CT DPH Drinking Water Action Levels for six PFAS, set July 2023

Cheryl Fields, Toxicologist

Xun Che, Toxicologist

Northeast Conference on the Science of PFAS

April 2, 2024

AGENDA

- Overview CT DPH PFAS Drinking Water Action Levels
- What are Cl-PFESAs and why should we care?
- Approach and Key Decision Points in Derivations
- Comparison with Other States
- Questions

Overview of CT DPH Drinking Water Action Levels

For Six PFAS

CT DPH Drinking Water PFAS Action Levels

Connecticut DPH Drinking Water Action Levels for 10 PFAS

	6:2 Cl-PFESA	8:2 Cl-PFESA	PFOS	PFNA	PFOA	HFPO-DA (GenX)	PFHxS	PFHxA	PFBS	PFBA
Action Levels (ng/L):	**2**	**5**	**10**	**12**	**16**	**19**	**49**	**240**	**760**	**1800**

Action Levels in CT: non-regulatory guidelines for drinking water that are protective of public health and also feasible based upon analytical detection and treatment technology.

CT DPH Drinking Water PFAS Action Levels

Connecticut DPH Drinking Water Action Levels for 10 PFAS

	6:2 Cl-PFESA	8:2 Cl-PFESA	PFOS	PFNA	PFOA	HFPO-DA (GenX)	PFHxS	PFHxA	PFBS	PFBA
Action Levels (ng/L):	2	5	10	12	16	19	49	240	760	1800

June 2022: PFOS, PFOA, PFNA, PFHxS

Action Levels: non-regulatory guidelines for drinking water that are protective of public health and also feasible based upon analytical detection and treatment technology.

CT DPH Drinking Water PFAS Action Levels

Connecticut DPH Drinking Water Action Levels for 10 PFAS

	6:2 Cl-PFESA	8:2 Cl-PFESA	PFOS	PFNA	PFOA	HFPO-DA (GenX)	PFHxS	PFHxA	PFBS	PFBA
Action Levels (ng/L):	**2**	**5**	10	12	16	**19**	49	**240**	**760**	**1800**

June 2022: PFOS, PFNA, PFOA, PFHxS

June 2023: PFHxA, PFBS, PFBA, HFPO-DA, and 6:2 – and 8:2 Cl-PFESA

Action Levels: non-regulatory guidelines for drinking water that are protective of public health and also feasible based upon analytical detection and treatment technology.

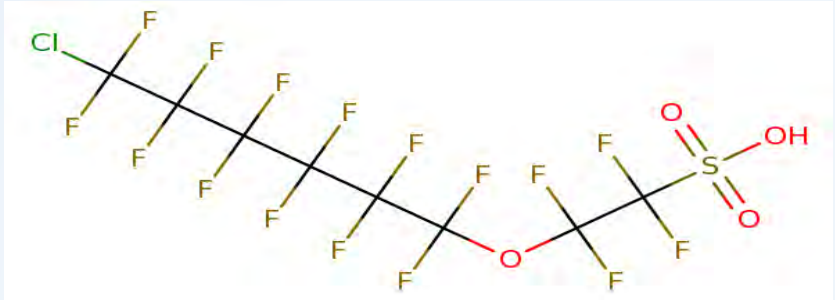
Uses, Sources and Environmental Occurrence

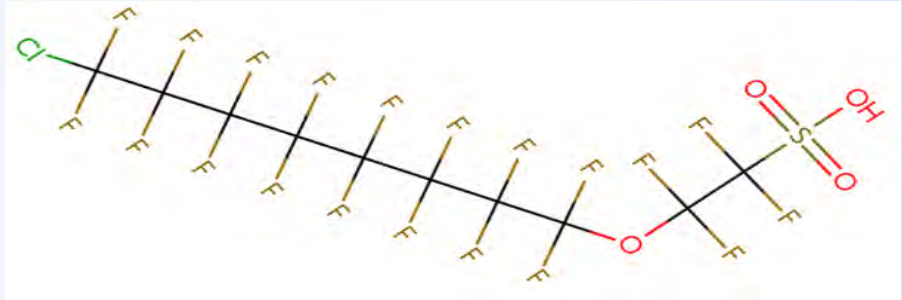
PFAS	Usage and sources	Environmental occurrence in CT
PFBS	Replacement for PFOS; found in consumer products, flame retardant etc.	soil, groundwater, surface water
PFBA	Photographic film; by products of stain-resistant fabrics, food packaging, carpets	soil, groundwater, surface water
PFHxA	Degradation product of surfactants; also found in AFFF	soil, groundwater, surface water
GenX	PFOA replacement; by-product of fluoromonomer production	soil
6:2 Cl-PFESA	Trade name “F-53B”, a replacement for PFOS used a mist suppressant in electroplating industry in China	drinking water
8:2 Cl-PFESA	Impurity of "F-53B" product	drinking water

