assessment and recent literature searches of the publicly available scientific information regarding health effects, exposure, analytical methods, and treatment technologies for GenX chemicals.

8.1 Comparative Analysis of Exposure Factors for Different Populations

The exposure duration in the critical study identified in the toxicity assessment for GenX chemicals (U.S. EPA, 2021a) is from pre-mating, through gestation, and to day 21 of lactation and the adverse liver effects were observed in the dams (not their offspring). Therefore, three potentially sensitive life stages of adult females—pregnant women, women of childbearing age (13 to < 50 years), and lactating women were identified (Table 5). The DWI-BW for lactating women was selected since it is the most health protective.

To evaluate whether all ages of the general population would be protected by the resulting lifetime HA value for GenX chemicals, based on the DWI-BW for lactating women, EPA calculated HAs using the 90th percentile DWI-BW for four populations: the general population (all ages), pregnant women, women of childbearing age, and lactating women. The HA values (rounded to one significant figure) using the EF for general population, pregnant women, or women of childbearing age are all 0.00002 mg/L (20 ppt) which is higher than the GenX HA value calculated using the EF for lactating women (0.00001 mg/L [10 ppt]) (Table 6). The comparison of the four candidate HA values indicates that the lifetime noncancer HA derived using the DWI-BW for lactating women is protective of the other candidate sensitive populations or life stages as well as the general population (all ages).

Table 6. Comparison of HA Values Using EPA Exposure Factors for Drinking Water Intake for Different Candidate Populations.

Population	DWI-BW (L/kg bw-day)	HA two sig figs/ HA one sig fig (mg/L)	Description of Exposure Metric	Source
General population, all ages	0.0338	0.000018/ 0.00002	90th percentile direct and indirect consumption of community water, consumer-only two-day average, all ages.	2019 Exposure Factors Handbook Chapter 3, Table 3-21, NHANES 2005–2010 (U.S. EPA, 2019a)
Pregnant women	0.0333	0.000018/ 0.00002	90th percentile direct and indirect consumption of community water, consumer-only two-day average.	2019 Exposure Factors Handbook Chapter 3, Table 3-63, NHANES 2005–2010 (U.S. EPA, 2019a)
Women of childbearing age	0.0354	0.000017/ 0.00002	90th percentile direct and indirect consumption of community water, consumer-only two-day average, 13 to < 50 years.	2019 Exposure Factors Handbook Chapter 3, Table 3-63, NHANES 2005–2010 (U.S. EPA, 2019a)
Lactating women	**0.0469**	0.000013/ **0.00001**	90th percentile direct and indirect consumption of community water, consumer-only two-day average.	2019 Exposure Factors Handbook Chapter 3, Table 3-63, NHANES 2005–2010[a] (U.S. EPA, 2019a)

Notes: L/kg bw-day = liters of water consumed per kilogram body weight per day. Sig fig = significant figure. The DWI-BW used to calculate the GenX chemicals' lifetime HA is in bold. EPA HAs are rounded to one significant figure.

[a] Estimates are less statistically reliable based on guidance published in the Joint Policy on Variance Estimation and Statistical Reporting Standards on NHANES III and CSFII Reports: HNIS/ NCHS Analytical Working Group Recommendations (NCHS, 1993).

8.2 Related Compounds of Emerging Concern

This HA addresses the two chemicals that are the two current commercial products of the GenX technology: the HFPO dimer acid and its ammonium salt. During the synthesis of HFPO dimer acid, which is manufactured from hexafluoropropene oxide (HFPO), other chemicals including the HFPO trimer acid (HFPO-TA) and HFPO tetramer acid (HFPO-TeA) can be produced in the synthesis process (Geng et al., 2016). These same HFPO chemicals are byproducts of longer chain perfluoropolyether synthesis. Health effects are indicated from *in vivo* and *in vitro* studies of the liver (Sheng et al., 2018) and the endocrine system after exposure to HFPO-TA and the HFPO-TeA (Xin et al., 2019). While some information is available on the occurrence and bioaccumulation of HFPO-TA (Pan et al., 2017), more research is needed to improve our understanding of the exposure information and health effects for HFPO-TA and HFPO-TeA.

