WESTFIELD RESIDENTS ADVOCATING FOR THEMSELVES

July 19, 2019

Elizabeth Callahan
Acting Division Director
Policy and Program Development
MassDEP Bureau of Waste Site Cleanup
One Winter Street, Boston, MA 02108

Dear Director Callahan,

Thank you for the opportunity to submit comments on the proposed revisions to the Massachusetts Contingency Plan (MCP: 310 CMR 40.0000). As the Co-founder and Director of Westfield Residents Advocating For Themselves and a member of the MassDEP PFAS MCL Stakeholder Group, I will confine my comments to the proposed revisions regarding Public Involvement and Per- and polyfluoroalkyl substances (PFAS).

Public Involvement

Regarding the proposed revisions to the Public Involvement section of the MCP (310 CMR 40.1403(11)), **I write to voice my strong support, and ask that you preserve these revisions in protection of Environmental Justice communities, like mine, across the Baystate.** Provisions like these allow residents to know more about hazardous chemicals in their environment as the problem is being assessed instead of after the fact. This earlier notification can have a dramatic effect on the exposure and stress of those affected and will have a direct impact on not only the protection of the public health, but the ability of those affected residents to take precautions to protect themselves and their families.

Per- and Polyfluoroalkyl Substances

With respect to the proposed revisions adding Per- and polyfluoroalkyl substances to the MCP, as I stated at the Public Hearing held in Springfield, MA, **we desperately need these PFAS additions and very much support their inclusion.**

With respect to your specific questions of reviewers, I would first like to bring to your attention a remark made by Dr. Linda Birnbaum, Director of the National Institute for Environmental Health Sciences at the second National PFAS Conference held in June at Northeastern University, and documented by Sharon Lerner of The Intercept (https://theintercept.com/2019/06/18/pfoa-pfas-teflon-epa-limit/), stating that **if pancreatic**

tumors on rats were used as the endpoint, a health protective regulatory level for PFOA would be more like 0.1 parts per trillion, citing work (attached) by the US Department of Health and Human Services National Toxicology Program documentation:

- P08: STATISTICAL ANALYSIS OF PRIMARY TUMORS
- PFOA Chronic Summary.

Second, I would like to mention that, in New Hampshire, just **yesterday, July 18, 2019, the Joint Legislative Committee on Administrative Rules (JLCAR) endorsed recommendations setting maximum limits on four polyfluoroalkyl substances (PFAS) ranging from 11 to 18 parts per trillion.** I mention this because, although higher than what MA is considering, it is evidence that a very industry supportive and environmentally permissive neighbor is setting low regulatory limits. So, when Massachusetts industry representatives give you pushback, I submit for your consideration the New Hampshire Department of Environmental Services's:

- Technical Background Report for the June 2019 Proposed Maximum Contaminant Levels (MCLs) and Ambient Groundwater Quality Standards (AGQSs) for Perfluorooctane sulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), and Perfluorohexane sulfonic Acid (PFHxS)
  And
  Letter from Dr. Stephen M. Roberts, Ph.D. dated 6/25/2019 – Findings of Peer Review Conducted on Technical Background Report
- PFAS MCL Stakeholder Meeting Presentation entitled, "Summary of the Technical Background Report for the Proposed Maximum Contaminant Levels and Ambient Groundwater Quality Standards for PFOA, PFOS, PFNA and PFHxS",

My third and last comment to the point of factors not considered by the PFAS standards proposed in the MCP revisions being considered, is **prior community exposure**. As I mentioned in our last PFAS MCL Stakeholder meeting (June 20), residents in communities like Westfield, Hyannis, Ayer, and Hudson have already been exposed to PFAS for sometimes decades. **Residents of those highly exposed and vulnerable communities need regulatory limits that protect our health as well, and allow our PFAS body burdens to decrease.** Continued exposure will extend our bodies' struggle to eliminate these persistent, bioaccumulative, toxic compounds.

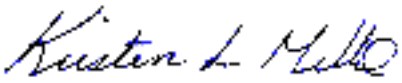
There is one last comment I would like to submit regarding the PFAS limits in biosolids / compost / sludge. I recognize that regulating biosolids will cause many adaptations to that industry. **Residents of PFAS contaminated communities - those with longtime exposures and high body burdens - very much need that regulation.** For non-occupational exposures, the second largest component to PFAS exposure behind drinking water is believed to be food. If that is the case, then PFAS must be strictly regulated in the biosolids we allow to be sold to our farmers. These materials fertilize fields growing both produce and feed grains and grasses. Persistent, bioaccumulative, toxic compounds will biomagnify in the good chain. **Eliminating**

biosolids as a source of PFAS contamination of the food supply is crucial to reduction of PFAS in humans.

Thank you, again, for the opportunity to add my comments on the proposed revisions to the Massachusetts Contingency Plan.

Respectfully submitted for your consideration.

Sincerely,



Kristen L Mello

Co-founder, WRAFT
Westfield Residents Advocating For Themselves
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Attached References (4) can also be located online at:

https://tools.niehs.nih.gov/cebs3/views/index.cfm?action=main.download&bin_id=13658&library_id=17109&fileIdsSelected=1de240ff64c2b9d20164d181b3830035

https://www.documentcloud.org/documents/6154935-PFOA-Chronic-Summary.html

https://www4.des.state.nh.us/nh-pfas-investigation/wp-content/uploads/Stakeholder-Talk-07-09-2019.pdf

https://www.des.nh.gov/organization/commissioner/legal/rulemaking/documents/pfas-scr-attch-1-w-ltr.pdf

Custom Rpt (Litter-Based) -- 0-0, 0-20, 0-40, 0-80

NTP Study Number:	C20614B		
Lock Date:	01/10/2012		
Cage Range:	ALL		
Date Range:	ALL		
Reasons For Removal:	25021 TSAC	25020 NATD	25019 MSAC
Removal Date Range:	ALL		
Treatment Groups:	Include 001 0/0 ppm	Include 003 0/20 ppm	Include 005 0/40 ppm
	Include 007 0/80 ppm		
Study Gender:	Male		
TDMSE Version:	2.5.0.0_sfh		
PWG Approval Date:	NONE		

FOR ALL DOSES THE TUMOR RATES IN THE FOLLOWING TISSUES/ORGANS ARE BASED ON NUMBER OF TISSUES EXAMINED. IN OTHER TISSUES/ORGANS RATES ARE BASED ON THE NUMBER OF ANIMALS NECROPSIED.

Adrenal Cortex
Adrenal Medulla
Brain
Islets, Pancreatic
Liver
Pancreas
Pituitary Gland
Prostate
Testes
Thyroid Gland

SUMMARY OF STATISTICALLY SIGNIFICANT (P<=.05) RESULTS IN THE ANALYSIS OF PERFLUOROOCTANOIC ACID

MALE RATS

Organ	Morphology
Adrenal Cortex	Adenoma
Adrenal Medulla	Pheochromocytoma Benign
	Pheochromocytoma: Benign, Complex, Malignant, NOS
Liver	Hepatocellular Adenoma
Pancreas	Adenoma
	Carcinoma or Adenoma
Skin	Basal or Sq. Cell Carcinoma, Carcinoma, Basosq. Tumor (M or B), Basal Cell Adenoma, Adenoma, Papilloma, Sq Papilloma, Keratoacanthoma, Trichoepithelioma
	Squamous Cell Papilloma, Papilloma, Squamous Cell Carcinoma or Keratoacanthoma
	Squamous Cell Papilloma, Papilloma, or Keratoacanthoma
Thyroid Gland: C-Cell	Adenoma
All Organs	Benign Tumors
	Malignant and Benign Tumors

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Adrenal Cortex Adenoma				
TUMOR RATES				
OVERALL (a)	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
LITTERS (b)	0/25 (0%)	0/25 (0%)	0/25 (0%)	3/25 (12%)
POLY-3 RATE (c)	0/43.13	0/47.35	0/42.02	3/41.66
POLY-3 PERCENT (g)	0%	0%	0%	7.2%
TERMINAL (d)	0/36 (0%)	0/42 (0%)	0/35 (0%)	3/37 (8%)
FIRST INCIDENCE	---	---	---	743 (T)
STATISTICAL TESTS				
POLY 3	P=0.010**	(e)	(e)	P=0.112
POLY 1.5	P=0.010**	(e)	(e)	P=0.114
POLY 6	P=0.009**	(e)	(e)	P=0.113
RAO-SCOTT	P=0.049*	(e)	(e)	P=0.237
LITTER C-A/FISHERS	P=0.011*	(e)	(e)	P=0.117

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Adrenal Medulla				
Pheochromocytoma Benign				
TUMOR RATES				
OVERALL (a)	8/50 (16%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
LITTERS (b)	8/25 (32%)	3/25 (12%)	1/25 (4%)	0/25 (0%)
POLY-3 RATE (c)	8/43.55	3/47.35	1/42.02	0/41.66
POLY-3 PERCENT (g)	18.4%	6.3%	2.4%	0%
TERMINAL (d)	6/36 (17%)	3/42 (7%)	1/35 (3%)	0/37 (0%)
FIRST INCIDENCE	675	743 (T)	743 (T)	---
STATISTICAL TESTS				
POLY 3	P<0.001N**	P=0.074N	P=0.018N*	P=0.004N**
POLY 1.5	P<0.001N**	P=0.080N	P=0.017N*	P=0.004N**
POLY 6	P<0.001N**	P=0.072N	P=0.019N*	P=0.004N**
RAO-SCOTT	P=0.004N**	P=0.106N	P=0.034N*	P=0.012N*
LITTER C-A/FISHERS	P<0.001N**	P=0.085N	P=0.012N*	P=0.002N**

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Adrenal Medulla				
Pheochromocytoma: Benign, Complex, Malignant, NOS				
TUMOR RATES				
OVERALL (a)	8/50 (16%)	4/50 (8%)	1/50 (2%)	0/50 (0%)
LITTERS (b)	8/25 (32%)	4/25 (16%)	1/25 (4%)	0/25 (0%)
POLY-3 RATE (c)	8/43.55	4/47.35	1/42.02	0/41.66
POLY-3 PERCENT (g)	18.4%	8.5%	2.4%	0%
TERMINAL (d)	6/36 (17%)	4/42 (10%)	1/35 (3%)	0/37 (0%)
FIRST INCIDENCE	675	743 (T)	743 (T)	---
STATISTICAL TESTS				
POLY 3	P<0.001N**	P=0.139N	P=0.018N*	P=0.004N**
POLY 1.5	P<0.001N**	P=0.147N	P=0.017N*	P=0.004N**
POLY 6	P<0.001N**	P=0.135N	P=0.019N*	P=0.004N**
RAO-SCOTT	P=0.003N**	P=0.171N	P=0.033N*	P=0.012N*
LITTER C-A/FISHERS	P<0.001N**	P=0.160N	P=0.012N*	P=0.002N**

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Brain				
Granular Cell Tumor Benign				
TUMOR RATES				
OVERALL (a)	2/50 (4%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
LITTERS (b)	2/25 (8%)	0/25 (0%)	0/25 (0%)	0/25 (0%)
POLY-3 RATE (c)	2/43.13	0/47.35	0/42.02	0/41.66
POLY-3 PERCENT (g)	4.6%	0%	0%	0%
TERMINAL (d)	2/36 (6%)	0/42 (0%)	0/35 (0%)	0/37 (0%)
FIRST INCIDENCE	743 (T)	---	---	---
STATISTICAL TESTS				
POLY 3	P=0.121N	P=0.217N	P=0.243N	P=0.245N
POLY 1.5	P=0.119N	P=0.222N	P=0.241N	P=0.243N
POLY 6	P=0.123N	P=0.213N	P=0.244N	P=0.244N
RAO-SCOTT	P=0.228N	P=0.380N	P=0.388N	P=0.388N
LITTER C-A/FISHERS	P=0.114N	P=0.245N	P=0.245N	P=0.245N

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Islets, Pancreatic Adenoma				
TUMOR RATES				
OVERALL (a)	5/50 (10%)	8/50 (16%)	8/50 (16%)	4/50 (8%)
LITTERS (b)	5/25 (20%)	8/25 (32%)	7/25 (28%)	4/25 (16%)
POLY-3 RATE (c)	5/43.30	8/47.35	8/42.02	4/41.66
POLY-3 PERCENT (g)	11.6%	16.9%	19%	9.6%
TERMINAL (d)	4/36 (11%)	8/42 (19%)	8/35 (23%)	4/37 (11%)
FIRST INCIDENCE	697	743 (T)	743 (T)	743 (T)
STATISTICAL TESTS				
POLY 3	P=0.401N	P=0.336	P=0.255	P=0.524N
POLY 1.5	P=0.386N	P=0.321	P=0.263	P=0.518N
POLY 6	P=0.404N	P=0.345	P=0.247	P=0.524N
RAO-SCOTT	P=0.400N	P=0.344	P=0.260	P=0.516N
LITTER C-A/FISHERS	P=0.317N	P=0.260	P=0.371	P=0.500N

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Islets, Pancreatic **Carcinoma or Adenoma**				
TUMOR RATES				
OVERALL (a)	5/50 (10%)	9/50 (18%)	8/50 (16%)	4/50 (8%)
LITTERS (b)	5/25 (20%)	9/25 (36%)	7/25 (28%)	4/25 (16%)
POLY-3 RATE (c)	5/43.30	9/47.63	8/42.02	4/41.66
POLY-3 PERCENT (g)	11.6%	18.9%	19%	9.6%
TERMINAL (d)	4/36 (11%)	8/42 (19%)	8/35 (23%)	4/37 (11%)
FIRST INCIDENCE	697	666	743 (T)	743 (T)
STATISTICAL TESTS				
POLY 3	P=0.363N	P=0.250	P=0.255	P=0.524N
POLY 1.5	P=0.348N	P=0.234	P=0.263	P=0.518N
POLY 6	P=0.367N	P=0.261	P=0.247	P=0.524N
RAO-SCOTT	P=0.364N	P=0.258	P=0.258	P=0.515N
LITTER C-A/FISHERS	P=0.279N	P=0.173	P=0.371	P=0.500N

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Liver				
Hepatocellular Adenoma				
TUMOR RATES				
OVERALL (a)	0/50 (0%)	0/50 (0%)	7/50 (14%)	11/50 (22%)
LITTERS (b)	0/25 (0%)	0/25 (0%)	6/25 (24%)	8/25 (32%)
POLY-3 RATE (c)	0/43.13	0/47.35	7/42.02	11/41.66
POLY-3 PERCENT (g)	0%	0%	16.7%	26.4%
TERMINAL (d)	0/36 (0%)	0/42 (0%)	7/35 (20%)	11/37 (30%)
FIRST INCIDENCE	---	---	743 (T)	743 (T)
STATISTICAL TESTS				
POLY 3	P<0.001**	(e)	P=0.007**	P<0.001**
POLY 1.5	P<0.001**	(e)	P=0.007**	P<0.001**
POLY 6	P<0.001**	(e)	P=0.006**	P<0.001**
RAO-SCOTT	P<0.001**	(e)	P=0.050*	P=0.010**
LITTER C-A/FISHERS	P<0.001**	(e)	P=0.011*	P=0.002**

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Mammary Gland Fibroadenoma				
TUMOR RATES	#	#	#	#
OVERALL (a)	2/50 (4%)	2/50 (4%)	2/50 (4%)	1/50 (2%)
LITTERS (b)	2/25 (8%)	2/25 (8%)	2/25 (8%)	1/25 (4%)
POLY-3 RATE (c)	2/44.06	2/47.35	2/42.65	1/41.66
POLY-3 PERCENT (g)	4.5%	4.2%	4.7%	2.4%
TERMINAL (d)	1/36 (3%)	2/42 (5%)	1/35 (3%)	1/37 (3%)
FIRST INCIDENCE	302	743 (T)	533	743 (T)
STATISTICAL TESTS				
POLY 3	P=0.405N	P=0.668N	P=0.682	P=0.520N
POLY 1.5	P=0.397N	P=0.675N	P=0.685	P=0.515N
POLY 6	P=0.406N	P=0.662N	P=0.682	P=0.519N
RAO-SCOTT	P=0.397N	P=0.661N	P=0.666	P=0.502N
LITTER C-A/FISHERS	P=0.370N	P=0.695	P=0.695	P=0.500N

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Pancreas				
Adenoma				
TUMOR RATES				
OVERALL (a)	3/50 (6%)	28/50 (56%)	26/50 (52%)	32/50 (64%)
LITTERS (b)	3/25 (12%)	21/25 (84%)	20/25 (80%)	22/25 (88%)
POLY-3 RATE (c)	3/43.13	28/47.90	26/42.21	32/41.81
POLY-3 PERCENT (g)	7%	58.5%	61.6%	76.5%
TERMINAL (d)	3/36 (8%)	26/42 (62%)	24/35 (69%)	30/37 (81%)
FIRST INCIDENCE	743 (T)	655	700	720
STATISTICAL TESTS				
POLY 3	P<0.001**	P<0.001**	P<0.001**	P<0.001**
POLY 1.5	P<0.001**	P<0.001**	P<0.001**	P<0.001**
POLY 6	P<0.001**	P<0.001**	P<0.001**	P<0.001**
RAO-SCOTT	P<0.001**	P<0.001**	P<0.001**	P<0.001**
LITTER C-A/FISHERS	P<0.001**	P<0.001**	P<0.001**	P<0.001**