What are Cl-PFESAs?

Why should we be concerned?

Cl-PFESAs: Naming Conventions





Naming convention adopted by DPH	6:2 chloropolyfluoroether sulfonic acid (6:2 Cl-PFESA)	8:2 chloropolyfluoroether sulfonic acid (8:2 Cl-PFESA)
CASRN	56426-58-1	763051-92-9
Commercial name	F-53B “major”	F-53B “minor”
EPA Methods 533, 537.1	9-Chlorohexadecafluoro-3-oxanonane-1-sulfonic acid **(9CL-PF3ONS)**	11-Chloroeicosafluoro-3-oxaundecane-1-sulfonic acid **(11CL-PF3OUdS)**
Synonyms	6:2 Cl-PFAES; C8 Cl-PFESA; chlorinated polyfluoroalkyl ether sulfonic acid	8:2 Cl-PFAES; C10 Cl-PFESA chlorinated polyfluoroalkyl ether sulfonic acid
NYSDOH (Brase et al 2021)	6:2 chlorinated polyfluoroethersulfonic acid (6:2 Cl-PFESA)	chlorinated polyfluoroethersulfonic acid (8:2 Cl-PFESA)

Cl-PFESAs: Overview

- No federal or state toxicity values
- Detected sporadically in CT private wells and in some instances, as the sole PFAS identified in drinking water
- Structurally similar to PFOS, 6:2 Cl-PFESA is environmentally persistent, a has higher bioaccumulative potential than PFOS
- Available toxicity data indicates toxicity is similar or more potent than PFOS

<u>Cl-PFESA time-line</u>

- 1970: first synthesized; used in China for decades
- 2013: first report of environmental occurrence, China
- 2018: detected in rivers & lakes globally, including U.S.

Cl-PFESAs: Human Exposure

- Detected in human blood, cord blood, placenta and breast milk
- Placenta transfer rates:

  8:2 Cl-PFESA (0.62) > 6:2 Cl-PFESA (0.44) > PFOS (0.43)
- Crosses blood-brain barrier
- Longest human half-life (15.3 years) of any PFAS

- China: 3rd most frequently detected PFAS in serum
- U.S.: detected in serum only infrequently

NHANES (2017-18)	6-2 Cl-PFESA Serum Levels (µg/L)			
Demographic	50th	75th	90th	95th
Total population	<LOD	<LOD	<LOD	0.1
Non-Hispanic Black	<LOD	<LOD	0.1	0.1
Non-Hispanic Asian	<LOD	0.2	1.3	2.5

Cl-PFESAs: Toxicity Data

Mammalian data (6:2 Cl-PFESA)

- Acute single dose studies: neurotoxicity in rats (Zhang 2016)
- Five subchronic (28-d to 10 wk) repeated dose oral toxicity studies
  - **Liver**: toxicity in two mice strains (Zhang 2018, Pan 2021) and in tigers (Wang 2020)
  - **Thyroid**: lower T3 and T4, but no effect on TSH in rats (Hong 2020)
  - **GI**: gut barrier dysfunction & colonic inflammation in mice (Pan 2019)
  - **Reproduction**:↓ testis & epididymis WT, but no effects on fertility in mice (Zhou 2018)
- Toxicokinetic study: half-life 4.1 d in male rats (Yi 2022), no TK info in mice
- Database limitations: No studies of chronic toxicity/carcinogenicity or neurotoxicity, no 2-gen study

Cl-PFESAs Toxicity Data (continued)

Non-mammalian data (6:2 Cl-PFESA):