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Appendix A: Relative Source Contribution – Literature Search and Screening Methodology

In support of U.S. Environmental Protection Agency's (EPA's) human health toxicity assessment for hexafluoropropylene oxide dimer acid (HPFO) and its ammonium salt (GenX chemicals) (EPA, 2021a), literature searches were conducted of four databases (PubMed, Toxline, Web of Science (WOS), and Toxic Substances Control Act Test Submissions (TSCATS) to identify publicly available literature using Chemical Abstracts Service Registry Number (CASRN), synonyms, and additional relevant search strings (see EPA (2021a) for details). Due to the limited search results, additional databases were searched for information on physicochemical properties, health effects, toxicokinetics, and mechanism of action. The initial date-unlimited database searches were conducted in July 2017 and January/February 2018, with updates completed in February 2019, October 2019, and March 2020. In addition, available information on toxicokinetics; acute, short-term, subchronic, and chronic toxicity; developmental and reproductive toxicity; neurotoxicity; immunotoxicity; genotoxicity; and cancer in animals was submitted with premanufacture notices to EPA by DuPont/Chemours, the manufacturer of GenX chemicals, as required under Toxic Substances Control Act pursuant to a consent order (EPA, 2009b) or reporting requirements (15 U.S.C. § 2607.8(e)). The results of the literature searches of publicly available sources and submitted studies from DuPont/Chemours are available through EPA's Health & Environmental Resource Online website at https://hero.epa.gov/hero/index.cfm/project/page/project_id/2627.

The GenX chemicals literature search results and all studies submitted from DuPont/Chemours were imported into SWIFT-Review (Sciome, LLC, Research Triangle Park, NC) and filtered through the Evidence Stream tags to identify human studies and non-human (i.e., those not identified as human) studies. Studies identified as human studies were further categorized into seven major PFAS pathways (Cleaning Products, Clothing, Environmental Media, Food Packaging, Home Products/Articles/Materials, Personal Care Products, and Specialty Products) as well as an additional category for Human Exposure Measures. Non-human studies were grouped into the same seven major PFAS pathway categories, except that the Environmental Media category did not include soil, wastewater, or landfill.

Application of the SWIFT-Review tags identified 52 studies for title and abstract screening. An additional three references were identified through gray literature sources that were included to supplement the search results. Title and abstract screening to determine relevancy followed the populations, exposures, comparators, and outcomes (PECO) criteria in Table A-1:

Table A-1. Populations, Exposures, Comparators, and Outcomes (PECO) Criteria

PECO Element	Inclusion Criteria
Population	Adults (including women of childbearing age) and/or children in the general populations from any country
Exposure	Primary data from peer-reviewed studies collected in any of the following media: ambient air, consumer products, drinking water, dust, food, food packaging, groundwater, human blood/serum/urine, indoor air, landfill, sediment, soil, surface water (freshwater), wastewater/biosolids/sludge

PECO Element	Inclusion Criteria
Comparator	Not applicable
Outcome	Measured concentrations of GenX chemicals (or measured emissions from food packaging and consumer products only)

The title and abstract of each study were independently screened for relevance by two screeners using *litstream*^{TM}. A study was included as relevant if it was unclear from the title and abstract whether it met the inclusion criteria. When two screeners did not agree if a study should be included or excluded, a third reviewer was consulted to make a final decision. The title and abstract screening resulted in 24 studies tagged as relevant (i.e., data on occurrence of GenX chemicals in one of the media of interest were presented in the study) that were further screened with full-text review using the same inclusion criteria. Of these 24 studies, 4 contain only human biomonitoring data and are not discussed further here. Based on full-text review, 15 studies were identified as relevant and are summarized below. At the full-text review stage, two additional studies were identified as only containing biomonitoring data.

To supplement the primary literature database, EPA also searched the following gray literature sources in February 2022 for information related to relative exposure of GenX chemicals for all potentially relevant routes of exposure (oral, inhalation, dermal) and exposure pathways relevant to humans:

- EPA's (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"*
- Agency for Toxic Substances and Disease Registry's (ATSDR's) *Toxicological Profiles*
- Centers for Disease Control and Prevention's (CDC's) national reports on human exposures to environmental chemicals
- EPA's CompTox Chemicals Dashboard
- EPA's fish tissue studies
- EPA's Toxics Release Inventory
- EPA's Unregulated Contaminant Monitoring Rule data
- Relevant documents submitted under the Toxics Substances Control Act and relevant reports from EPA's Office of Chemical Safety and Pollution Prevention
- U.S. Food and Drug Administration's (FDA's) *Total Diet Studies* and other similar publications from FDA, U.S. Department of Agriculture, and Health Canada
- National Oceanic and Atmospheric Administration's (NOAA's) National Centers for Coastal Ocean Science data collections
- National Science Foundation direct and indirect food and/or certified drinking water additives
- PubChem compound summaries
- Relevant sources identified in the relative source contribution discussions (section 5) of EPA's *Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level*

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- Additional sources, as needed

EPA has included available information from these gray literature sources for GenX chemicals relevant to their uses, chemical and physical properties, and for occurrence in drinking water (directly or indirectly in beverages like coffee, tea, commercial beverages, or soup), ambient air, foods (including fish and shellfish), incidental soil/dust ingestion, and consumer products. EPA has also included available information specific to GenX chemicals below on any regulations that may restrict levels of GenX chemicals in media (e.g., water quality standards, air quality standards, food tolerance levels).

EPA incorporated 3 references (Feng et al., 2021; Li et al., 2021; and Semerád et al., 2020) that were not identified in the contractor’s RSC literature search strategy; these references were provided by Chemours as part of their outreach to EPA on uses and sources for GenX chemicals in April 2022.

Appendix B: Compilation of Data on HFPO Dimer Acid Occurrence in Surface Water Collected from Primary Literature

This appendix includes a table resulting from the efforts to identify and screen primary literature (i.e., peer-reviewed journal articles), described in Appendix A, as well as extract data that may be relevant to informing the RSC derivation for GenX chemicals.

Table B-1. Compilation of Studies Describing of HFPO Dimer Acid Occurrence in Surface Water

Study	Location	Site Details	Results
North America			
Sun et al. (2016)	United States (North Carolina, Cape Fear River Basin)	Source waters of three community drinking water treatment plants, two upstream and one downstream of a PFAS manufacturing plant (LOQ = 10 ng/L)	Community A (upstream): DF 0% Community B (upstream): DF NR, median (range) = ND (ND-10 ng/L) Community C (downstream): DF NR, mean = 631 ng/L, median (range) = 304 (55–4,560) ng/L
McCord et al. (2018)	United States (North Carolina, Cape Fear River Basin)	Source water of a drinking water treatment plant near the industrial waste outfall of a fluorochemical manufacturer, before and after the manufacturer diverted a waste stream (exact values NR, estimated values from Figure 3)	Before waste diversion (estimated): DF NR, measured concentration = ~ >700 ng/L After waste diversion (estimated): DR NR, measured concentration = < 140 ng/L
Galloway et al. (2020)	United States (Ohio and West Virginia, Ohio River Basin)	Rivers and tributaries located upstream, downstream, and downwind of a fluoropolymer production facility; some sample locations potentially impacted by local landfills	DF = 21/24 unique sites with detections > LOQ, median[a] (range) = 46.7 (ND–227) ng/L

Study	Location	Site Details	Results
Europe			
Gebbink et al. (2017)	The Netherlands	Upstream and downstream of the Dordrecht fluorochemical production plant; two control sites	Control sites: DF 0% Upstream of plant (n=3): DF[a] 33%, point = 22 ng/L Downstream of plant (n=13): DF 100%, mean[a] (range) = 178 (1.7–812) ng/L (MQL = 0.2)
Vughs et al. (2019)	The Netherlands and Belgium	Thirteen surface water samples collected from eleven water suppliers, some near a fluoropolymer manufacturing plant. The study did not map the distribution of reported concentrations by geographic location or with respect to distance from the fluoropolymer manufacturing plant.	DF 77%, mean (range) = 2.2 (ND–10.2) ng/L (LOQ = 0.2 ng/L)
Asia			
Pan et al. (2017)	China (Xiaoqing River and tributary)	Upstream and downstream of a fluoropolymer production plant in an industrialized region	Upstream of plant in the Xiaoqing River (n=6): DF[a] 100%, median[a] (range) = 2.10 (1.61–3.64) ng/L Tributary directly receiving plant effluent (n=4): DF[a] 100%, median[a] (range) = 1,855 (2.34-2,060) ng/L Downstream of plant in the Xiaoqing River receiving tributary waters (n=8): DF[a] 100%, median[a] (range) = 311 (118–960) ng/L
Song et al. (2018)	China (Xiaoqing River)	Near the Dongyue group industrial park, including a fluoropolymer production plant	DF NR, mean, median (range) = 519, 36.7 (<LOQ–9,350) ng/L (n=25 sites; LOQ=0.24 ng/L)