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Pancreas				
Carcinoma				
TUMOR RATES				
OVERALL (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
LITTERS (b)	0/25 (0%)	3/25 (12%)	1/25 (4%)	3/25 (12%)
POLY-3 RATE (c)	0/43.13	3/47.35	1/42.02	3/41.72
POLY-3 PERCENT (g)	0%	6.3%	2.4%	7.2%
TERMINAL (d)	0/36 (0%)	3/42 (7%)	1/35 (3%)	2/37 (5%)
FIRST INCIDENCE	---	743 (T)	743 (T)	726
STATISTICAL TESTS				
POLY 3	P=0.152	P=0.137	P=0.495	P=0.113
POLY 1.5	P=0.155	P=0.132	P=0.497	P=0.114
POLY 6	P=0.153	P=0.140	P=0.493	P=0.113
RAO-SCOTT	P=0.179	P=0.188	P=0.527	P=0.154
LITTER C-A/FISHERS	P=0.160	P=0.117	P=0.500	P=0.117

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Pancreas				
Carcinoma or Adenoma				
TUMOR RATES				
OVERALL (a)	3/50 (6%)	29/50 (58%)	26/50 (52%)	32/50 (64%)
LITTERS (b)	3/25 (12%)	21/25 (84%)	20/25 (80%)	22/25 (88%)
POLY-3 RATE (c)	3/43.13	29/47.90	26/42.21	32/41.81
POLY-3 PERCENT (g)	7%	60.5%	61.6%	76.5%
TERMINAL (d)	3/36 (8%)	27/42 (64%)	24/35 (69%)	30/37 (81%)
FIRST INCIDENCE	743 (T)	655	700	720
STATISTICAL TESTS				
POLY 3	P<0.001**	P<0.001**	P<0.001**	P<0.001**
POLY 1.5	P<0.001**	P<0.001**	P<0.001**	P<0.001**
POLY 6	P<0.001**	P<0.001**	P<0.001**	P<0.001**
RAO-SCOTT	P<0.001**	P<0.001**	P<0.001**	P<0.001**
LITTER C-A/FISHERS	P<0.001**	P<0.001**	P<0.001**	P<0.001**

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Pituitary Gland: Pars Distalis or Unspecified Site				
Adenoma				
TUMOR RATES				
OVERALL (a)	5/50 (10%)	6/50 (12%)	2/50 (4%)	2/50 (4%)
LITTERS (b)	5/25 (20%)	5/25 (20%)	2/25 (8%)	2/25 (8%)
POLY-3 RATE (c)	5/43.44	6/47.54	2/42.41	2/42.11
POLY-3 PERCENT (g)	11.5%	12.6%	4.7%	4.8%
TERMINAL (d)	4/36 (11%)	5/42 (12%)	0/35 (0%)	1/37 (3%)
FIRST INCIDENCE	655	694	683	609
STATISTICAL TESTS				
POLY 3	P=0.107N	P=0.563	P=0.225N	P=0.228N
POLY 1.5	P=0.103N	P=0.547	P=0.222N	P=0.226N
POLY 6	P=0.106N	P=0.573	P=0.227N	P=0.226N
RAO-SCOTT	P=0.138N	P=0.573	P=0.260N	P=0.263N
LITTER C-A/FISHERS	P=0.103N	P=0.637	P=0.209N	P=0.209N

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Prostate **Adenoma**				
TUMOR RATES				
OVERALL (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)	2/50 (4%)
LITTERS (b)	3/25 (12%)	1/25 (4%)	0/25 (0%)	2/25 (8%)
POLY-3 RATE (c)	3/43.13	1/47.35	0/42.02	2/41.66
POLY-3 PERCENT (g)	7%	2.1%	0%	4.8%
TERMINAL (d)	3/36 (8%)	1/42 (2%)	0/35 (0%)	2/37 (5%)
FIRST INCIDENCE	743 (T)	743 (T)	---	743 (T)
STATISTICAL TESTS				
POLY 3	P=0.467N	P=0.273N	P=0.123N	P=0.516N
POLY 1.5	P=0.460N	P=0.281N	P=0.122N	P=0.512N
POLY 6	P=0.470N	P=0.267N	P=0.124N	P=0.514N
RAO-SCOTT	P=0.484N	P=0.331N	P=0.176N	P=0.534N
LITTER C-A/FISHERS	P=0.443N	P=0.305N	P=0.117N	P=0.500N

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Skin				
Basal or Sq. Cell Carcinoma, Carcinoma, Basosq. Tumor (M or B), Basal Cell Adenoma, Adenoma, Papilloma, Sq Papilloma, Keratoacanthoma, Trichoepithelioma				
TUMOR RATES	#	#	#	#
OVERALL (a)	6/50 (12%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
LITTERS (b)	6/25 (24%)	3/25 (12%)	1/25 (4%)	1/25 (4%)
POLY-3 RATE (c)	6/43.13	3/47.35	1/42.24	1/41.66
POLY-3 PERCENT (g)	13.9%	6.3%	2.4%	2.4%
TERMINAL (d)	6/36 (17%)	3/42 (7%)	0/35 (0%)	1/37 (3%)
FIRST INCIDENCE	743 (T)	743 (T)	683	743 (T)
STATISTICAL TESTS				
POLY 3	P=0.030N*	P=0.198N	P=0.059N	P=0.061N
POLY 1.5	P=0.029N*	P=0.209N	P=0.058N	P=0.060N
POLY 6	P=0.031N*	P=0.190N	P=0.059N	P=0.060N
RAO-SCOTT	P=0.041N*	P=0.222N	P=0.077N	P=0.079N
LITTER C-A/FISHERS	P=0.023N*	P=0.232N	P=0.049N*	P=0.049N*

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Skin				
Fibroma				
TUMOR RATES	#	#	#	#
OVERALL (a)	1/50 (2%)	5/50 (10%)	1/50 (2%)	1/50 (2%)
LITTERS (b)	1/25 (4%)	5/25 (20%)	1/25 (4%)	1/25 (4%)
POLY-3 RATE (c)	1/43.13	5/47.35	1/42.02	1/41.66
POLY-3 PERCENT (g)	2.3%	10.6%	2.4%	2.4%
TERMINAL (d)	1/36 (3%)	5/42 (12%)	1/35 (3%)	1/37 (3%)
FIRST INCIDENCE	743 (T)	743 (T)	743 (T)	743 (T)
STATISTICAL TESTS				
POLY 3	P=0.324N	P=0.125	P=0.755	P=0.753
POLY 1.5	P=0.321N	P=0.119	P=0.757	P=0.755
POLY 6	P=0.323N	P=0.129	P=0.754	P=0.754
RAO-SCOTT	P=0.357N	P=0.163	P=0.747	P=0.744
LITTER C-A/FISHERS	P=0.309N	P=0.095	P=0.755	P=0.755

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Skin				
Fibroma, Fibrosarcoma, Sarcoma, Myxoma, Myxosarcoma, or Malignant Fibrous Histiocytoma				
TUMOR RATES	#	#	#	#
OVERALL (a)	2/50 (4%)	5/50 (10%)	1/50 (2%)	2/50 (4%)
LITTERS (b)	2/25 (8%)	5/25 (20%)	1/25 (4%)	2/25 (8%)
POLY-3 RATE (c)	2/43.13	5/47.35	1/42.02	2/41.75
POLY-3 PERCENT (g)	4.6%	10.6%	2.4%	4.8%
TERMINAL (d)	2/36 (6%)	5/42 (12%)	1/35 (3%)	1/37 (3%)
FIRST INCIDENCE	743 (T)	743 (T)	743 (T)	720
STATISTICAL TESTS				
POLY 3	P=0.389N	P=0.256	P=0.509N	P=0.682
POLY 1.5	P=0.384N	P=0.246	P=0.506N	P=0.685
POLY 6	P=0.388N	P=0.263	P=0.511N	P=0.685
RAO-SCOTT	P=0.405N	P=0.274	P=0.505N	P=0.668
LITTER C-A/FISHERS	P=0.368N	P=0.209	P=0.500N	P=0.695

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Skin				
Keratoacanthoma				
TUMOR RATES	#	#	#	#
OVERALL (a)	5/50 (10%)	2/50 (4%)	1/50 (2%)	1/50 (2%)
LITTERS (b)	5/25 (20%)	2/25 (8%)	1/25 (4%)	1/25 (4%)
POLY-3 RATE (c)	5/43.13	2/47.35	1/42.24	1/41.66
POLY-3 PERCENT (g)	11.6%	4.2%	2.4%	2.4%
TERMINAL (d)	5/36 (14%)	2/42 (5%)	0/35 (0%)	1/37 (3%)
FIRST INCIDENCE	743 (T)	743 (T)	683	743 (T)
STATISTICAL TESTS				
POLY 3	P=0.068N	P=0.180N	P=0.105N	P=0.109N
POLY 1.5	P=0.066N	P=0.189N	P=0.104N	P=0.107N
POLY 6	P=0.069N	P=0.174N	P=0.106N	P=0.108N
RAO-SCOTT	P=0.087N	P=0.212N	P=0.132N	P=0.135N
LITTER C-A/FISHERS	P=0.055N	P=0.209N	P=0.095N	P=0.095N

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Skin				
Lipoma				
TUMOR RATES	#	#	#	#
OVERALL (a)	0/50 (0%)	2/50 (4%)	0/50 (0%)	0/50 (0%)
LITTERS (b)	0/25 (0%)	2/25 (8%)	0/25 (0%)	0/25 (0%)
POLY-3 RATE (c)	0/43.13	2/47.35	0/42.02	0/41.66
POLY-3 PERCENT (g)	0%	4.2%	0%	0%
TERMINAL (d)	0/36 (0%)	2/42 (5%)	0/35 (0%)	0/37 (0%)
FIRST INCIDENCE	---	743 (T)	---	---
STATISTICAL TESTS				
POLY 3	P=0.401N	P=0.259	(e)	(e)
POLY 1.5	P=0.402N	P=0.253	(e)	(e)
POLY 6	P=0.399N	P=0.263	(e)	(e)
RAO-SCOTT	P=0.490N	P=0.404	(e)	(e)
LITTER C-A/FISHERS	P=0.405N	P=0.245	(e)	(e)

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Skin				
Squamous Cell Papilloma, Papilloma, Squamous Cell Carcinoma or Keratoacanthoma				
TUMOR RATES	#	#	#	#
OVERALL (a)	5/50 (10%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
LITTERS (b)	5/25 (20%)	3/25 (12%)	1/25 (4%)	1/25 (4%)
POLY-3 RATE (c)	5/43.13	3/47.35	1/42.24	1/41.66
POLY-3 PERCENT (g)	11.6%	6.3%	2.4%	2.4%
TERMINAL (d)	5/36 (14%)	3/42 (7%)	0/35 (0%)	1/37 (3%)
FIRST INCIDENCE	743 (T)	743 (T)	683	743 (T)
STATISTICAL TESTS				
POLY 3	P=0.057N	P=0.307N	P=0.105N	P=0.109N
POLY 1.5	P=0.055N	P=0.319N	P=0.104N	P=0.107N
POLY 6	P=0.058N	P=0.298N	P=0.106N	P=0.108N
RAO-SCOTT	P=0.072N	P=0.328N	P=0.127N	P=0.130N
LITTER C-A/FISHERS	P=0.045N*	P=0.351N	P=0.095N	P=0.095N

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Skin				
Squamous Cell Papilloma, Papilloma, or Keratoacanthoma				
TUMOR RATES	#	#	#	#
OVERALL (a)	5/50 (10%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
LITTERS (b)	5/25 (20%)	3/25 (12%)	1/25 (4%)	1/25 (4%)
POLY-3 RATE (c)	5/43.13	3/47.35	1/42.24	1/41.66
POLY-3 PERCENT (g)	11.6%	6.3%	2.4%	2.4%
TERMINAL (d)	5/36 (14%)	3/42 (7%)	0/35 (0%)	1/37 (3%)
FIRST INCIDENCE	743 (T)	743 (T)	683	743 (T)
STATISTICAL TESTS				
POLY 3	P=0.057N	P=0.307N	P=0.105N	P=0.109N
POLY 1.5	P=0.055N	P=0.319N	P=0.104N	P=0.107N
POLY 6	P=0.058N	P=0.298N	P=0.106N	P=0.108N
RAO-SCOTT	P=0.072N	P=0.328N	P=0.127N	P=0.130N
LITTER C-A/FISHERS	P=0.045N*	P=0.351N	P=0.095N	P=0.095N

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Testes				
Adenoma				
TUMOR RATES				
OVERALL (a)	0/50 (0%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
LITTERS (b)	0/25 (0%)	0/25 (0%)	3/25 (12%)	0/25 (0%)
POLY-3 RATE (c)	0/43.13	0/47.35	3/42.09	0/41.66
POLY-3 PERCENT (g)	0%	0%	7.1%	0%
TERMINAL (d)	0/36 (0%)	0/42 (0%)	2/35 (6%)	0/37 (0%)
FIRST INCIDENCE	---	---	725	---
STATISTICAL TESTS				
POLY 3	P=0.501	(e)	P=0.114	(e)
POLY 1.5	P=0.510	(e)	P=0.116	(e)
POLY 6	P=0.501	(e)	P=0.113	(e)
RAO-SCOTT	P=0.569	(e)	P=0.243	(e)
LITTER C-A/FISHERS	P=0.539	(e)	P=0.117	(e)

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Thyroid Gland: C-Cell Adenoma				
TUMOR RATES				
OVERALL (a)	11/49 (22%)	11/50 (22%)	4/50 (8%)	12/49 (24%)
LITTERS (b)	8/25 (32%)	8/25 (32%)	3/25 (12%)	11/25 (44%)
POLY-3 RATE (c)	11/42.22	11/47.77	4/42.02	12/41.94
POLY-3 PERCENT (g)	26.1%	23%	9.5%	28.6%
TERMINAL (d)	11/36 (31%)	9/42 (21%)	4/35 (11%)	10/37 (27%)
FIRST INCIDENCE	743 (T)	679	743 (T)	609
STATISTICAL TESTS				
POLY 3	P=0.474	P=0.465N	P=0.042N*	P=0.493
POLY 1.5	P=0.484	P=0.495N	P=0.041N*	P=0.489
POLY 6	P=0.476	P=0.441N	P=0.043N*	P=0.509
RAO-SCOTT	P=0.480	P=0.483N	P=0.070N	P=0.503
LITTER C-A/FISHERS	P=0.253	P=0.619	P=0.085N	P=0.280

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Thyroid Gland: C-Cell Carcinoma				
TUMOR RATES				
OVERALL (a)	0/49 (0%)	3/50 (6%)	2/50 (4%)	1/49 (2%)
LITTERS (b)	0/25 (0%)	3/25 (12%)	2/25 (8%)	1/25 (4%)
POLY-3 RATE (c)	0/42.22	3/47.47	2/42.65	1/41.43
POLY-3 PERCENT (g)	0%	6.3%	4.7%	2.4%
TERMINAL (d)	0/36 (0%)	2/42 (5%)	1/35 (3%)	1/37 (3%)
FIRST INCIDENCE	---	711	533	743 (T)
STATISTICAL TESTS				
POLY 3	P=0.541	P=0.141	P=0.239	P=0.496
POLY 1.5	P=0.543	P=0.136	P=0.240	P=0.497
POLY 6	P=0.544	P=0.145	P=0.239	P=0.498
RAO-SCOTT	P=0.538	P=0.189	P=0.282	P=0.524
LITTER C-A/FISHERS	P=0.557	P=0.117	P=0.245	P=0.500

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
Thyroid Gland: C-Cell Carcinoma or Adenoma				
TUMOR RATES				
OVERALL (a)	11/49 (22%)	14/50 (28%)	6/50 (12%)	13/49 (27%)
LITTERS (b)	8/25 (32%)	10/25 (40%)	5/25 (20%)	12/25 (48%)
POLY-3 RATE (c)	11/42.22	14/47.90	6/42.65	13/41.94
POLY-3 PERCENT (g)	26.1%	29.2%	14.1%	31%
TERMINAL (d)	11/36 (31%)	11/42 (26%)	5/35 (14%)	11/37 (30%)
FIRST INCIDENCE	743 (T)	679	533	609
STATISTICAL TESTS				
POLY 3	P=0.451	P=0.460	P=0.133N	P=0.397
POLY 1.5	P=0.459	P=0.427	P=0.132N	P=0.394
POLY 6	P=0.455	P=0.489	P=0.132N	P=0.413
RAO-SCOTT	P=0.452	P=0.476	P=0.167N	P=0.415
LITTER C-A/FISHERS	P=0.208	P=0.384	P=0.260N	P=0.193

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
All Organs				
Leukemia: Lymphocytic, Monocytic, Mononuclear, or Undifferentiated				
TUMOR RATES	#	#	#	#
OVERALL (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
LITTERS (b)	3/25 (12%)	0/25 (0%)	0/25 (0%)	1/25 (4%)
POLY-3 RATE (c)	3/43.33	0/47.35	0/42.02	1/42.39
POLY-3 PERCENT (g)	6.9%	0%	0%	2.4%
TERMINAL (d)	2/36 (6%)	0/42 (0%)	0/35 (0%)	0/37 (0%)
FIRST INCIDENCE	689	---	---	478
STATISTICAL TESTS				
POLY 3	P=0.264N	P=0.104N	P=0.124N	P=0.313N
POLY 1.5	P=0.259N	P=0.107N	P=0.122N	P=0.312N
POLY 6	P=0.267N	P=0.102N	P=0.126N	P=0.311N
RAO-SCOTT	P=0.318N	P=0.186N	P=0.200N	P=0.380N
LITTER C-A/FISHERS	P=0.245N	P=0.117N	P=0.117N	P=0.305N