- 2-generation repro/developmental study (180-d) in zebrafish (Shi 2018):
  - ↑ serum testosterone, ↓egg production. **In F0 adult males**: ↑ serum estradiol & vitellogenin, disrupted spermatogenesis. **In F1**: maternal transfer of F-53B adversely affected growth & reproduction; **F1 & F2:** ↑malformations and ↓ survival
- Developmental toxicity:
  - Zebrafish (Shi 2017): delayed hatching,↑ malformations, ↓ survival, disrupted cardiac development and ↓heartrate
  - Chickens (Briels 2018): ↓ heartrate before hatching, but no effects chick survival, hatching, or body mass
- Liver toxicity: 4 studies: in larvae (7d) and adult (21-d, 28-d, 56-d) zebrafish
  - Duration and dose-related cytoplasmic vacuolation (Shi 2019, Wang 2022, Wu 2019, Yi 2019)
  - **Aberrant hepatic lipid metabolism, hepatotoxicity via PPAR-γ** (Wang 2022)

In vitro data:

- 6:2 Cl **disturbed lipid homeostasis** in **Human HepG2 cells** via enhancement of lipid accumulation and fatty acid β-oxidation (Li 2023). Cytotoxic to human liver HL-7702 cells (Sheng 2018)
- both Cl-PFESAs bind to and activate all 3 PPARs and **promote adipogenesis** (Li 2018)
- thyroid hormone receptor binding affinity: 6:2 Cl > PFOS > 8:2 Cl-PFESA; all interact with transthyretin (Xin 2018)

Cl-PFESAs: Human Epi data

In humans, 6:2 Cl-PFESA-related effects are similar or more serious than PFOS

- Development: lower birth WT and preterm birth (Chu 2020)
- Endocrine effects:
  - Newborn thyroid homeostasis - 70% greater potency than PFOS for FT3 (Liu et al 2023)
  - 29% ↑ odds of PCOS – similar to PFOS (Zhan et al 2023) (EPA: Radke et al 2023)
  - Estradiol levels (ref 40)
- Lipids:
  - Tot Chol, Trig, LDL-C and HDL-C, and dyslipidemia (Mi 2022) (Liu 2022)
  - In diabetics: ↑Tot Chol and LDL, but no effect on Trig of HbA1c (Han 2021)
  - Metabolic syndrome (Yu 2021)
  - 6:2 Cl ↑ Tot Chol and LDL-C, 8:2 ↓HDL-C (Cong 2021, China C-8 Project)
- Liver cancer (Cao 2022)

6:2 Cl-PFESAs: Selection of Critical Study

- Liver toxicity in (56-d to 10 wk) repeated dose oral toxicity studies

Study	Duration (species)	Dose (mg/kg-d)	Animal POD (mg/kg-d)	Target Organ; Description
Zhang* (2018)	56-d gavage (male Balb/c mice)	0, 0.04, 0.2, 1	NOAEL: 0.2 LOAEL: 1.0	dose-related ↑ absolute liver WT of 10, 30 and 260% across all doses. ↑ relative liver WT at 0.2 and 1 mg/kg-d (~ 30 and 250%); **hepatocellular necrosis, steatosis and ballooning at 1 mg/kg** ↑ serum ALT and ALP, ↑ Trig and LDL, ↓ Tot Chol and HDL **↑ liver fatty acids (Tot Chol and Trig)**
Pan** (2021)	10-wk water (female C57Bl/6 mice)	0, 1, 3, 10 (µg/L)	LOAEL (10 ug/L) for sig. ↑ AST, ALT	Liver damage & disorders in lipid metabolism via **PPAR-γ** (hepatic cytoplasmic vacuolation and hepatomegaly, ↑ a. acids ↓acyl-carnitine (fatty acid transport, metabolic disease). ↑ ALT and AST, **↑ liver: Tot Chol and Trig**

***Zhang (2018)** selected as Critical Study
****Pan (2021)** did not report serum PFAS concentration or estimate a dose per BW

Derivation of 6 PFAS Action Levels

Approaches used and Key Decision Points

Key Decision Points for Toxicity Values

Critical Effects

- Liver effects: GenX, 6:2 Cl-PFESA
- Thyroids effects: PFBS, PFBA [PFHxS]
- Developmental effects: PFHxA [PFOA, PFNA]