Study	Location	Site Details	Results
Li et al. (2020a)	China (Hai River Basin)	40 surface water samples from 8 rivers and 3 reservoirs – many of the rivers flowed through industrialized areas, some with potential PFAS point sources	DF[b] 80%, mean (range) = 0.316 (<MDL–2.6) ng/L (MDL = 0.0132 ng/L)
Multiple Continents			
Heydebreck et al. (2015)	Germany (Elbe and Rhine Rivers), the Netherlands (Rhine-Meuse delta)	All sampling locations in industrialized areas	Rhine River (n=23): DF[a] 17%, range = ND–86.08 ng/L Elbe River (n=22): DF 0%
	China (Xiaoqing River)	Some sampling locations were downstream of PFAS point sources	Xiaoqing River (n=20): DF[a] 65%, range = ND–3,060 ng/L
Pan et al. (2018)	United States (Delaware River)	Sampling sites along industrialized river systems that were not proximate to known point sources of PFAS from fluorochemical facilities	Delaware River (n=12): DF 100%, mean, median (range) = 3.32, 2.02 (0.78–8.75) ng/L
	United Kingdom (Thames River), Germany and the Netherlands (Rhine River), Sweden (Malaren Lake)	Sampling sites along industrialized river systems that were not proximate to known point sources of PFAS from fluorochemical facilities	Thames River (n=6): DF 100%, mean, median (range) = 1.12, 1.10 (0.70–1.58) ng/L Rhine River (n=20): DF 100%, mean, median (range) = 0.99, 0.90 (0.59–1.98) ng/L Malaren Lake (n=10): DF 100%, mean, median (range) = 1.47, 1.38 (0.88–2.68) ng/L

Study	Location	Site Details	Results
	South Korea (Han River), China (Liao, Huai, Yellow, Yangtze, and Pearl Rivers; Chao and Tai Lakes)	Sampling sites along industrialized river systems that were not proximate to known point sources of PFAS from fluorochemical facilities	Han River (n=6): DF 100%, mean, median (range) = 1.38, 1.16 (0.78–2.49) ng/L Liao River (n=6): DF 100%, mean, median (range) = 1.44, 0.88 (0.62–4.51) ng/L Huai River (n=9): DF 100%, mean, median (range) = 1.66, 1.40 (0.83–3.62) ng/L Yellow River (n=15): DF 67%, mean, median (range) = 1.01, 1.30 (< LOQ–1.74) ng/L Yangtze River (n=35): DF 94%, mean, median (range) = 0.73, 0.67 (< LOQ–1.54) ng/L Pearl River (n=13): DF 100%, mean, median (range) = 1.51, 0.70 (0.21–10.3) ng/L Chao Lake (n=13): DF 100%, mean, median (range) = 1.92, 1.81 (0.93–3.32) ng/L Tai Lake (n=15): DF 100%, mean, median (range) = 14.0, 0.77 (0.38–143.7) ng/L (LOQ = 0.05 ng/L; MDL = 0.38 ng/L)
	All locations	Sampling sites were not proximate to known point sources of any fluorochemical facilities	All locations (n=160): DF 96%, mean, median (range) = 2.55, 0.95 (0.18–144) ng/L (LOQ = 0.05 ng/L; MDL = 0.38 ng/L)

Notes:

DF = detection frequency; LOQ = limit of quantification; ND = not detected.; ng/L = nanograms per liter; NR = not reported; MQL = method quantification limit; MDL = method detection limit.

[a] The DF, median and/or mean was not reported in the study and was calculated in this synthesis. Mean values were only calculated if DF = 100%.

[b] The DF in Li et al. (2020a) was reported as 82.5% in the main article. The DF of 80% shown in this table is based on the supporting information data, which show only 32/40 samples with data > MDL.

[c] The Xiaoqing River results reported in Heydebreck et al. (2015) included samples from Laizhou Bay. EPA considered freshwater samples only.