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
All Organs				
Malignant Lymphoma: Histiocytic, Lymphocytic, Mixed, NOS, or Undifferentiated Cell Type				
TUMOR RATES	#	#	#	#
OVERALL (a)	1/50 (2%)	2/50 (4%)	2/50 (4%)	0/50 (0%)
LITTERS (b)	1/25 (4%)	2/25 (8%)	2/25 (8%)	0/25 (0%)
POLY-3 RATE (c)	1/43.53	2/47.35	2/42.39	0/41.66
POLY-3 PERCENT (g)	2.3%	4.2%	4.7%	0%
TERMINAL (d)	0/36 (0%)	2/42 (5%)	0/35 (0%)	0/37 (0%)
FIRST INCIDENCE	624	743 (T)	659	---
STATISTICAL TESTS				
POLY 3	P=0.319N	P=0.529	P=0.491	P=0.509N
POLY 1.5	P=0.313N	P=0.522	P=0.494	P=0.506N
POLY 6	P=0.321N	P=0.533	P=0.489	P=0.509N
RAO-SCOTT	P=0.340N	P=0.556	P=0.509	P=0.534N
LITTER C-A/FISHERS	P=0.294N	P=0.500	P=0.500	P=0.500N

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
All Organs				
Benign Tumors				
TUMOR RATES	#	#	#	#
OVERALL (a)	32/50 (64%)	40/50 (80%)	31/50 (62%)	38/50 (76%)
LITTERS (b)	22/25 (88%)	23/25 (92%)	22/25 (88%)	24/25 (96%)
POLY-3 RATE (c)	32/44.97	40/48.09	31/43.14	38/42.26
POLY-3 PERCENT (g)	71.2%	83.2%	71.9%	89.9%
TERMINAL (d)	27/36 (75%)	37/42 (88%)	26/35 (74%)	35/37 (95%)
FIRST INCIDENCE	302	655	533	609
STATISTICAL TESTS				
POLY 3	P=0.043*	P=0.120	P=0.566	P=0.019*
POLY 1.5	P=0.079	P=0.099	P=0.584N	P=0.036*
POLY 6	P=0.029*	P=0.129	P=0.540	P=0.013*
RAO-SCOTT	P=0.050*	P=0.132	P=0.556	P=0.028*
LITTER C-A/FISHERS	P=0.258	P=0.500	P=0.666	P=0.305

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
All Organs **Malignant Tumors**				
TUMOR RATES	#	#	#	#
OVERALL (a)	9/50 (18%)	12/50 (24%)	8/50 (16%)	8/50 (16%)
LITTERS (b)	8/25 (32%)	12/25 (48%)	6/25 (24%)	7/25 (28%)
POLY-3 RATE (c)	9/45.96	12/48.03	8/43.72	8/44.09
POLY-3 PERCENT (g)	19.6%	25%	18.3%	18.1%
TERMINAL (d)	4/36 (11%)	9/42 (21%)	4/35 (11%)	3/37 (8%)
FIRST INCIDENCE	137	666	502	432
STATISTICAL TESTS				
POLY 3	P=0.377N	P=0.353	P=0.545N	P=0.538N
POLY 1.5	P=0.371N	P=0.337	P=0.538N	P=0.536N
POLY 6	P=0.376N	P=0.363	P=0.549N	P=0.533N
RAO-SCOTT	P=0.382N	P=0.359	P=0.541N	P=0.534N
LITTER C-A/FISHERS	P=0.247N	P=0.193	P=0.377N	P=0.500N

STATISTICAL ANALYSIS OF PRIMARY TUMORS IN RATS(HSD)
TERMINAL SACRIFICE AT 107 WEEKS

Males

DOSE	0/0 ppm	0/20 ppm	0/40 ppm	0/80 ppm
All Organs				
Malignant and Benign Tumors				
TUMOR RATES	#	#	#	#
OVERALL (a)	37/50 (74%)	46/50 (92%)	35/50 (70%)	41/50 (82%)
LITTERS (b)	24/25 (96%)	24/25 (96%)	22/25 (88%)	25/25 (100%)
POLY-3 RATE (c)	37/47.56	46/48.77	35/44.76	41/44.54
POLY-3 PERCENT (g)	77.8%	94.3%	78.2%	92.1%
TERMINAL (d)	28/36 (78%)	40/42 (95%)	27/35 (77%)	35/37 (95%)
FIRST INCIDENCE	137	655	502	432
STATISTICAL TESTS				
POLY 3	P=0.120	P=0.016*	P=0.583	P=0.045*
POLY 1.5	P=0.167	P=0.012*	P=0.585N	P=0.064
POLY 6	P=0.101	P=0.019*	P=0.573	P=0.038*
RAO-SCOTT	P=0.154	P=0.034*	P=0.584	P=0.076
LITTER C-A/FISHERS	P=0.408	P=0.755	P=0.305N	P=0.500

LEGEND

(a)	Number of tumor-bearing animals/number of animals examined at site.
(b)	Number of litters with tumor-bearing animals/number of litters examined at site
(c)	Number of tumor-bearing animals/Poly-3 number
(d)	Observed incidence at terminal kill.
(e)	Value of statistic cannot be computed.
(f)	Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between the controls and that dosed group.
(g)	Poly-3 adjusted lifetime tumor incidence.
(I)	Interim sacrifice
(T)	Terminal sacrifice
#	Tumor rates based on numbers of animals necropsied.
*	To the right of any statistical result, indicates significance at (P<=0.05).
**	To the right of any statistical result, indicates significance at (P<=0.01).
N	Indicates a negative trend for all tests
	The Rao-Scott statistic performs the Poly-3 test with an adjustment for within-litter correlation.
	The Litter C-A/Fishers statistic compares directly the litter incidence rates.

*** END OF REPORT ***

NEW HAMPSHIRE DEPARTMENT OF Environmental Services

Summary of the Technical Background Report for the Proposed Maximum Contaminant Levels and Ambient Groundwater Quality Standards for PFOA, PFOS, PFNA and PFHxS.

Stakeholder Meeting
07/09/2019

NEW HAMPSHIRE DEPARTMENT OF Environmental Services

Presentation Overview

1. Health-Based Risk Assessment Process

2. Chemical-Specific Reference Doses for:
   PFOA PFOS
   PFNA PFHxS

3. Exposure Assumptions
   Use of the “Minnesota” Model
   Relative Source Contribution

4. Modeled Exposures & Proposed MCLs

5. Questions

image: medium.com

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- **academic institutions,**
- **community advocacy groups,**
- **representatives for the business community,**
- **and municipalities.**

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- **Environmental Council of the States (ECOS) PFAS Caucus**
- **Federal-State Toxicology & Risk Analysis Committee (FSTRAC)**
- **Interstate Technology & Regulatory Council (ITRC) PFAS Working Group**
- **Massachusetts Department of Environmental Protection (MADEP)**
- **Michigan Department of Health & Human Services (MIDHHS)**
- **Minnesota Department of Health (MDH)**
- **New England Interstate Water Pollution Control Commission (NEIWPCC)**
- **New Jersey Department of Environmental Protection (NJDEP)**
- **Northeast Waste Management Officials' Association (NEWMOA)**

Health-Based Risk Assessment Process

1. **Identify the chemicals of concern**:

Perfluorooctanoic acid (PFOA)	Perfluorooctane sulfonic acid (PFOS)
Perfluorononanoic acid (PFNA)	Perfluorohexane sulfonic acid (PFHxS)

2. Identify sensitive and human-relevant health effects due to exposure to the chemical, and **derive a reference dose (RfD)** for the effects.
   - Is the chemical a carcinogen?
   - Are non-cancer health effects more protective than cancer endpoints?
   - Do epidemiological studies provide clear evidence?
   - Are there appropriate animal models for quantifying toxicity?

3. **Characterize an exposure scenario** using protective assumptions to determine an environmental concentration (*i.e.*, drinking water level) that will not exceed the RfD.

Health-Based Risk Assessment Process

Per the CDC's **Agency for Toxic Substances and Disease Registry** (ATSDR) draft toxicity profile on PFAS (ATSDR, 2018), suspected health outcomes include:

Rodent Experiments

- Immune system modulation
- Altered lipid metabolism
- Liver stress and inflammation
- Altered liver enzyme levels
- Thyroid disruption
- Reduced birth weight
- Fetal skeletal defects
- Fetal loss (death)
- Neurobehavioral defects
- Delayed mammary gland development
- Liver, testicular & kidney cancer

?

Human Epidemiology

Possible effects based on associations:

- Immune system modulation
- Altered lipid metabolism
- Altered liver enzyme levels
- Altered thyroid hormone levels
- Altered behavior in infants, children & adolescents
- Infertility in women
- Reduced birth weight
- Potentially testicular & kidney cancer

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Health-Based Risk Assessment Process

Proposed MCLs based on non-cancer endpoints

Specific PFAS	NHDES Revised MCLs	Animal Health Outcome
PFOA	12 ng/L	Liver toxicity & altered lipid metabolism
PFOS	15 ng/L	Suppressed immune response to vaccines
PFHxS	18 ng/L	Reduced female fertility
PFNA	11 ng/L	Liver toxicity & altered lipid metabolism

Chemical-Specific Reference Doses

A **reference dose (RfD)** is:
"An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." – EPA 2002

RfDs are not synonymous to ATSDR minimal risk levels (MRLs).

Measured internal dose from animal study

Estimated an external (oral) dose

Used for the calculation of a drinking water or other environmental standard

$$\frac{\textbf{Animal Serum (ng/mL)}}{\textbf{Total Uncertainty}} \times \textbf{Dosimetric Adjustment Factor (mL/kg–d)} = \textbf{Reference Dose (ng/kg–d)}$$

Accounts for animal-to-human differences and quality of studies

Chemical-Specific Reference Doses

Animal studies selected for RfDs in the Initial (January) MCL proposal.

Specific PFAS	Animal Study Health Effect	Notes & Corresponding Animal Serum Concentration
Perfluorooctanoic acid (PFOA)	Increased relative liver weight	Male mouse study Duration: 14 days 4,351 ng/mL $BMDL_{10}$; Loveless et al. 2006, NJDWQI 2017
Perfluorooctane sulfonic acid (PFOS)	Delayed pup growth & development	Reproductive & transgenerational rat study Duration: 2 generations 6,260 ng/mL Modeled; Luebker 2005ab, EPA 2016
Perfluorohexane sulfonic acid (PFHxS)	Reduced litter size	Reproductive & developmental CD-1 mouse study Duration: 14 days prior to & through gestation 27,200 ng/mL NOAEL; Chang et al. 2018
Perfluorononanoic acid (PFNA)	Increased relative liver weight	Reproductive & developmental CD-1 mouse study Duration: through gestation, 17 days 4,900 ng/mL $BMDL_{10}$; Das et al. 2015, NJDWQI 2018

Perfluorooctanoic acid (PFOA) RfD Derivation

Animal Starting Point (Internal Dose and Effect)

Animal Serum Level
(Benchmark Model, NJDWQI calculation)

Increased relative liver weight, or the onset of hepatotoxicity — 4,351 ng/mL

Uncertainty Factors

Human-to-Human Variation	10
Rodent versus Human Sensitivity (assumes humans are more sensitive than mice)	$10^{0.5}$
Database Uncertainty (suspected growth & immune effects)	$\times 10^{0.5}$
Total Uncertainty Factor	100

Internal Target Serum Level →

4,351 ng/mL
÷ 100
43.5 ng/mL

Estimation of Human External Dose

Dosimetric Adjustment Factor (DAF)

Converts the internal blood dose (above) to an external (oral) dose of the chemical.

$$DAF = Vd \times \left(\frac{Ln2}{Halflife\ (days)}\right)$$

$$DAF = 0.17\ L/kg \times \left(\frac{Ln2}{\mathbf{840\ days}}\right) = 1.40 \times 10^{-4}\ L/kg\text{-}d$$

Assumed a **2.3 year half-life**

43.5 ng/mL
1.40×10^{-4} L/kg-d
× 1,000 mL/L
6.1 ng/kg-d

PFOA RfD, 6.1 ng/kg-d

Perfluorooctane sulfonic acid (PFOS) RfD Derivation

Animal Starting Point (Internal Dose and Effect)

Animal Serum Level
(No Observed Adverse Effect Level, Agreed with MDH 2019 Assessment)

Decreased immunoglobulin production, Or reduced vaccine response — 2,360 ng/mL

Uncertainty Factors

Human-to-Human Variation	10
Rodent versus Human Sensitivity (assumes humans are more sensitive than mice)	$10^{0.5}$
Database Uncertainty (suspected growth & fetal thyroid effects)	$\times 10^{0.5}$
Total Uncertainty Factor	100

Internal Target Serum Level →

2,360 ng/mL
÷ 100
23.6 ng/mL

Estimation of Human External Dose

Dosimetric Adjustment Factor (DAF)

Converts the internal blood dose (above) to an external (oral) dose of the chemical.

$$DAF = Vd \times \left(\frac{Ln2}{Halflife\ (days)}\right)$$

$$DAF = 0.23\ L/kg \times \left(\frac{Ln2}{1{,}241\ days}\right) = 1.28 \times 10^{-4}\ L/kg\text{-}d$$

Assumed a 3.4 year half-life

23.6 ng/mL
1.28×10^{-4} L/kg-d
× 1,000 mL/L
3.0 ng/kg-d

PFOS RfD, 3.0 ng/kg-d

Perfluorononanoic acid (PFNA) RfD Derivation

Animal Starting Point (Internal Dose and Effect)

Animal Serum Level
(Benchmark Model, NJDWQI calculation)

Increased relative liver weight, or the onset of hepatotoxicity — 4,900 ng/mL

Uncertainty Factors

Human-to-Human Variation	10
Rodent versus Human Sensitivity (assumes humans are more sensitive than mice)	$10^{0.5}$
Database Uncertainty (lack of multigenerational studies)	$\times 10^{0.5}$
Total Uncertainty Factor	100

4,900 ng/mL
÷ 100
49.0 ng/mL

Internal Target Serum Level →

Estimation of Human External Dose

Dosimetric Adjustment Factor (DAF)

Converts the internal blood dose (above) to an external (oral) dose of the chemical.

$$DAF = Vd \times \left(\frac{Ln2}{Halflife\ (days)}\right)$$

$$DAF = 0.20\ L/kg \times \left(\frac{Ln2}{\mathbf{1{,}570\ days}}\right) = 8.83 \times 10^{-5}\ L/kg\text{-}d$$

Assumed a **4.3 year half-life**

49.0 ng/mL
8.83×10^{-5} L/kg-d
× 1,000 mL/L
4.3 ng/kg-d

PFNA RfD, 4.3 ng/kg-d

Perfluorohexane sulfonic acid (PFHxS) RfD Derivation

Animal Starting Point (Internal Dose and Effect)

Animal Serum Level
(Benchmark Model, *under peer-review*)

Reduced litter size in female mice, 13,900 ng/mL

Uncertainty Factors

Human-to-Human Variation	10
Rodent versus Human Sensitivity (assumes humans are more sensitive than mice)	$10^{0.5}$
Duration of Exposure (14-day effect)	$10^{0.5}$
Database Uncertainty (lack of studies, fetal thyroid effects)	$\times 10^{0.5}$
Total Uncertainty Factor	300

Internal Target Serum Level →

13,900 ng/mL
÷ 300
46.3 ng/mL

Estimation of Human External Dose

Dosimetric Adjustment Factor (DAF)

Converts the internal blood dose (above) to an external (oral) dose of the chemical.

$$DAF = Vd \times \left(\frac{Ln2}{Halflife\ (days)}\right)$$

$$DAF = 0.213\ L/kg \times \left(\frac{Ln2}{\mathbf{1{,}716\ days}}\right) = 8.61 \times 10^{-5}\ L/kg\text{-}d$$

Assumed a **4.7 year half-life**

46.3 ng/mL
8.61×10^{-5} L/kg-d
× 1,000 mL/L
4.0 ng/kg-d

PFHxS RfD, 4.0 ng/kg-d

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Comparison of Reference Doses

RfDs for the four evaluated PFAS in comparison to values from other agencies.
All values below are presented in **ng/kg-d**

Specific PFAS	NHDES (01/2019) (RfD)	NHDES (06/2019) (RfD)	US EPA 2016 (RfD)	ATSDR 2018 (MRL)	EFSA 2019 (RfD)
PFOA	5.2	**6.1**	20	3.0	0.8
PFOS	8.0	**3.0**	20	2.0	1.8
PFHxS	9.3	**4.0**	-	20	-
PFNA	2.5	**4.3**	-	3.0	-

USEPA. 2016. Drinking Water Advisory for Perfluoroctanoic acid (PFOA).
USEPA. 2016. Drinking Water Advisory for Perfluorooctane sulfonic acid (PFOS).
ASTDR. 2018. Toxicological Profile for Perfluoroalkyls Draft for Public Comment. https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=1117&tid=237
EFSA.

Exposure Assumptions

Exposure characterization considers how much PFAS is permissible given:

1. Protective assumptions about drinking water ingestion rates
2. Estimation of other non-drinking water sources of exposure.

The U.S. EPA (2016) assumed the drinking water ingestion rate of the 90th percentile of lactating women, and that 20% of exposure is permissible through drinking water (PFOA & PFOS at 70 ng/L).