Point of Departure

- NOAEL, LOAEL, or BMDL

Dosimetric Adjustment

- Ratio of clearance when POD is an administered dose
- Clearance when POD is an internal dose

$$RfD = POD \times DAF \div UF$$

Uncertainty Factors

- differences between humans and animals
- variability among humans
- use of a LOAEL instead of a NOAEL or BMD for the POD
- use of data from short-term studies to protect against effects from long-term exposure
- deficiencies of the database

Key Decision Points for Exposure Assumptions

- **Water Ingestion Rate (IR)**

	Water intake (L/d)	Body weight (kg)	Per-BW water IR (L/kg-d)
Infant	1.106	7.8	**0.142**
Lactating Women	3.061	73	**0.042**
Adult (ages 21 to <80)	3.192	80	**0.040**

  - Upper percentile, consumer only intake values (EPA EFH, 2011)
  - Central Tendency body weight (EPA EFH, 2011; ATSDR 2021)

Action Level =

RfD × RSC ÷ Water Ingestion Rate

- **Relative Source Contribution**
  - EPA's default minimal value 20%

Summary Key Decision Points_Tox values

	GenX	PFHxA	PFBS	PFBA	6:2 Cl-PFESA	8:2 Cl-PFESA
Critical Health Effect/ Target organ	LIVER	DEVELOPMENTAL	THYROID	THYROID	LIVER	LIVER
Dose-Response Approach	$BMDL_{10ER}$	$BMDL_{5RD}$	$BMDL_{0.5SD}$	NOAEL	NOAEL	
POD (administered dose, mg/kg/d) / Animal Serum dose (mg/L)	0.09 (admin)	10.6 (admin)	22.5 (admin)	6 (admin)	0.2 (admin), 18.9 (serum)	
Total Uncertainty Factors	3000	300	100	1000	3000	Based on surrogate data for 6:2 Cl-PFESA
DAF (unitless)/ Clearance Factor (L/kg-d)	0.14 (DAF)	0.0048 (DAF)	0.0027 (DAF)	0.23 (DAF)	0.000029	
Vol. of distribution (L/kg)	-	*0.73*	*0.23*	*0.48*	*0.23*	
Human half-live	-	*11.5 days*	*43.8 days*	*2.8 days*	*15.3 years*	
Reference Dose (ng/kg-d)	**4**	**170**	**540**	**1300**	**0.2**	**0.2**

Summary Key Decision Points_Exposure Assumptions

	GenX	PFHxA	PFBS	PFBA	6:2 Cl-PFESA	8:2 Cl-PFESA
Critical Effect /target organ	Liver	Developmental	Thyroid	Thyroid	Liver	(surrogate)
RfD (ng/kg-d)	**4**	**170**	**540**	**1300**	**0.2**	**0.2** (surrogate)
Relative Source Contribution	20%	20%	20%	20%	20%	20%
Water Ingestion Rate (L/kg-d)	0.042	0.142	0.142	0.142	0.040	0.040
Sensitive Receptor	Lactating woman	Infant, 0-1 yrs	Infant, 0-1 yrs	Infant, 0-1 yrs	Adult	Adult
ACTION LEVEL (ng/L, ppt)	**19**	**240**	**760**	**1800**	**<1; use MRL of 2**	**<1; use MRL of 5**

Derivation of Action Levels for GenX, PFHxA, PFBS, PFBA

Approaches used and Key Decision Points

CT DPH Chemical-Specific Derivation

Hexafluoropropylene Oxide-Dimer Acid (HFPO-DA, GenX)

Point of Departure (POD)

$BMDL_{10ER}$= 0.09 mg/kg/d, based on liver effects in female mice (DuPont 2010, NTP 2019 reanalysis) –administered dose

Dosimetric Adjustment Factor (DAF)

$(BW_{adult\ human} / BW_{female\ mouse})^{3/4} / (BW_{adult\ human} / BW_{female\ mouse}) =$
$(80kg/0.0349kg)^{-1/4} = 0.14$

Uncertainly Factors

Rodent vs. Human Sensitivity	3
Human-to-Human Variation	10
Use of LOAEL	1
Shorter exposure duration	10
Database Uncertainty	10
Total Uncertainty Factor	**3000**

$$RfD = POD \times (MW_{GenX\ acid} \div MW_{GenX\ ammonium\ salt}) \times DAF \div Total\ UF = 4\ ng/kg\text{-}d$$