These assumptions vary by state agencies, sometimes resulting in different drinking water values despite similar RfDs.

image: medium.com

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Exposure Assumptions: Initial Proposal (January 4th, 2019)

$$\frac{\text{RfD (ng/kg–day)} \times \text{Relative Source Contribution (\%)}}{\text{Water Ingestion Rate (L/kg–day)}} = \text{Maximum Contaminant Level (ng/L)}$$

Specific PFAS	Reference Dose (ng/kg-day)	Water Ingestion Rate (L/kg-day)	Relative Source Contribution	Proposed MCL (ng/L)
PFOA	These values changed in response to technical comments	These values changed in the EPA Exposure Factor Handbook (Feb 2019)	These values changed in response to technical comments	38
PFOS				70
PFHxS				85
PFNA				23

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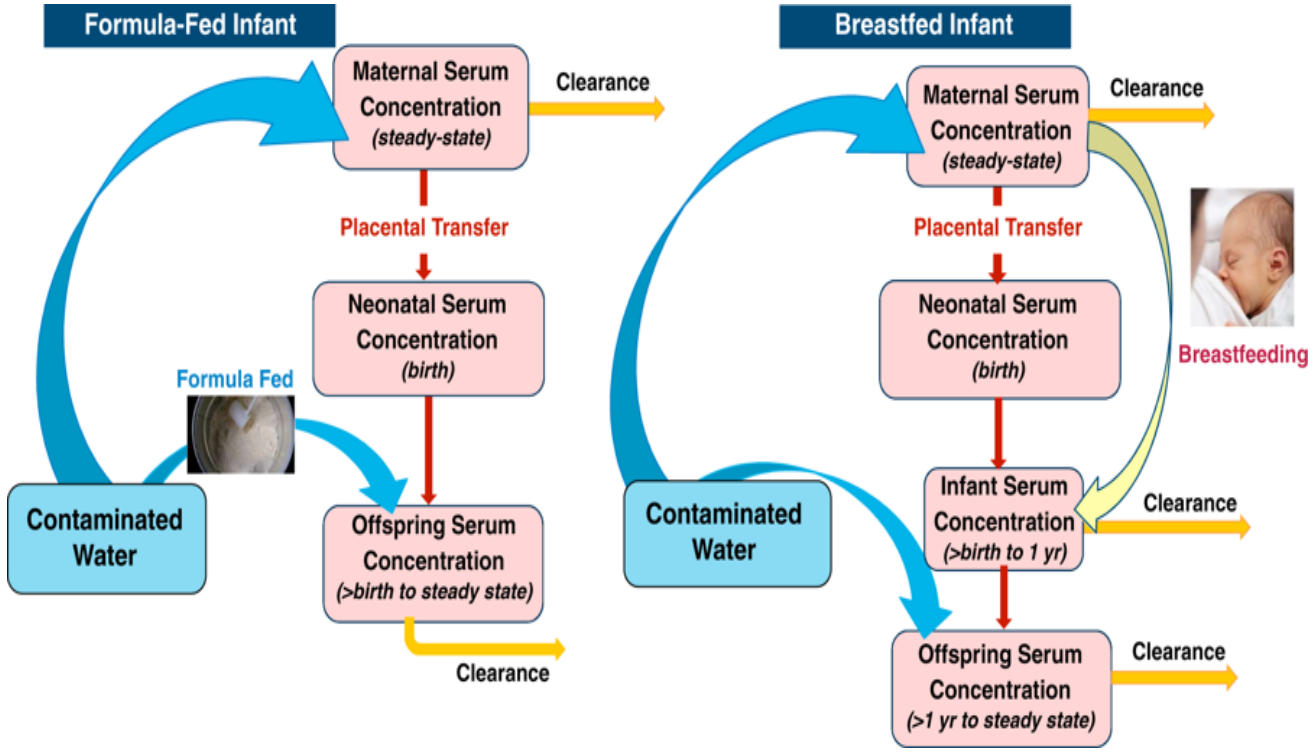
Exposure Assumptions: Example using June 2019 proposal

$$\frac{\text{RfD (ng/kg–day)} \times \text{Relative Source Contribution (\%)}}{\text{Water Ingestion Rate (L/kg–day)}} = \text{Maximum Contaminant Level (ng/L)}$$

Specific PFAS	Reference Dose (ng/kg-day)	Water Ingestion Rate (L/kg-day)	Relative Source Contribution	*Example* Drinking Water Value (ng/L)
PFOA	6.1	These values do not account for the transfer of PFAS across the placenta and into breastmilk.	50%	These values would result in unacceptable serum levels in breastfed infants.
PFOS	3.0		50%	
PFHxS	4.0		50%	
PFNA	4.3		50%	

Exposure Assumptions: Minnesota Model

What is the Transgenerational (or Minnesota) Model?



The conceptual diagram for the toxicokinetic model.
Image from: Goeden et al. (2019), *Journal of Exposure Science & Environmental Epidemiology* vol. 29, 183–195.

Excel-based model is available upon request from Minnesota Department of Health.

Human Half-life Assumptions

- NHDES applied **average** (**central tendency**) half-life estimates for PFOA (2.3 years), PFOS (3.4 years), PFNA (4.3 years) and PFHxS (4.7 years).
- NHDES did not apply the 95th percentile, or other high-end values derived from occupational exposures.

Placental & breastmilk transfer efficiencies

- NHDES applied **average** (**central tendency**) transfer efficiencies, similar to MDH and MIDHHS.

Duration of *exclusive* breastfeeding

- NHDES applied a **conservative** **12-month exclusive breastfeeding duration** for the modeled exposure scenarios.

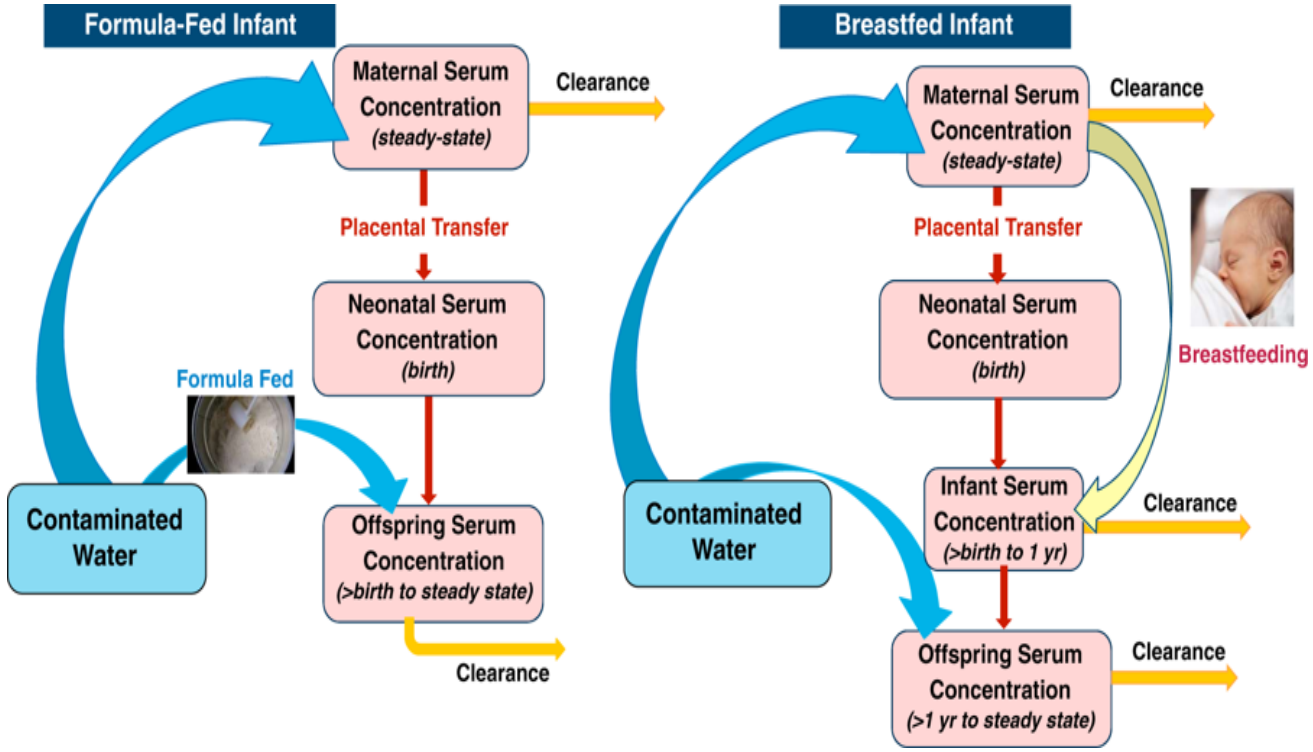
Breastmilk & water ingestion rates

- NHDES applied the **95th percentile** (**conservative**) ingestion rates for water and breastmilk across life.

Values are summarized in Table 3 of the June Report.

Exposure Assumptions: Minnesota Model

What is the Transgenerational (or Minnesota) Model?



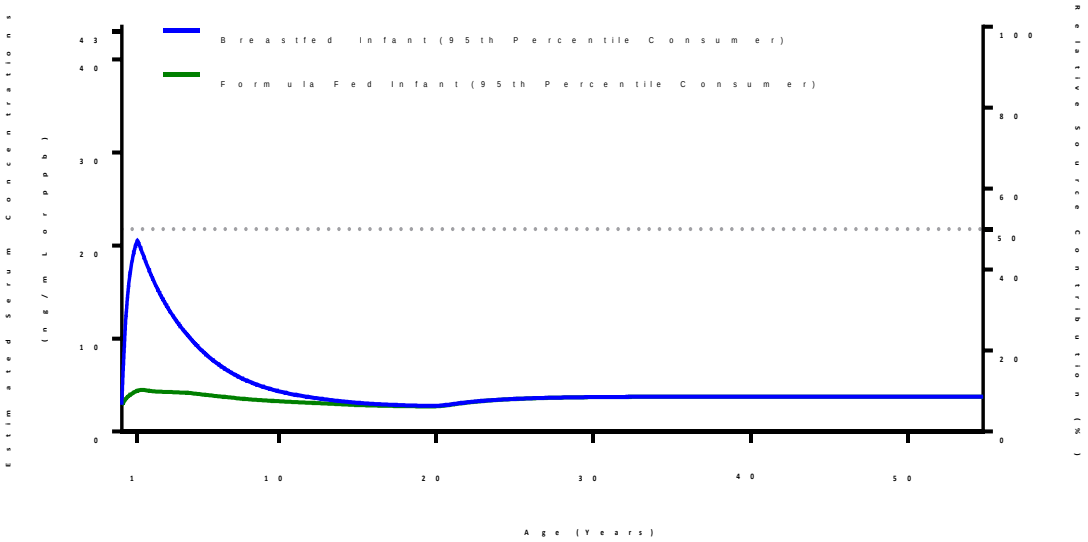
The conceptual diagram for the toxicokinetic model.
Image from: Goeden et al. (2019), *Journal of Exposure Science & Environmental Epidemiology* vol. 29, 183–195.

Excel-based model is available upon request from Minnesota Department of Health.

The model allows for the comparison of:

- **predicted blood levels (left y-axis) to**
- **the % of allowable maximum dose (right y-axis).**

Example model output for a PFOA MCL of 12 ng/L using NHDES's risk assessment assumptions.

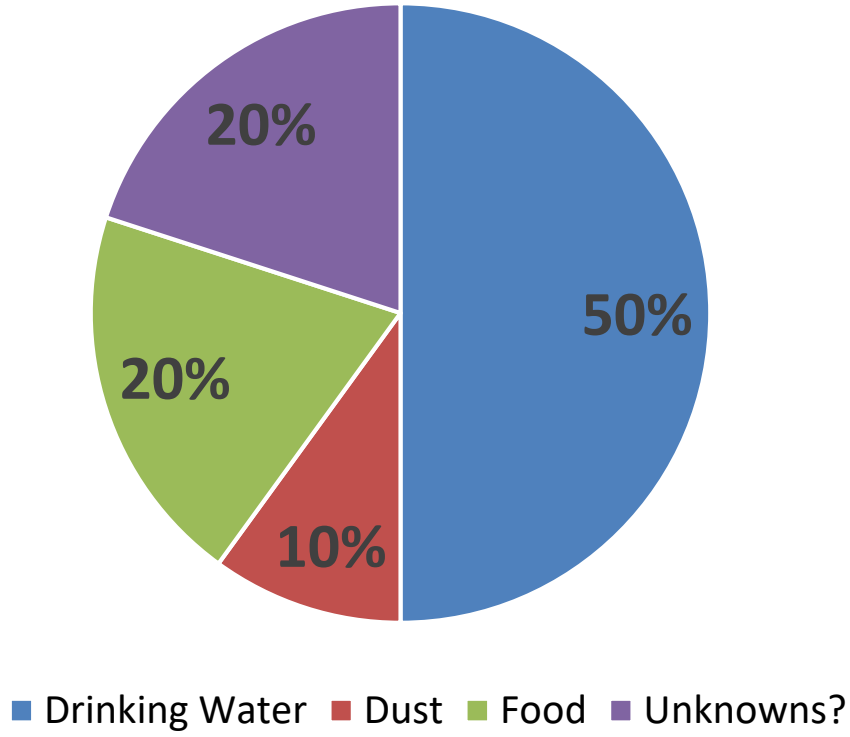


Exposure Assumptions: Relative Source Contribution

This is **how we "budget" the daily dose (RfD)** for water versus non-drinking water sources of exposure.

- **20%** - Low and the default EPA recommendation when "we don't know". Results in the most restrictive MCL.
- **50%** - Consistent with values derived from NHANES to estimate background
- **80%** -Results in a higher MCL value and assumes that other sources are not contributing to exposure (20% or less).

Relative Source Contribution
(example below for visualization purposes)



Exposure Assumptions: Relative Source Contribution

20%

U.S. EPA (2016)
- **20% RSC for PFOA & PFOS** for the lifetime health advisory of 70 ng/L, based on RfDs of 20 ng/kg-d.

Vermont - VTDOH (2016-2017)
- **20% RSC across all** for health-based screening values (HBSVs).

New Jersey - NJDWQI (2017-2018)
- **20% RSC for PFOA & PFOS** because of insufficient serum data (proposed MCL).
- **50% RSC for PFNA** because of sufficient serum data from NHANES and a NJ community (MCL).

New York - NYDWQC (2018)
- **≤60% RSC for PFOA & PFOS** recommendation based on serum data (proposed MCL).

Minnesota - MDH (2017-2019)
- **50% RSC for PFOA, PFOS & PFHxS** in their model for (HBSVs).

50-60%

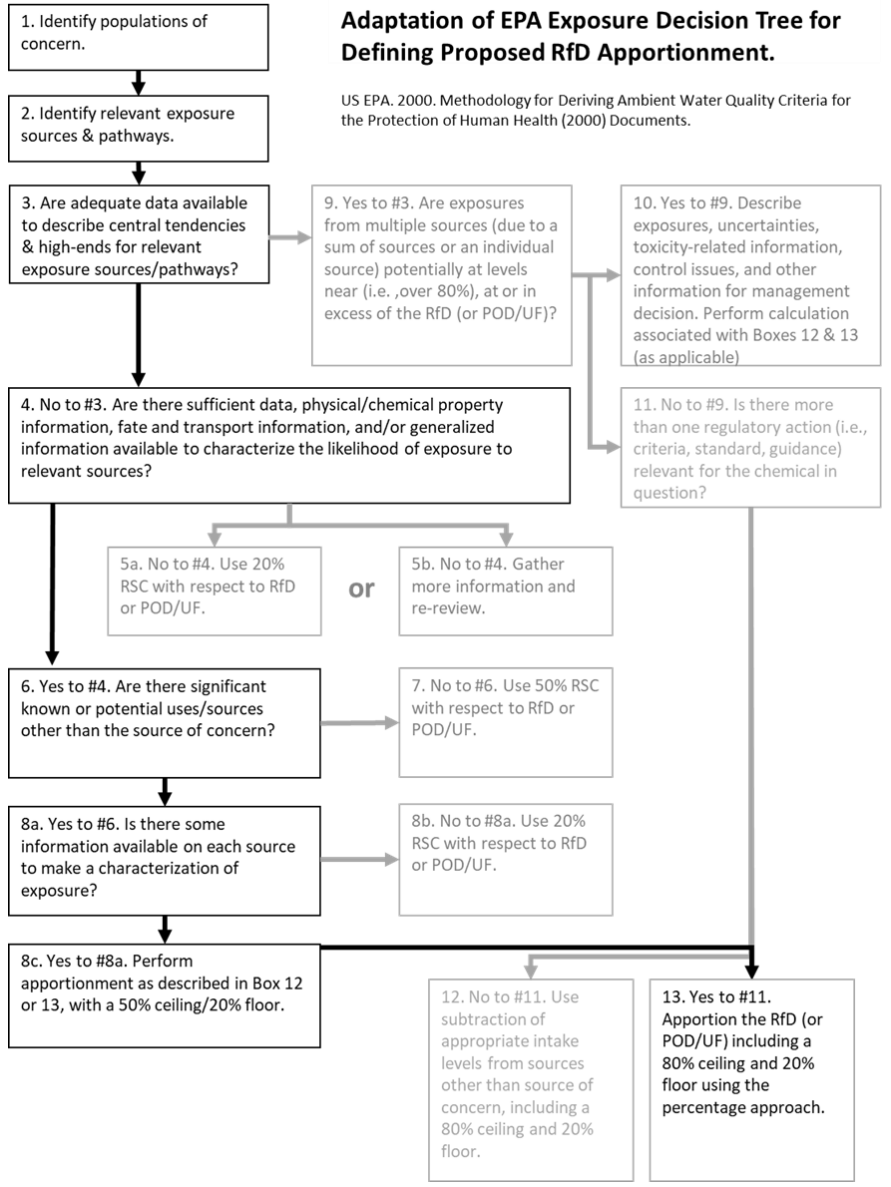
Michigan - MIDHHS (2019)
- **50% RSC for PFOA, PFOS, PFNA & PFHxS** in MDH's transgenerational model (HBSVs).

How did the NHDES MCLs arrive at a 50% RSC?

Exposure Assumptions: Relative Source Contribution

NHDES referred to the EPA Decision Tree for determining the relative source contribution.

Arrived at a **50% ceiling** combined with apportionment (**subtraction method**) to derive chemical specific RSCs.



US EPA. 2000. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) Documents.

Accessed online at: https://www.epa.gov/wqc/methodology-deriving-ambient-water-quality-criteria-protection-human-health-2000-documents

Exposure Assumptions: Relative Source Contribution

In the initial proposal, NHDES estimated "background" using existing blood data. However, this value should reflect the typical non-drinking water exposures.

Used the EPA subtraction method:

$$\frac{\text{Target serum level (ng/mL)} - \text{Population background (ng/mL)}}{\text{Target serum level (ng/mL)}} = \text{RSC}$$

Using the NHANES (average) for PFOA:

$$\frac{43.5\ \text{ng/L} - 1.8\ \text{ng/L}}{43.5\ \text{ng/L}} = 0.96 \text{ or } 96\%$$

Using Adults from Southern NH (95th percentile) for PFOA:

$$\frac{43.5\ \text{ng/L} - 26.6\ \text{ng/L}}{43.5\ \text{ng/L}} = 0.39 \text{ or } 39\%$$

The use of the *NH-specific data likely overestimates* the background (non-drinking water) exposure.

But, the current lack of regulations on PFAS means an 80% RSC, especially for adults, is inadequately protective.

US EPA. 2000. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) Documents.
Accessed online at: https://www.epa.gov/wqc/methodology-deriving-ambient-water-quality-criteria-protection-human-health-2000-documents

Exposure Assumptions: Relative Source Contribution

Estimation of RSC by Subtraction Method Using NH-specific data

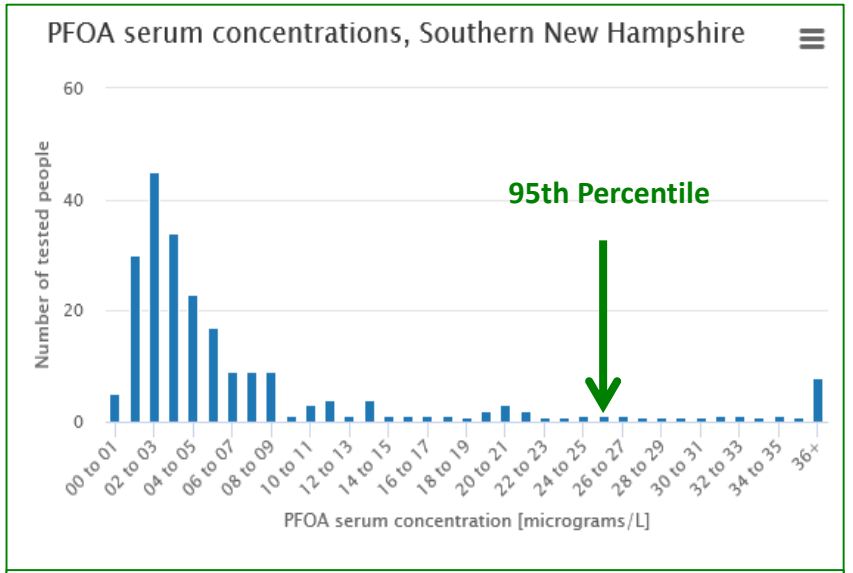
Subtraction method applied to all 4 PFAS using blood data collected by NH Dept. Health & Human Services from highest exposed populations.

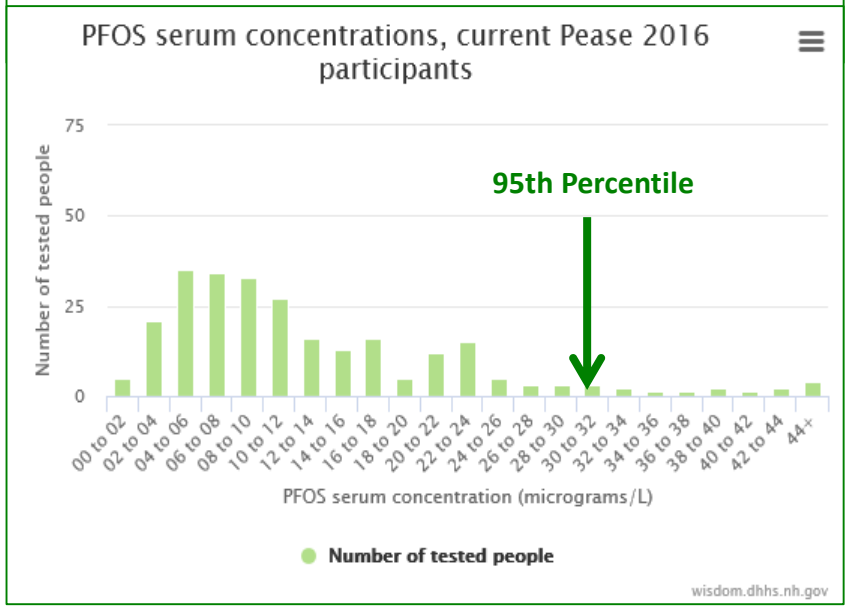
Used NH-specific PFAS blood concentrations:

	Geometric mean	95th Percentile
PFOA*	4.40 ng/mL	**26.6 ng/mL**
PFOS**	10.2 ng/mL	**31.7 ng/mL**
PFHxS**	4.50 ng/mL	**26.0 ng/mL**
PFNA	0.66 ng/mL	**1.70 ng/mL**

* **PFOA** concentrations from exposed population in Merrimack (217 participants) & Southern NH (219 participants).

** **PFOS** & **PFHxS** concentrations from exposed population in Pease, NH (256 participants).





NH Wisdom Portal, Per- and Polyfluoroalkyl Substances (PFAS) Blood Testing and Community Exposure: https://wisdom.dhhs.nh.gov/wisdom/#TopicGroup_8203D9F1281247419C5C417B8E591CE7

Exposure Assumptions: Relative Source Contribution

Estimation of RSC Using NHANES data

RSC estimates using the NHANES 2013-2014 dataset (summarized by Daly et al. 2018):

- **geometric mean (GM) and**
- **95th percentile.**

NHANES data more likely to reflect background exposure levels from non-drinking water sources.

Reference Population	Reference Serum level (ng/mL)	Target Serum Level (ng/mL)	Resulting RSC Allotment for Drinking Water (%)
PFOA			
3-5 year olds (GM)	2.00	43.5	**95.4**
6-11 year olds (GM)	1.89	43.5	**95.7**
12-19 year olds (GM)	1.66	43.5	**96.2**
3-5 year olds (95th percentile)	5.58	43.5	**87.2**
6-11 year olds (95th percentile)	3.84	43.5	**91.2**
12-19 year olds (95th percentile)	3.47	43.5	**92.0**
PFOS			
3-5 year olds (GM)	3.38	24.0	**85.9**
6-11 year olds (GM)	4.15	24.0	**82.7**
12-19 year olds (GM)	3.54	24.0	**85.3**
3-5 year olds (95th percentile)	8.82	24.0	**63.3**
6-11 year olds (95th percentile)	12.40	24.0	**48.3**
12-19 year olds (95th percentile)	9.30	24.0	**61.3**
PFNA			
3-5 year olds (GM)	0.76	49.0	**98.4**
6-11 year olds (GM)	0.81	49.0	**98.3**
12-19 year olds (GM)	0.60	49.0	**98.8**
3-5 year olds (95th percentile)	3.49	49.0	**92.9**
6-11 year olds (95th percentile)	3.19	49.0	**93.5**
12-19 year olds (95th percentile)	2.00	49.0	**95.9**
PFHxS			
3-5 year olds (GM)	0.72	46.3	**98.4**
6-11 year olds (GM)	0.91	46.3	**98.0**
12-19 year olds (GM)	1.27	46.3	**97.3**
3-5 year olds (95th percentile)	1.62	46.3	**96.5**
6-11 year olds (95th percentile)	4.14	46.3	**91.1**
12-19 year olds (95th percentile)	6.30	46.3	**86.4**

Modeled Exposures & Proposed MCLs

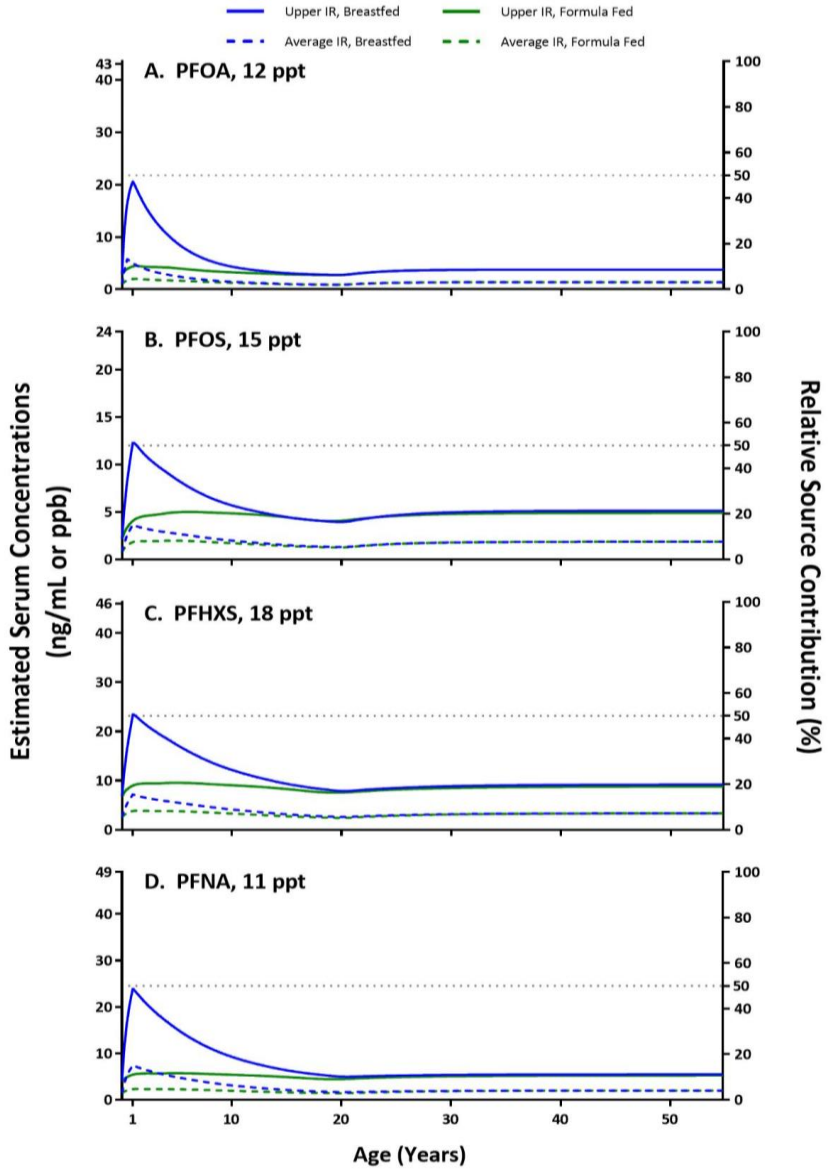
Given these **reference doses** and **exposure assumptions**, the proposed MCLs/AGQS are:

PFOA	**12 ng/L**
PFOS	**15 ng/L**
PFHxS	**18 ng/L**
PFNA	**11 ng/L**

Because of the unique properties of PFAS, accounting for breastmilk transfer is necessary.

The 50% RSC (upper limit) protects children from additional exposures to from other non-drinking water sources of PFAS.

Thus, these proposed MCLs are protective across all life stages for associated chronic health outcomes.



Modeled Exposures & Proposed MCLs

Where was NHDES conservative in its health-based risk assessment?

Central Tendency Assumptions	Conservative (High-End) Assumptions
1. Application of Uncertainty Factors (see page 23 of the June Technical Report)	1. Accounting for breastmilk & placental transfer in a drinking water standard (MDH model)
2. Human half-life estimates (average values)	2. 95th percentile water consumptions rates, *throughout life*
3. Placental & breastmilk transfer estimates (average values)	3. Assumed 12-month exclusive breastfeeding period
4. Individual MCLs specific to each compound instead of a class-based MCL.	4. Assuming 100% absorption in GI tract
5. Relative Source Contribution cap of 50%*	5. Relative Source Contribution cap of 50%*

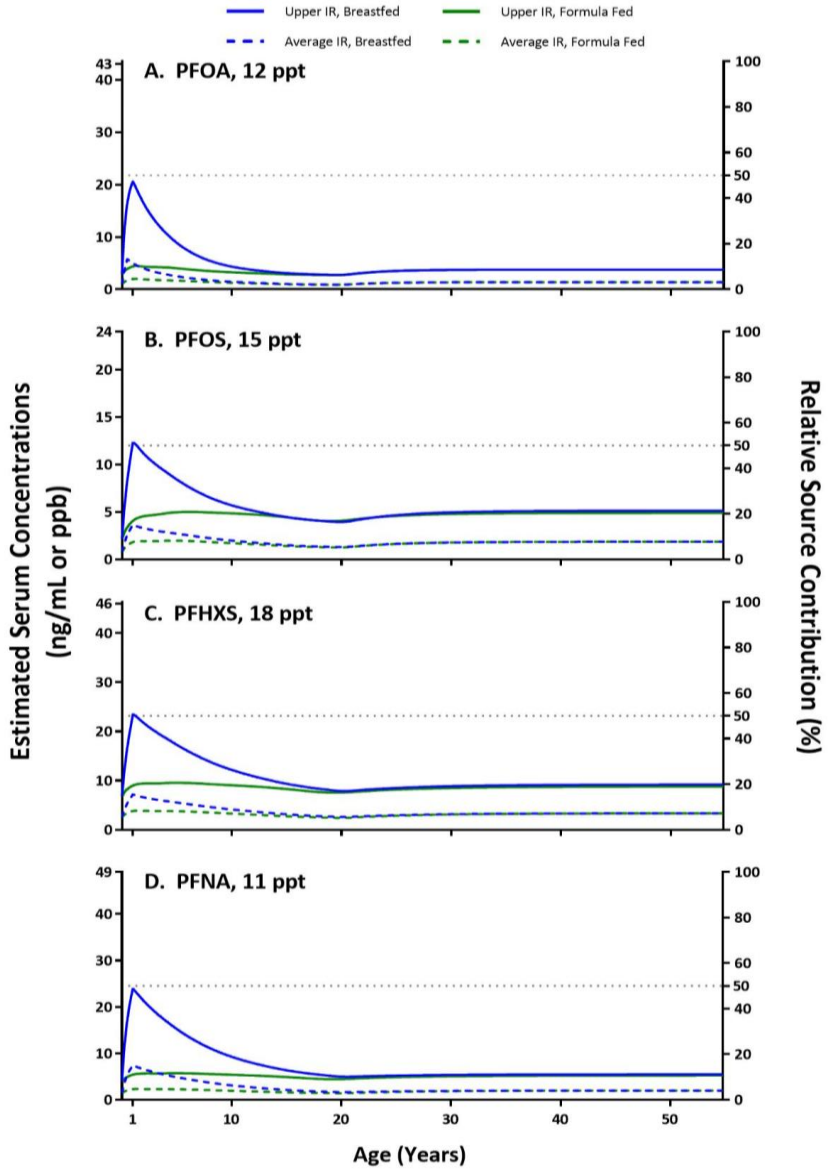
Modeled Exposures & Proposed MCLs

Given these **reference doses** and **exposure assumptions**, the proposed MCLs/AGQS are:

PFOA	**12 ng/L**
PFOS	**15 ng/L**
PFHxS	**18 ng/L**
PFNA	**11 ng/L**

NHDES is *currently* not recommending a class- or subclass-based approach to regulating PFAS.

NHDES is committed to continuing to review the scientific literature for advances in risk assessment for these and other PFAS.