Action Level = 4.0×10^{-6} mg/kg-d (RfD) × 0.2 (RSC) ÷ 0.042 L/kg-d (IR) × 1000000 ng/mg (unit conversion factor) = **19 ng/L**

CT DPH Chemical-Specific Derivation

Perfluorohexanoic Acid (PFHxA)

Point of Departure (POD)

$BMDL_{5RD}$= 10.6 mg/kg/d, based on decreased body weight in rat pups (Loveless *et al.* 2009) –administered dose

Dosimetric Adjustment Factor (DAF)

$clearance_{human} \div clearance_{animal}$ = 0.00184 L/kg-h ÷ 0.383 L/kg-h = 0.0048

Uncertainly Factors

Rodent vs. Human Sensitivity	3
Human-to-Human Variation	10
Use of LOAEL	1
Shorter exposure duration	1
Database Uncertainty	10
Total Uncertainty Factor	**300**

$$RfD = POD \times DAF \div Total\ UF = 1.7 \times 10^{-4}\ mg/kg\text{-}d$$

Action Level = 1.7×10^{-4} mg/kg-d × 0.2 ÷ 0.142 L/kg-d × 1000000 ng/mg =239ng/L → **240 ng/L**

RfD RSC IR unit conversion factor

CT DPH Chemical-Specific Derivation

Perfluorobutane Sulfate (PFBS)

Point of Departure (POD)

$BMDL_{0.5SD}$= 22.5 mg/kg/d, based on decreased serum total thyroxine (T4) in mice pups (Feng *et al.* 2017) –administered dose

Uncertainly Factors

Rodent vs. Human Sensitivity	3
Human-to-Human Variation	10
Use of LOAEL	1
Shorter exposure duration	1
Database Uncertainty	3
Total Uncertainty Factor	**100**

Dosimetric Adjustment Factor (DAF)

$clearance_{human} \div clearance_{animal}$= (ln2 * human $V_d \div$ human $t_{1/2}) \div clearance_{animal}$ = 0.693 * 0.23 L/kg ÷ 1051.2 h ÷ 0.056 L/kg-h = 0.0027

$$RfD = POD \times (MW_{PFBS\ acid} \div MW_{PFBS\ potassium\ salt}) \times DAF \div Total\ UF = 5.4 \times 10^{-4}\ mg/kg\text{-}d$$

Action Level = 5.4×10^{-4} mg/kg-d × 0.2 ÷ 0.142 L/kg-d × 1000000 ng/mg =761 ng/L → **760 ng/L**

RfD RSC IR unit conversion factor

CT DPH Chemical-Specific Derivation

Perfluorobutanoic Acid (PFBA)

Point of Departure (POD)

NOAEL = 6 mg/kg/d, based on decreased serum total thyroxine (T4) in male rats (Butenhoff *et al.* 2012) – administered dose

Uncertainly Factors

Rodent vs. Human Sensitivity	3
Human-to-Human Variation	10
Use of LOAEL	1
Shorter exposure duration	10
Database Uncertainty	3
Total Uncertainty Factor	**1000**

Dosimetric Adjustment Factor (DAF)

$clearance_{human} \div clearance_{animal} = (\ln 2 * \text{human } V_d \div \text{human } t_{1/2}) \div clearance_{animal} = 0.693 * 0.4845 \text{ L/kg} \div 67.9 \text{ h} \div 0.02161 \text{ L/kg-h} = 0.23$

$$RfD = POD \times (MW_{PFBA\ acid} \div MW_{PFBA\ ammonium\ salt}) \times DAF \div \text{Total UF} = 1.3 \times 10^{-3} \text{ mg/kg-d}$$

Action Level = 1.3×10^{-3} mg/kg-d (RfD) × 0.2 (RSC) ÷ 0.142 L/kg-d (IR) × 1000000 ng/mg (unit conversion factor) =1831ng/L → **1800 ng/L**

CT DPH Chemical-Specific Derivation

6:2 chloropolyfluoroether sulfonic acid (6:2 Cl-PFESA)

Point of Departure (POD)

NOAEL = 18.9 mg/L, based on liver effects in male mice (Zhang *et al.* 2018) –internal dose

Dosimetric Adjustment Factor (DAF)