Questions

References and Supporting Documents can be found in the Reference List of the June 2019 Technical Report:
https://www.des.nh.gov/organization/commissioner/legal/rulemaking/documents/pfas-scr-attch-1-w-ltr.pdf

Technical Questions about this presentation can be submitted to the **NHDES Permitting & Environmental Health Bureau**:

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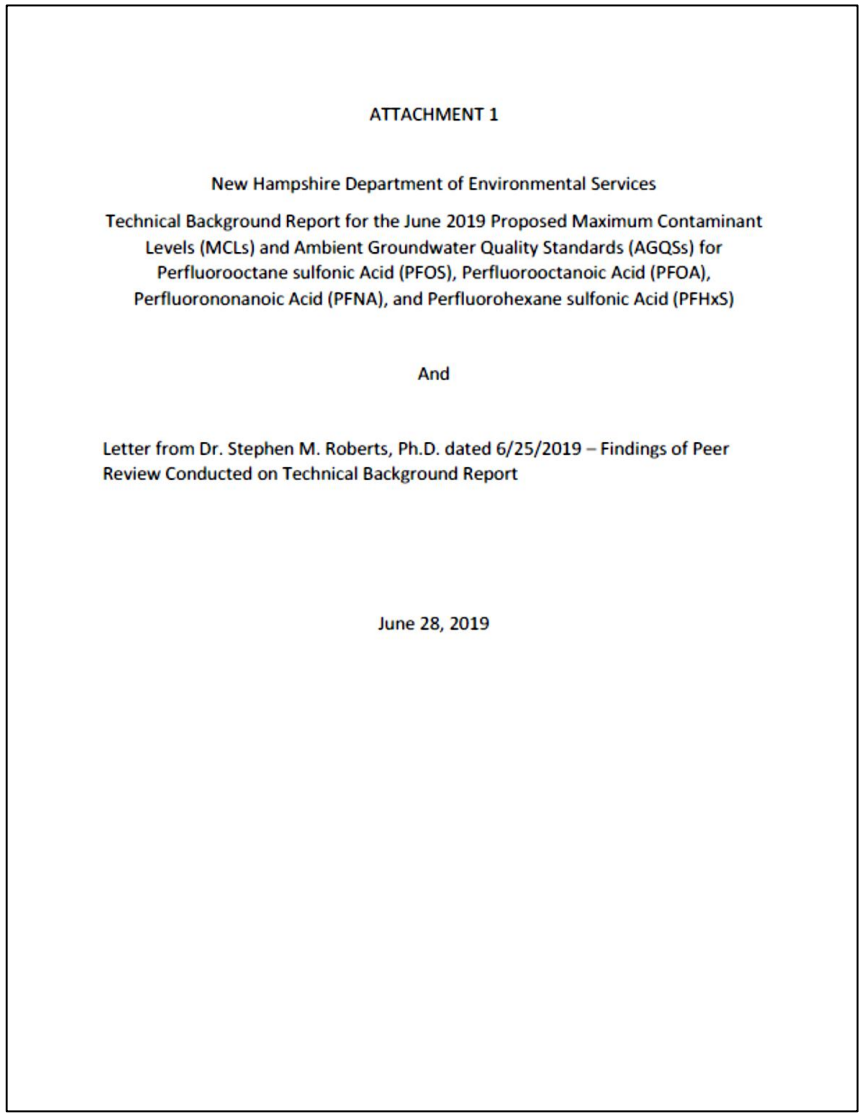

ATTACHMENT 1

New Hampshire Department of Environmental Services

Technical Background Report for the June 2019 Proposed Maximum Contaminant Levels (MCLs) and Ambient Groundwater Quality Standards (AGQSs) for Perfluorooctane sulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), and Perfluorohexane sulfonic Acid (PFHxS)

And

Letter from Dr. Stephen M. Roberts, Ph.D. dated 6/25/2019 – Findings of Peer Review Conducted on Technical Background Report

June 28, 2019

PFOA Chronic Summary

Male Liver Incidence

				Post Wean Exposure			
Sex	**Organ**	**Lesion**	**G/L**	**0**	**20**	**40**	**80**
Male	Liver	Adenoma	**0**	0	0	7*	11*
Male	Liver	Adenoma	**300**	0	1	5	10*
Male	Liver	Carcinoma	**0**	0	0	0	0
Male	Liver	Carcinoma	**300**	0	0	0	4
Male	Liver	Adenoma and Carcinoma	**0**	0	0	7*	11*
Male	Liver	Adenoma and Carcinoma	**300**	0	1	5	12*

G/L = Gestation/Lactation Exposure
50 animals evaluated per group

Male Pancreas Incidence

Pancreas

				Post Wean Exposure			
Sex	**Organ**	**Lesion**	**G/L**	**0**	**20**	**40**	**80**
Male	Pancreas	Acinus Hyperplasia	**0**	18 [2.7]	32 [3.7]*	37 [3.2]*	31 [3.2]*
Male	Pancreas	Acinus Hyperplasia	**300**	23 [2.7]	27 [3.2]	38 [3.3]*	33 [3.4]*
Male	Pancreas	Adenoma	**0**	3	28*	26*	32*
Male	Pancreas	Adenoma	**300**	7	18*	30*	30*
Male	Pancreas	Carcinoma	**0**	0	3	1	3
Male	Pancreas	Carcinoma	**300**	0	2	1	3
Male	Pancreas	Adenoma or Carcinoma	**0**	3	29*	26*	32*
Male	Pancreas	Adenoma or Carcinoma	**300**	7	20*	30*	30*

G/L = Gestation/Lactation Exposure; 50 animals evaluated; [ ] denotes severity score of 1 to 5

Female Hepatocellular Incidence

				Post Wean Exposure		
Sex	**Site**	**Neoplasm**	**G/L**	**0**	**300**	**1000**
Female	Liver	Adenoma	**0**	2	0	1
Female	Liver	Adenoma	**150**		0	
Female	Liver	Adenoma	**300**			3
Female	Liver	Carcinoma	**0**	1	1	3
Female	Liver	Carcinoma	**150**		0	
Female	Liver	Carcinoma	**300**			4
Female	Liver	Adenoma and Carcinoma	**0**	3	1	4
Female	Liver	Adenoma and Carcinoma	**150**		0	
Female	Liver	Adenoma and Carcinoma	**300**			6

G/L = Gestation/Lactation Exposure
50 animals evaluated per group

Female Pancreas Incidence

Acinar Cell Tumors (ACT)

				Post Wean Exposure		
Sex	**Site**	**Neoplasm**	**G/L**	**0**	**300**	**1000**
Female	Pancreas	Adenoma	**0**	0	0	1
Female	Pancreas	Adenoma	**150**		0	
Female	Pancreas	Adenoma	**300**			3
Female	Pancreas	Carcinoma	**0**	0	0	2
Female	Pancreas	Carcinoma	**150**		0	
Female	Pancreas	Carcinoma	**300**			2
Female	Pancreas	Adenoma and Carcinoma	**0**	0	0	2
Female	Pancreas	Adenoma and Carcinoma	**150**		0	
Female	Pancreas	Adenoma and Carcinoma	**300**			5
Female	Pancreas	Duct, Adenocarcinoma	**0**	0	0	0
Female	Pancreas	Duct, Adenocarcinoma	**150**		0	
Female	Pancreas	Duct, Adenocarcinoma	**300**			1

G/L = Gestation/Lactation Exposure
50 animals evaluated per group

ATTACHMENT 1

New Hampshire Department of Environmental Services

Technical Background Report for the June 2019 Proposed Maximum Contaminant Levels (MCLs) and Ambient Groundwater Quality Standards (AGQSs) for Perfluorooctane sulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), and Perfluorohexane sulfonic Acid (PFHxS)

And

Letter from Dr. Stephen M. Roberts, Ph.D. dated 6/25/2019 – Findings of Peer Review Conducted on Technical Background Report

June 28, 2019

New Hampshire Department of Environmental Services

Technical Background Report for the June 2019 Proposed Maximum Contaminant Levels (MCLs) and Ambient Groundwater Quality Standards (AGQSs) for Perfluorooctane sulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), and Perfluorohexane sulfonic Acid (PFHxS)

June 28, 2019

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Abbreviations

AFFF - aqueous film forming foam

AGQS - Ambient Groundwater Quality Standard

APFO – ammonium perfluorooctanoate

ATSDR – Agency for Toxic Substances and Disease Registry

BMD – benchmark dose

BMDL – benchmark dose lower-bound confidence limit

C8 – an alternative name for perfluorooctanoic acid

CAR – constitutive androstane receptor

CAS# - Chemical Abstracts Service Registry Number

CDC – Centers for Disease Control and Prevention

CSF – cancer slope factor

d - day

DAF – dosimetric adjustment factor

IR – ingestion rate

IRIS - Integrated Risk Information System

kg - kilogram

L - liter

LHA – lifetime health advisory

Ln – natural logarithm

LOAEL – lowest observed adverse effect level

MCL – maximum contaminant level

mg - milligram

MDH – Minnesota Department of Health

MRL – minimal risk level

ng - nanogram

NHDES – New Hampshire Department of Environmental Services

NH DHHS – New Hampshire Department of Health & Human Services

NIS - National Immunization Survey

NJDWQI – New Jersey Drinking Water Quality Institute

NOAEL – no observed adverse effect level

NTP – National Toxicology Program

PFAS – perfluoroalkyl substances

PFHxS – perfluorohexane sulfonic acid

PFNA – perfluorononanoic acid

PFOA – perfluorooctanoic acid

PFOS – perfluorooctane sulfonic acid

POD – point of departure

PPAR - peroxisome proliferator-activated receptor

ppb –parts-per-billion

ppt – parts-per-trillion

RME – reasonable maximum exposure

RSC – relative source contribution

$t_{1/2}$ – half-life

UF – uncertainty factor

USEPA – U.S. Environmental Protection Agency

V_d – volume of distribution

WHO – World Health Organization

α – alpha, used to denote specific subtypes of biological molecules (i.e., proteins)

β – beta, used to denote specific subtypes of biological molecules (i.e., proteins)

γ - gamma, used to denote specific subtypes of biological molecules (i.e., proteins)

Acknowledgements

New Hampshire Department of Environmental Services would like to thank the numerous New Hampshire stakeholders and residents who provided valuable technical commentary on the initially proposed MCLs for PFOA, PFOS, PFNA and PFHxS. This includes New Hampshire's residents, academic institutions, community advocacy groups, representatives for the business community and municipalities. The science followed in deriving the currently proposed maximum contaminant levels was enacted in part as a result of their contributions. Additionally, NHDES is grateful for insights and information shared by professionals from other state agencies, interstate collaborative working groups and professional societies.

Section I. Executive Summary

The objective of the health-based risk assessment was identifying drinking water concentrations of perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS) that provide adequate protection of human health at all life stages, including but not limited to pre-natal development. This document provides the technical basis for the proposed maximum contaminant levels (MCLs,) which by law become Ambient Groundwater Quality Standards (AGQSs), following evaluation of technical comments submitted up to April 12th, 2019, public comment deadline, as well as peer-reviewed scientific literature published since January 1st, 2019, and external review by Dr. Stephen Roberts at the University of Florida. As a result of this process, NHDES is proposing the following maximum contaminant levels (MCLs):

- **12 ng/L for Perfluorooctanoic acid, or perfluorooctanoate (PFOA)**
- **15 ng/L for Perfluorooctane sulfonic acid, or perfluorooctane sulfonate (PFOS)**
- **11 ng/L for Perfluorononanoic acid, or perfluorononanoate (PFNA)**
- **18 ng/L for Perfluorohexane sulfonic acid, or perfluorohexane sulfonate (PFHxS)**

These health-based values are intended as health-protective limits against the chronic health effects for a through-life exposure. The primary associated health outcomes are hepatotoxicity and changes in lipid metabolism (PFOA and PFNA), suppressed immune response to vaccines (PFOS) and impaired female fertility (PFHxS). Secondary associated health effects that are expected to be less sensitive are changes in thyroid and sex hormone levels, early-life growth delays, changes in cholesterol levels and biomarkers of liver function, neurobehavioral effects, and a possible risk for certain cancers (i.e., testicular and kidney cancer).

These proposed MCLs are lower than those proposed in January 2019 (NHDES 2019) as a result of new studies and models that indicate the standards need to be lower to be adequately protective of health at all life stages. Specifically, a peer reviewed toxicokinetic model was published by the Minnesota Department of Health (Goeden et al., 2019) that predicts blood serum levels across a lifetime. Using similar studies as those from the initial proposal and those suggested in technical comments submitted by April 12th, 2019, this model indicates lower standards are necessary to avoid unacceptable elevations in the serum levels of breastfed infants and children who were breastfed as infants.

The technical basis for the proposed MCLs is detailed in Sections III and IV, and the modeling results and conclusions are presented in Section V. Briefly, this risk assessment utilized upper value, “conservative” estimates regarding: daily water consumption rates throughout life, breastmilk consumption rates through infancy, the duration of exclusive breastfeeding (12 months), relative source contribution, absorption efficiency and consideration of breastmilk transfer. Central tendency, or less conservative, assumptions included: use of uncertainty factors, human half-life estimates, placental and breastmilk transfer efficiencies of PFAS, and the recommendation of individual MCLs instead of assuming toxicological equivalency among the four PFAS evaluated.

The health effects of PFAS is an evolving area of research and it is expected that future research will improve our understanding of the quantitative risks associated with PFAS. This may result in higher or lower recommendations for these and other PFAS in the future. NHDES is committed to reviewing new scientific information on PFAS to improve the understanding of this large group of chemicals and making future recommendations for evidence-based health protective drinking water standards.

Section II. Introduction

Perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorohexanesulfonic acid (PFHxS) are individual compounds in a large class of chemicals known as perfluorinated compounds (PFCs) and more broadly as per- and polyfluoroalkyl substances (PFAS). They have been widely used since the 1940s in commercial, industrial, and household products and applications, including production of water, grease, and stain-resistant materials, fire suppression foams, non-stick cookware, wax removers, etc. (ATSDR 2018b).

All four compounds have been detected in New Hampshire's groundwater and surface water. Their widespread use, persistence and mobility in the environment and bioaccumulative properties has resulted in the detection of PFAS in blood serum in humans and animals worldwide. This has led to considerable research into their toxicity and health effects. The health effects associated with PFAS exposure are currently being researched extensively by toxicologists and epidemiologists worldwide, resulting in numerous publications being released on a continuous basis.

According to the Agency for Toxic Substances and Disease Registry (ATSDR)(ATSDR 2018b) the following health impacts may be associated with PFAS (specific compounds as noted by ATSDR):

- Hepatotoxicity - changes in certain liver enzymes in serum (PFOA, PFOS, PFHxS)
- Increases in total and LDL cholesterol levels (PFOA, PFOS, PFNA)
- Small decreases in birth weight (PFOA, PFOS)
- Endocrine system effects (PFOA, PFOS)
- Reproductive toxicity - decreased fertility (PFOA, PFOS)
- Immunotoxicity - decreased vaccine response (PFOA, PFOS, PFHxS)
- Suggestive evidence of carcinogenicity, specifically testicular and kidney cancer (PFOA, PFOS)
- Suggestive evidence of association with pregnancy-induced hypertension and/or pre-eclampsia (PFOA, PFOS)

For additional information on the toxicity and health effects of these compounds, please visit the ATSDR webpage at: https://www.atsdr.cdc.gov/pfas/health-effects.html

In addition to the ATSDR draft toxicological profile on perfluoroalkyls, several other state (NJDWQI 2017, 2018ab; MDH 2018, 2019ab; MI PFAS Science Advisory Panel 2018), federal (EPA 2016ab; NTP 2016) and international agencies (IARC 2016; Health Canada 2016ab; EFSA 2018) have reviewed the toxicological data related to PFAS and identified similar associated health impacts.

This document presents the health-based risk assessment that derived the proposed MCLs and Ambient Groundwater Quality Standards (AGQS) for these four compounds. In January 2019, NHDES released its initially proposed MCLs along with a supporting document that explained the rationale used and scientific literature reviewed to arrive at its recommendation (NHDES, 2019). The current report is not an exhaustive review of all existing studies that reference PFOA, PFOS, PFNA, PFHxS or other PFAS; rather, it is an update to the previous assessment after evaluation of newer studies and technical comments since the initial MCL proposal in January 2019 (NHDES, 2019).

Section III. Reference Dose Derivation

The U.S. EPA (2002) defines a reference dose (RfD) as:

> "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime."

For PFAS, a RfD can be expressed in units of nanograms of specified PFAS (ng), per kilogram of a person's body weight (kg), per day (ng/kg-d). This allows for estimation of chemical-specific daily doses that are readily scaled to persons of differing sizes. A RfD is not the same as the minimal risk levels (MRLs) developed and used by ATSDR in that 1) MRLs are not developed with the same considerations as RfDs, and 2) MRLs are not used to define action or clean up levels for chemical contaminants (EPA 2002; ATSDR 2018a). NHDES derived RfDs for PFOA, PFOS, PFNA and PFHxS (Table 1). *Additionally, it is important to note that a RfD is a population-level value and its associated blood concentration is not considered a clinically-relevant value for individuals.*

Table 1. Summary of RfDs and MCLs.

Compound	Reference dose (RfD)	Exposure Assumptions	Maximum Contaminant Level (MCL)
Perfluorooctanoic acid (PFOA)	6.1 ng/kg-d	See Section IV	12 ng/L
Perfluorooctanesulfonic acid (PFOS)	3.0 ng/kg-d	See Section IV	15 ng/L
Perfluorononanoic acid (PFNA)	4.3 ng/kg-d	See Section IV	11 ng/L
Perfluorohexanesulfonic acid (PFHxS)	4.0 ng/kg-d	See Section IV	18 ng/L

Derivation of a RfD requires selection of three components (Equation 2): a point of departure (POD), uncertainty factors (UF) and, where appropriate, a dosimetric adjustment factor (DAF). The POD is based on a sensitive and human-relevant critical health effect from either animal or human studies. For PFAS, this is typically a blood concentration of a certain compound at which there is no observable adverse effect in animals (e.g. rodents). As rodents are not humans, the UF is applied to be protective by reducing the animal POD to a lower and acceptable human target serum level. The DAF then converts, by estimation, the blood concentration (ng/mL) to a body weight-adjusted (kg) amount of the chemical (ng) external to the body that would need to be ingested on a daily basis to reach the human target serum level.

$$\text{Reference dose (ng/kg/d)} = \frac{\text{Point of departure (ng/mL)}}{\text{Total uncertainty factors (unitless)}} \times \text{Dosimetric adjustment factor (mL/kg/d)}$$

As the EPA RfDs for PFOA and PFOS were deemed insufficiently protective, and there are no values for PFNA or PFHxS in the EPA Integrated Risk Information System (IRIS) database, NHDES evaluated the RfDs proposed by other agencies and derived its own values. The remainder of Section III describes how RfDs for PFOA, PFOS, PFNA and PFHxS were derived following evaluation of relevant studies and technical comments submitted to NHDES by April 12th, 2019, as well as scientific uncertainties specific to the RfDs.

Perfluorooctanoic acid or perfluorooctanoate (PFOA), CAS# 335-67-1

Principal study & consideration of health effects

For the derivation of a RfD and MCL for PFOA, NHDES recommends the critical health effect of increased relative liver weight (Loveless et al., 2006; NJDWQI 2017) as an indicator for the onset of hepatotoxicity. This is the same critical health effect previously selected in the initial MCL proposal (NHDES 2019), and based on review of the literature and technical comments received, NHDES remains confident in this recommendation.

Since the initial MCL proposal by NHDES at the start of January 2019, additional studies have been published related to associations between PFOA and human health impacts along with studies demonstrating toxicity in rodent models. Relative to the critical effect proposed by NHDES, there are three new studies that merit acknowledgment with regard to relative liver toxicity. This includes two studies from highly-exposed populations (Bassler et al., 2019; Nian et al., 2019) and evaluation of background exposure levels from the 2011-2014 NHANES dataset (Jain and Ducatman 2019). Bassler and colleagues (2019) reported associations between non-clinical biomarkers of hepatocyte apoptosis (cell death) as well as altered inflammatory disease of the liver with exposure to PFOA and other PFAS within a subset of subjects from the C8 Cohort (mean PFOA serum level 94.6 ng/mL). In the C8 Health Study of China (n = 1,605 participants, median PFOA serum level of 6.19 ng/mL), liver enzyme markers such as ALT and AST showed significant increases with natural log (ln)-unit changes of PFOA, other PFAS and their isomers (Nian et al., 2019). Analysis of the 2011-2014 NHANES data (n=2,883 subjects) detected consistent associations between PFAS, including PFOA, and increased ALT and GGT in obese individuals. It is noted that the cross-sectional design of certain studies and the lack of adjustments for false discovery following multiple comparisons underscore typical challenges of relying on epidemiological studies to demonstrate causal relationships, or their utility for determining the POD in RfD development. Qualitatively, these studies reinforce NHDES consideration of altered liver function and hypertrophy in rodents as a critical health effect for the basis of its PFOA RfD.

Studies published prior to 2019 were considered as a part of the initial PFAS MCL proposal put forward by NHDES (2019). This included evaluation of peer-reviewed evidence for:

- associated immunotoxicity as summarized by the National Toxicology Program (NTP 2016), ATSDR (2018b), DeWitt et al., (2012), Kirk et al., (2018) and Chang et al., (2016),
- developmental toxicity in animal models (Butenhoff et al., 2004; Lau et al., 2006; White et al., 2007; Wolf et al., 2007; Hu et al., 2010; Onishchenko et al., 2011; White et al., 2011; Albrecht et al., 2013; Cheng et al., 2013; Koustas et al., 2014; Quist et al., 2015ab; Koskela et al., 2016), associated fetal and neonatal growth impacts in humans (reviewed by Verner et al., 2015; Negri et al., 2017; Rappazzo et al., 2017; Liew et al., 2018 and ATSDR 2018b) and consideration of developmental outcomes evaluated in the U.S. EPA LHA for PFOA of 70 ng/L (EPA 2016a),
- associated human-health outcomes based on the C8 studies (Frisbee et al., 2009, 2010; Steenland et al., 2009, 2010ab, 2013; Stein et al. 2009, 2013; Lopez-Espinosa et al., 2011, 2012ab; Gallo et al., 2012; Savitz et al., 2012ab; Steenland and Woskie 2012; Barry et al., 2013; Darrow et al., 2013; Fletcher et al., 2013; Vieira et al., 2013; Watkins et al., 2013; Winquist et al., 2013; Darrow et al., 2016),

- and delayed mammary gland development in mice (White et al., 2007, 2009, 2011; Macon et al., 2011; Tucker et al., 2015).

In its initial proposal, NHDES agreed with the assessment made by the New Jersey Drinking Water Quality Institute (NJDWQI) relative to adverse effects on the liver and NHDES maintains this position. In their 2017 document, NJDWQI summarized evidence from studies in non-human primates, various strains of rodents, including PPARα knock-out mice, as well as the existing epidemiologic studies. This lead the NJDWQI to the conclusion that there was "consistency among non-occupational studies, as well as evidence of specificity, exposure-response, strength, and biological plausibility for PFOA and ALT. These findings provide evidence supporting a causal relationship between PFOA and ALT" (NJDWQI 2017). They also acknowledge the limited epidemiologic evidence, as of 2017, to definitively prove a causal relationship with PFOA and liver disease, and the available studies did not find an association. (NJDWQI 2017). While NHDES does not agree with the application of a full database uncertainty factor (NJDWQI 2018), the arguments made for consideration of hepatic effects for human health risk assessment were deemed appropriate given the existing information on PFOA.

The ATSDR 2018 draft toxicity profile for perfluoroalkyls recognized the likely associations between PFOA and hepatotoxicity (e.g., increased serum enzyme concentrations and effects on serum bilirubin) after consideration of similar epidemiological studies and the NJDWQI 2017 report (NJDWQI 2017; ATSDR 2018b). After additional review of this same document (ATSDR 2018b), NHDES agrees there is concern for the associations between exposure to PFOA and the following human health outcomes: increases in serum lipids (i.e., total and LDL cholesterol), disruption of thyroid hormone function and transport, decreased vaccine response, decreased fertility and reduced birth weight. The scientific evidence is less clear regarding other suggested human health associations and merit further investigation to establish whether these effects are truly linked to PFOA exposure. As this relates to the RfD derived by NHDES, it was determined that the animal study selected by ATSDR was not appropriate for RfD derivation following NHDES understanding of EPA methodology (EPA 2002) and was therefore not selected for use in the initial or final MCL proposal.

Regarding carcinogenicity, NHDES derived a PFOA MCL based on non-cancer endpoints. The U.S. EPA and International Agency for Research on Cancer (IARC) determined that the current evidence indicates that PFOA is a suggestive (EPA 2016) or possible (IARC 2016) carcinogen in humans. This is specific to suggestive evidence for increased risks of kidney and testicular cancer seen in rodents and mixed associations from human studies (Barry et al., 2013). Two other agencies, the USEPA (2016a) and NJDWQI (2017), have derived cancer values for PFOA using the same principal rodent study for PFOA carcinogenicity (Butenhoff et al. 2012). The U.S. EPA (2016a) and NJDWQI (2017) arrived at possible MCL values of 500 ng/L and 14 ng/L, respectively, for a one-in-a-million risk for testicular cancer. More recently, the California Office of Environmental Health Hazard Assessment (2019) has recommended a similar value of 14 ng/L for PFOA citing concern for liver damage and cancer. This discrepancy in cancer-based MCL estimates highlights the need for better information to inform cancer risk assessment for PFOA, and is expected to be an evolving area of research in years to come. Regardless of whichever is the more accurate assessment, the proposed MCL for PFOA is lower than the more conservative of these two estimates.

Determination of a point of departure

As previously proposed by NHDES (2019), the principal study and point of departure (POD) was the same study (Loveless et al., 2006) recommended and benchmark dose modeled by the NJDWQI (2017). The critical health effect was increased relative liver weight in male mice following a 14-d oral exposure to APFO (Loveless et al., 2006). There is consistent evidence for liver toxicity across wild-type and PPARα knock-out mice (Butenhoff et al., 2004; Loveless et al., 2008; Son et al., 2008; Cui et al., 2009; Elcombe et al., 2010; Yahia et al., 2010; Tan et al., 2013; Wang et al., 2015; Rebholz et al., 2016; Li et al., 2017), as well as persistent effect on liver size and structure following gestational exposure to similar dosing regimens (Quist et al., 2015). Rat studies have suggested that this effect is an adaptive response that will dissipate following cessation of the exposure to PFOA (Butenhoff et al., 2004; Hall et al., 2012). Beyond rodent models, cynomolgus monkeys display hepatic hypertrophy, increased serum triglycerides and decreased serum T_4 following chronic exposure (26 weeks) to APFO (Butenhoff et al., 2002). As it relates to the present human health risk assessment for an MCL, these effects are not entirely adaptive as animal studies suggest persistent changes in the liver following exposure during early life stages (Quist et al., 2015a). NHDES also maintains its previous position that whether the response is adaptive is not relevant to drinking water exposures as the general population should not require recovery periods from public water. Furthermore, unlike rodents that display relatively short half-lives for PFOA and other PFAS, once humans are exposed to increased levels of PFOA they will maintain elevated serum levels on a time scale of months to years. This means that brief external exposures become chronic internal doses, especially if the external dose is relatively high. The effects on liver function are considered a chronic health outcome based on the existing body of literature.

This POD is based on the benchmark dose modeling work conducted by the NJDWQI (2017) in their technical documents for their proposed RfD and MCL of 2.0 ng/kg-d and 14 ng/L, respectively, that identified a POD for PFOA of 4,351 ng/mL based on increased liver weight. NHDES did not arrive at the same RfD due to differences in the application of uncertainty factors. Differences in the final MCL are due to NH's use of the transgenerational exposure model for breastfeeding (Goeden et al., 2019).

Application of uncertainty factors

A total uncertainty factor of 100 was applied to the POD for PFOA based on:

Intraspecies variability (10) × Interspecies variability (3) × Database limitations (3) = 100

For the non-risk assessor, the units of 3 and 10 are for partial (half) and full log units. So, a full log unit of 10 equals 10^1, but a half log unit of $10^{½}$ or $10^{0.5}$ is equal to 3.162. As a convention of risk assessment using EPA methodology (EPA 2002), the value of 3.162 is presented as 3. Thus, 10 × 3 × 3 is rounded to 100 from 99.982.

The full factor of 10 for intraspecies variability was deemed appropriate to protect for the poorly characterized differences in toxico-dynamics (× 3) and -kinetics (× 3) within the human population. As NHDES applied a DAF to convert the rodent serum concentration to an oral human dose, only a partial uncertainty factor (× 3) was applied for interspecies variability. As the NJDWQI (2017) derived a benchmark dose, there was no need for any additional uncertainty factors to account for lowest

observed adverse effect level (LOAEL) to no observed adverse effect level (NOAEL) conversion. As the critical effect of hepatic hypertrophy is considered the onset of the adverse effect in a sensitive model species, no additional uncertainty factor was applied to account for acute-to-chronic duration of exposure.

Although NHDES agrees with the NJDWQI selection of a critical health effect and derivation of the POD for PFOA (NJDWQI 2017), NHDES concluded there is insufficient evidence supporting the application of the more conservative full database uncertainty factor (× 10). In technical comments submitted on the initially proposed MCLs, this decision was the subject of multiple critiques. On one hand, some have argued the use of a partial uncertainty factor was under-protective as the NJDWQI applied a full factor (× 10) due to concerns for observations of delayed mammary gland development in mice exposed to PFOA during perinatal development (NJDWQI 2017, and references therein). NHDES notes that the USEPA LHA (2016a) and CDC's ATSDR draft report (2018b) did not apply any database uncertainty factor with respect to the mammary gland development studies in rodents given the lack of clarity towards human health relevance (Table 3). Similar to New Hampshire, two other state agencies, Minnesota (MDH 2018) and New York (presentation, October, 2018), derived RfDs for PFOA affording only a partial uncertainty factor for this and other adverse health impacts observed in rodent and epidemiological studies. It should be noted that both of these other agencies did not use the same POD as NJDWQI or NHDES, where Minnesota utilized a higher POD and New York utilized a lower POD compared to the benchmark dose (BMD) value from Loveless et al., (2006). Thus, NHDES believes that the application of a partial database uncertainty factor (× 3) is appropriately protective without being overly conservative given the critical health effect selected and the existing toxicological and epidemiological database.

Estimation of a human equivalent oral dose

The POD represents an internal animal serum level associated with the adverse health outcome of concern. Dividing the POD by the total uncertainty factor yields a protective target serum level equivalent for the human population. *This is not a clinical or diagnostic value, nor should it be interpreted as such*.

$$\text{Target serum level for PFOA} = \frac{4{,}351 \text{ ng/mL}}{100} = 43.5 \text{ ng/mL}$$

To estimate how this internal blood level corresponds to an external oral dose of the specified compound, a dosimetric adjustment factor is applied by multiplication to identify a dose in ng of specified PFAS, per kg of individual body weight, per day (ng/kg-d). This step accounts for the highly-bioaccumulative nature and unique half-life estimates of each compound, and is consistent with prior risk assessment methods for derivation of RfDs for PFAS (USEPA 2016ab; NJDWQI 2017, 2018a; ATSDR 2018b; MDH 2018, 2019ab). The human equivalent oral dose is estimated by the following equations:

$$\text{Reference dose (RfD)} = \frac{\text{Point of departure (POD)}}{\text{Total uncertainty factors (UF)}} \times \text{Dosimetric adjustment factor (DAF)}$$

Where the DAF is equal to,

$$DAF = V_d \times \left(\frac{Ln(2)}{t_{1/2}}\right)$$

$$DAF = 170\ mL/kg \times \left(\frac{Ln(2)}{840\ days}\right) = 1.40\times10^{-1}\ mL/kg\text{-}d$$

Consistent with the initial PFOA MCL proposal (NHDES 2019), the volume of distribution (V_d) for PFOA was 170 mL/kg (Thompson et al., 2010; EPA, 2016a). For its revised and final proposal, NHDES selected the serum half-life of 2.3 years for PFOA (Bartell et al., 2010). NHDES acknowledges that the half-life of 2.3 years is slightly less conservative than the initially proposed value for RfD derivation of 2.7 years (Li et al. 2018; NHDES 2019). This change was due, in part, to the consideration of this half-life being more appropriate given the significantly higher exposure specific to PFOA described in Bartell et al. (2010) and the larger sample size than that in Li et al. (2018).

Thus, using this chemical-specific DAF and the aforementioned point of departure and uncertainty factors, NHDES derived an oral reference dose for PFOA of 6.1 ng/kg-d.

$$\text{Reference dose (RfD)} = \frac{4{,}351\ ng/mL}{100} \times 1.40\times10^{-1}\ mL/kg\text{-}d = 6.1\ ng/kg\text{-}d$$

Perfluorooctane sulfonic acid or perfluorooctane sulfonate (PFOS), CAS# 1763-23-1

Principal study & consideration of health effects

For the derivation of a RfD for PFOS, NHDES recommends the critical health effect of suppressed immunoglobulin M (IgM) production in male mice as proposed by the Minnesota Department of Health (Dong et al., 2011; MDH, 2019a). While NHDES previously proposed a RfD based on developmental toxicity, the review of existing and emerging evidence and technical comments suggest that the use of this immunotoxic endpoint represents a more appropriately cautious approach for the risk assessment of PFOS.

Since the initial MCL proposal by NHDES at the start of January 2019, additional studies have been published related to associations between PFOS and human health impacts along with studies demonstrating toxicity in rodent models. In the same studies that found associations between PFOA and serological markers of liver function (Nian et al., 2019; Jain and Ducatman, 2019; Bassler et al., 2019), PFOS was also associated with liver dysfunction and markers of hepatic inflammatory responses. Relative to the critical health effect selected by NHDES, one additional study on immunosuppression in humans was published since January 2019. In a prospective study of 3-month old infants from China (n = 201 participants), cord blood levels of branched isomers of PFOS were associated with reduced concentrations of antibodies towards enterovirus 71 (a causative viral agent of hand-foot-and-mouth disease; Zeng et al., 2019). Aside from hepatic and immune effects, additional studies have suggested associations between prenatal PFOS levels and early onset of puberty in girls from the Danish Birth Cohort (Ernst et al., 2019) and an estrogen-mediated relationship between cord blood levels of PFOS and birth weight (Wang et al., 2019). As with many epidemiological studies on PFAS, many of these recent studies possessed various combinations of limitations including a lack of analysis for other environmental contaminants, limited sample size and lack of analysis for the influence of breastfeeding. However, they collectively demonstrate that there is a growing body of evidence for adverse health impacts associated with PFOS.

Studies published prior to 2019 were considered as a part of the initial PFAS MCL proposal put forward by NHDES (2019). This included evaluation of peer-reviewed evidence for:

- immunotoxicity as summarized by the National Toxicology Program (NTP 2016), ATSDR (2018b) DeWitt et al., (2012) and Chang et al., (2016),
- developmental toxicity in animal models (Lau et al., 2003; Thibodeaux et al., 2003; Luebker et al., 2005ab; Yahia et al., 2008; Butenhoff et al., 2009; Onishchenko et al., 2011; Rogers et al., 2014; Wan et al., 2014), fetal and neonatal growth impacts in humans (reviewed by Verner et al., 2015; Negri et al., 2017; Rappazzo et al., 2017; Liew et al., 2018 and ATSDR 2018b) and consideration of delayed development in the U.S. EPA LHA for PFOS of 70 ng/L (EPA 2016b),
- neurobehavioral and thyroid hormone-associated effects (as reviewed by ATSDR 2018b).

NHDES acknowledges that the current understanding of the immunotoxic effects of PFOS, other PFAS and their interactions is an evolving area of research. As described by DeWitt et al. (2019), the interpretation of immunosuppression is important to consider when evaluating the relevance of associated outcomes from human studies, as well as measured responses from rodents. The current body of literature is not mature enough to clearly evaluate clinical relevance to humans, or lack thereof

(Chang et al., 2016); however, the NTP (2016) concluded that PFOS is "presumed to be an immune hazard to humans" based on animal and human data available at that time. Mouse studies indicate that PFOS impairs the T cell-dependent antibody response at low doses following sub-chronic exposure durations (Dong et al., 2009, 2011; reviewed by DeWitt et al., 2012, 2019), and was selected as the basis for a PFOS RfD by several agencies including NJDWQI (NJDWQI 2018; further detailed by Pachkowski et al. 2019), NYDOH (2018) and proposed by MDH (2019a). Although the ATSDR MRL for PFOS was based on developmental delays (Luebker et al., 2005ab), they applied an additional uncertainty factor of 10 due to the evidence for immunotoxicity (ATSDR, 2018b). Collectively, this indicates that the lower dose range at which the immunotoxic effects occur in rodents is recognized as an appropriately protective range for selection of a POD. There is a critical need for replication and use of larger study populations for understanding the immunomodulatory associations reported for PFOS and other PFAS.