V_d x (ln2/ $t_{1/2}$) = 0.23 L/kg x (0.693/5585 d) = 0.0000285 L/kg-d → 0.000029

Uncertainly Factors

Rodent vs. Human Sensitivity	3
Human-to-Human Variation	10
Use of LOAEL (n/a)	1
Shorter exposure duration	10
Database Uncertainty	10
Total Uncertainty Factor	**3000**

$$RfD = POD \times (MW_{6:2\ Cl\text{-}PFESA\ acid} \div MW_{6:2\ Cl\text{-}PFESA\ ammonium\ salt}) \times DAF \div Total\ UF = 1.7\times 10^{-7}\ mg/kg\text{-}d$$

Action Level = 1.7×10^{-7} mg/kg-d × 0.2 ÷ 0.04 L/kg-d × 1000000 ng/mg = 0.85 ng/L → **2 ng/L**

RfD RSC IR unit conversion factor MRL

CT DPH Chemical-Specific Derivation

8:2 chloropolyfluoroether sulfonic acid (8:2 Cl-PFESA)

Point of Departure (POD)

NOAEL = 18.9 mg/L, based on liver effects in male mice (Zhang *et al.* 2018) –internal dose

Dosimetric Adjustment Factor (DAF)

V_d x (ln2/ $t_{1/2}$) = 0.23 L/kg x (0.693/5585 d) = 0.0000285 L/kg-d → 0.000029

Uncertainly Factors

Rodent vs. Human Sensitivity	3
Human-to-Human Variation	10
Use of LOAEL	1
Shorter exposure duration	10
Database Uncertainty	10
Total Uncertainty Factor	**3000**

$$RfD = POD \times (MW_{6:2\ Cl\text{-}PFESA\ acid} \div MW_{6:2\ Cl\text{-}PFESA\ ammonium\ salt}) \times DAF \div Total\ UF = 1.7\times 10^{-7}\ mg/kg\text{-}d$$

Action Level = 1.7×10^{-7} mg/kg-d (RfD) × 0.2 (RSC) ÷ 0.04 L/kg-d (IR) × 1000000 ng/mg (unit conversion factor) = 0.85 ng/L → **5 ng/L** (MRL)

Comparison with EPA and other states

Drinking water guidance and regulatory values

Comparison with EPA and Other States

	EPA (2022)	NY (2022)	NJ (2023)	CT (2022)	NH	MA	VT	MI (2019)	MN (2018-2021)	CA (2021)	OH (2022)
PFBS	2,000	$\sum_{13}100^{a}$	-	760	-	-	-	**420**	100	500	2100
PFBA	-	$\sum_{13}100^{a}$	-	1,800	-	-	-	-	7,000	-	-
PFHxA	-	$\sum_{13}100^{a}$	-	240	-	-	-	**400,000**	200	-	-
GenX	10	$\sum_{6}30^{a}$	20	19	-	-	-	**370**	-	-	21
6:2 Cl-PFESA	-	$\sum_{6}30^{a}$	2^{b}	2^{c}	-	-	-	-	-	-	-
8:2 Cl-PFESA	-	$\sum_{6}30^{a}$	2^{b}	$5^{c,d}$	-	-	-	-	-	-	-

All values are in units of ppt (ng/L); values in grey cells are Notification Levels; values in bold are regulatory levels.

a. NY **sum of 6**: PFHpS, PFUnA, PFDoA, GenX, 6:2 Cl; 8:2 Cl; **sum of 13**: PFBA, PFBS, PFPeA, PFPeS, PFHxA; ADONA, 4:2 FTS, 6:2 FTS, 8:2 FTS, NFDHA, PFEESA, PFMPA, PFMBA
b. NJ DEP guidance is for a group of related chlorinated perfluoroether carboxylates (Cl-PFPECAs)
c. CT DPH AL based on EPA's Method 533 Detection Limit (MDL) used for UCMR5 for 6:2 Cl-PFESA (aka 9Cl-PF3ONS)
d. CT DPH AL derived using surrogate RfD for 6:2 CL-PFESA and set at EPA Method 533 MDL used for UCMR5 for 11Cl-PF3OUdS)

QUESTIONS?

Thank You!

For questions or additional information:

Cheryl.Fields@ct.gov

Xun.Che@ct.gov