NHDES derived a PFOS MCL based on non-cancer endpoints due to a lack of adequate carcinogenicity studies. IARC has not classified the carcinogenicity of PFOS at this time. The U.S. EPA determined that PFOS was a suggestive carcinogen (EPA, 2016b). This is specific to suggestive evidence for increased incidence of liver and thyroid adenomas in rats following chronic exposure. The recommendation of using non-cancer endpoints over cancer endpoints is not unique to NHDES, as other agencies have concluded that non-cancer health endpoints are adequately protective (MDH 2018; Michigan PFAS Science Advisory Panel 2018). Should additional information become available that is adequate for derivation of a cancer slope factor (CSF) for PFOS, NHDES will consider this in the framework of the MCL process.

Determination of point of departure

Following review of the technical documents deriving RfDs for PFOS based on immunosuppression in mice (NJDWQI, 2018; ATSDR 2018b; Pachkowski et al., 2019; MDH, 2019), NHDES agreed with the RfD derivation recently proposed by the Minnesota Department of Health (MDH 2019). This POD is based on serum concentrations of PFOS at the no observable adverse effect level (NOAEL) for suppressed IgM production in male mice following 60-d oral exposure (Dong et al. 2011). As summarized by MDH (2019), the critical effect reported in Dong et al. (2011) was suppressed IgM production with a NOAEL of 2,620 ng/mL (oral dose, 0.0167 mg/kg-d) and a LOAEL of 10,750 ng/mL (oral dose, 0.083 mg/kg-d). A prior study by Dong et al. (2009) reported a NOAEL of 674 ng/mL (oral dose, 0.008 mg/kg-d) for reduced plaque forming cell response to sheep red blood cells, and a similar oral LOAEL as Dong et al. (2011). However, the early work by Dong et al. (2009) did not include the intermediate dose of 0.0167 mg/kg-d that was identified as a NOAEL in their later work (Dong et al. 2011). This is further complicated as the specific effect was not replicated in both studies where plaque forming cell response was only measured in Dong et al. (2009) and IgM concentrations in the later Dong et al. (2011). As both of these metrics describe different aspects of the same immune process they do support the consideration of immunosuppression at these low doses as a POD. There remains the issue of discordance in dosing. While benchmark dose modeling of these endpoints using the original data might prove valuable to demonstrating these different metrics support a similar POD, the original data was not available for modeling and the reported data has been described as unamenable to benchmark dose modeling (NJDWQI 2018). As a result, NHDES agreed with the use of the NOAEL (2,620 ng/mL) for IgM suppression (Dong et al., 2011) instead of the lower NOAEL of 674 ng/mL (Dong et al., 2009) as a POD.

Application of uncertainty factors

A total uncertainty factor of 100 was applied to the POD for PFOS based on:

Intraspecies variability (10) × Interspecies variability (3) × Database limitations (3) = 100

For the non-risk assessor, the units of 3 and 10 are for partial (half) and full log units. So, a full log unit of 10 equals 10^1, but a half log unit of $10^{½}$ or $10^{0.5}$ is equal to 3.162. As a convention of risk assessment using EPA methodology (EPA 2002), the value of 3.162 is presented as 3. Thus, 10 × 3 × 3 is rounded to 100 from 99.982.

The full factor of 10 for intraspecies variability was deemed appropriate to protect for the poorly characterized differences in toxico-dynamics (× 3) and -kinetics (× 3) within the human population. As NHDES applied a DAF to convert the rodent serum concentration to an oral human dose, only a partial uncertainty factor (× 3) was applied for interspecies variability. The POD was based on the NOAEL described in Dong et al. (2011); thus, there was no need for additional uncertainty factors to account for LOAEL to NOAEL conversion. Dong et al. (2011) conducted a 60-day exposure so no additional uncertainty factor was applied for acute-to-chronic duration of exposure. As described by MDH (2019), an additional partial (× 3) database uncertainty factor was applied due to concerns for reports of thyroid disruption (decreased T_4) in neonatal animals and the implications of these observations in terms of neurodevelopment that has not yet been adequately studied. NHDES agreed with this consideration given the suggestive evidence for the human relevance of altered T_4 levels (reviewed by Ballesteros et al., 2017 and ATSDR, 2018b) and their potential implications for impaired neurodevelopment in humans (Grandjean and Landrigan, 2014).

Estimation of a human equivalent oral dose

The POD represents an internal animal serum level associated with the adverse health outcome of concern. Dividing the POD by the total uncertainty factor yields a protective target serum level equivalent for the human population. *This is not a clinical or diagnostic value, nor should it be interpreted as such*.

$$\text{Target serum level for PFOS} = \frac{2{,}360\ \text{ng/mL}}{100} = 23.6\ \text{ng/mL}$$

To estimate how this internal blood level corresponds to an external oral dose of the specified compound, a dosimetric adjustment factor is applied by multiplication to identify a dose in ng of specific PFAS per kg of individual body weight per day (ng/kg-d). This step accounts for the highly-bioaccumulative nature and unique half-life estimates of each compound, and is consistent with prior risk assessment methods for derivation of RfDs for PFAS (EPA, 2016ab; NJDWQI, 2017, 2018a; ATSDR, 2018b; MDH, 2018, 2019ab). The human equivalent oral dose is estimated by the following equations:

$$\text{Reference dose (RfD)} = \frac{\text{Point of departure (POD)}}{\text{Total uncertainty factors (UF)}} \times \text{Dosimetric adjustment factor (DAF)}$$

Where the DAF is equal to,

$$DAF = V_d \times \left(\frac{Ln(2)}{t_{1/2}}\right)$$

$$DAF = 230\ mL/kg \times \left(\frac{Ln(2)}{1{,}241\ days}\right) = 1.28\times10^{-1}\ mL/kg\text{-}d$$

Consistent with the initial PFOS MCL proposal (NHDES 2019), the V_d for PFOS was 230 mL/kg (Thompson et al., 2010). In its revised and final proposal, NHDES maintains its use of a 3.4-year half-life estimate based on the average across men and women, described in Li et al. (2018; NHDES 2019). NHDES considered the longer half-life values reported for retired fluorochemical workers (Olsen et al. 2007), and deemed these to be inappropriately conservative given the use of the Minnesota transgenerational model for exposure assessment which emphasizes early-life and breastfeeding exposures.

Thus, using this chemical-specific DAF and the aforementioned point of departure and uncertainty factors, NHDES derived an oral reference dose for PFOS of 3.0 ng/kg-d.

$$\text{Reference dose (RfD)} = \frac{2{,}360\ ng/mL}{100} \times 1.28\times10^{-1}\ mL/kg\text{-}d = 3.0\ ng/kg\text{-}d$$

Perfluorononanoic acid or perfluorononanoate (PFNA), CAS# 375-95-1

Principal study & consideration of health effects

For the derivation of a RfD and MCL for PFNA, NHDES recommends the critical health effect of increased relative liver weight in pregnant mice (Das et al., 2015; NJDWQI, 2018) as an indicator for the onset of hepatotoxicity. This is the same critical health effect previously selected in the initial MCL proposal (NHDES, 2019), and based on additional review of the literature NHDES remains confident in this decision.

Since the initial MCL proposal by NHDES at the start of January 2019, additional studies have been published related to associations between PFNA and associated human health impacts along with studies demonstrating toxicity in rodent models. In the same studies that found associations between PFOA and serological markers of liver function (Nian et al., 2019; Jain and Ducatman, 2019; Bassler et al., 2019), PFNA was also associated with liver dysfunction and markers of hepatic inflammatory responses. As discussed later, this co-association between multiple PFAS and the same health outcomes is acknowledged as a present challenge of epidemiological research. The same study of the Danish Birth Cohort that associated PFOS with an early onset of puberty in girls found that prenatal serum levels of PFNA were associated with delayed onset of puberty in boys (Ernst et al., 2019). Ernst and colleagues (2019) noted that these associations merit caution in their interpretation and require replication due to their novelty. Unlike PFOA and PFOS, PFNA has been the subject of relatively less research and its lower background serum concentrations compared to PFOA and PFOS present a challenge to identifying its effects in human populations.

Studies published prior to 2019 were considered as a part of the initial PFAS MCL proposal put forward by NHDES (2019). At the time, two major documents reviewed the toxicity of PFNA in humans and rodents (NJDWQI, 2018; ATSDR, 2018b). As noted in both documents, relatively little research has been conducted on PFNA despite its historical use and presence in a variety of environmental media. The NJDWQI concluded there was limited evidence associating PFNA with changes in serum ALT as a biomarker of hepatotoxicity (NJDWQI, 2018), whereas the ATSDR determined these inconsistencies in epidemiological data did not merit inclusion of hepatotoxicity as an associated health outcome for PFNA (ATSDR, 2018b). In its initial proposal, NHDES agreed with the assessment made by the NJDWQI relative to adverse effects on the liver and NHDES maintains this position. Given the limited amount of epidemiological data currently available for PFNA and its similarity in chemical structure to PFOA and biological activities in animal models, NHDES determined that the associated hepatotoxic effects were more relevant and sensitive for human health risk assessment than the developmental and endocrine effects reported in animal studies. While NHDES does not agree with the application of the database uncertainty factor or animal-to-human dose extrapolation, the arguments made for consideration of hepatotoxicity by NJDWQI (2018) were deemed appropriate given the existing information.

To date, the carcinogenicity of PFNA has not been reported in a rodent model. The human carcinogenicity of PFNA has not been classified by the U.S. EPA, IARC or CDC (ATSDR). Therefore, NHDES did not conduct a cancer-based risk assessment for PFNA. Should additional information become available that is adequate for consideration of a cancer slope factor (CSF) for PFNA, NHDES recommends consideration as to whether its development and application of such values would be more protective than the proposed MCL.

Determination of a point of departure

As previously proposed by NHDES (2019), the principal study and point of departure (POD) was the same study (Das et al., 2015) recommended and benchmark dose modeled by the NJDWQI (2018). The critical health effect was increased relative liver weight in pregnant mice following a 17-d (duration of gestation) oral exposure to PFNA (Das et al., 2015). The internal LOAEL for these mice was 12,400 ng/mL which corresponded to an oral dose of 1.0 mg/kg-d (Das et al., 2015). While no significant mortality was observed at this dose, higher oral doses (>5.0 mg/kg-d) were associated with neonatal mortality in mice. Wolf et al. (2010) demonstrated the profound effects of PFNA on mouse pups were due to PPARα activation which raises uncertainty about the qualitative and quantitative relevance of this outcome to human health. Additional studies demonstrate that rodent models display hepatotoxic responses towards PFNA (Wolf et al., 2010; Wang et al., 2015), with evidence of PPARα-independent mechanisms (Rosen et al., 2017).

This POD is based on the benchmark dose modeling work conducted by the NJDWQI (2018) in their technical documents for their proposed MCL of 13 ng/L. It should be noted that NJDWQI did not derive a RfD as a part of the MCL development, as a ratio method was used instead of a DAF with water ingestion rate to convert the target serum level to a corresponding water concentration. NHDES did not arrive at the same MCL because NHDES opted to derive a RfD consistent with the other PFAS evaluated, as well as use of the transgenerational exposure model for breastfeeding (Goeden et al., 2019; MIDHHS, 2019).

Application of uncertainty factors

A total uncertainty factor of 100 was applied to the POD for PFNA based on:

Intraspecies variability (10) × Interspecies variability (3) × Database limitations (3) = 100

For the non-risk assessor, the units of 3 and 10 are for partial (half) and full log units. So, a full log unit of 10 equals 10^{1}, but a half log unit of $10^{½}$ or $10^{0.5}$ is equal to 3.162. As a convention of risk assessment using EPA methodology (EPA 2002), the value of 3.162 is presented as 3. Thus, 10 × 3 × 3 is rounded to 100 from 99.982.

The full factor of 10 for intraspecies variability was deemed appropriate to protect for the poorly characterized differences in toxico-dynamics (× 3) and -kinetics (× 3) within the human population. As NHDES applied a DAF to convert the rodent serum concentration to an oral human dose, only a partial uncertainty factor (× 3) was applied for interspecies variability. As the NJDWQI (2018) derived a benchmark dose, there was no need for any additional uncertainty factors to account for LOAEL to NOAEL conversion. As with PFOA, the critical effect of hepatic hypertrophy is considered the onset of the adverse effect in a sensitive model species. Consistent with PFOA, no additional uncertainty factor was applied to account for acute-to-chronic duration of exposure. The NJDWQI applied a full LOAEL to NOAEL uncertainty factor (× 10) to account for differences between the 17-d exposure in Das et al. (2015) and longer exposures resulting in reported adverse effects (summarized in NJDWQI, 2018). As increased liver weight in mice is already considered to be a highly-sensitive critical effect in response to PFAS, NHDES determined this was overly conservative given similar uncertainty factor considerations for the similar perfluorinated carboxylic acid, PFOA.

In its original proposal, NHDES applied a full database uncertainty factor (× 10) to account for the limited existing literature on PFNA (× 3), as well as the absence of a serum-derived human half-life estimate (× 3; NHDES 2019). As a part of its revision to the proposed RfDs and subsequent MCLs, NHDES utilized the more conservative half-life of PFNA derived for men and older women. Given the application of this more conservative half-life estimate, NHDES removed the associated partial uncertainty factor for PFNA. NHDES retained the partial uncertainty factor of × 3 to account for a lack of multigenerational rodent studies using PFNA, as well as concern for potential immunotoxic impacts seen with other PFAS (NTP 2016; DeWitt et al., 2012, 2019).

Estimation of a human equivalent oral dose

The POD represents an internal animal serum level associated with the adverse health outcome of concern. Dividing the POD by the total uncertainty factor yields a protective target serum level equivalent for the human population. *This is not a clinical or diagnostic value, nor should it be interpreted as such*.

$$\text{Target serum level for PFNA} = \frac{4{,}900\ \text{ng/mL}}{100} = 49.0\ \text{ng/mL}$$

To estimate how this internal blood level corresponds to an external oral dose of the specified compound, a dosimetric adjustment factor is applied by multiplication to identify a dose in ng of specific PFAS per kg of individual body weight per day (ng/kg-d). This step accounts for the highly-bioaccumulative nature and unique half-life estimates of each compound, and is consistent with prior risk assessment methods for derivation of RfDs for PFAS (USEPA 2016ab; NJDWQI 2017, 2018a; ATSDR 2018b; MDH 2019ab). The human equivalent oral dose is estimated by the following equations:

$$\text{Reference dose (RfD)} = \frac{\text{Point of departure (POD)}}{\text{Total uncertainty factors (UF)}} \times \text{Dosimetric adjustment factor (DAF)}$$

Where the DAF is equal to,

$$\text{DAF} = V_d \times \left(\frac{\text{Ln}(2)}{t_{1/2}}\right)$$

$$\text{DAF} = 200\ \text{mL/kg} \times \left(\frac{\text{Ln}(2)}{1{,}570\ \text{days}}\right) = 8.83 \times 10^{-2}\ \text{mL/kg-d}$$

Consistent with the initial PFNA MCL proposal (NHDES 2019), the V_d for PFNA was 200 mL/kg based on similar assumptions made by ATSDR (ATSDR 2018b). In this revised proposal, NHDES adjusted the half-life value from 2.5 to 4.3 years based on urinary half-lives estimated for men and older women, groups that tend to eliminate PFAS slower than younger and reproductive age women (Zhang et al., 2013; NHDES, 2019). As previously discussed in its initial proposal (NHDES, 2019), NHDES would prefer to have more reliable serum half-life estimates for PFNA instead of the urinary-derived estimates reported by Zhang and colleagues (2013). However, since the submission of the initial proposal no additional studies have been published that report a serum-based estimate for the half-life of PFNA in humans. Should additional peer-reviewed studies emerge that provide more rigorous estimates of these values, NHDES recommends consideration as to whether such data would represent and merit a significant change for the PFNA RfD.

Thus, using this chemical-specific DAF and the aforementioned point of departure and uncertainty factors, NHDES derived an oral reference dose for PFNA of 4.3 ng/kg-d.

$$\text{Reference dose (RfD)} = \frac{4{,}900 \text{ ng/mL}}{100} \times 8.83\times10^{-2} \text{ mL/kg-d} = 4.3 \text{ ng/kg-d}$$

Perfluorohexane sulfonic acid or perfluorohexane sulfonate (PFHxS), CAS# 355-46-4

Principal study & consideration of health effects

For the derivation of a RfD and MCL for PFHxS, NHDES recommends the critical health effect of impaired female reproduction as determined by reduced litter size initially reported in Chang et al. (2018). This RfD derivation is currently under peer-review with a scientific journal (Ali et al. *in review*). This is the same critical health effect previously proposed in the initial MCL proposal (NHDES 2019), albeit the present value is adjusted for benchmark dose modeling and selection of endpoint specific factors for dosimetric adjustment. NHDES developed the revised RfD in collaboration with external collaborators, Dr.'s Leah Stuchal and Stephen Roberts at the University of Florida, and awaits external peer-review on the soundness of its derivation. Should peer-review recommend revision and adjustment of the proposed RfD, NHDES will review the current MCL to determine if adjustments are required to be adequately protective of human health.

Since its initial proposal (NHDES, 2019), there has been a limited amount of new information generated relative to PFHxS. The Minnesota Department of Health proposed a RfD for PFHxS of 9.7 ng/kg-d based on reduced free T_4 in exposed rats using unpublished data from the NTP. At the time of writing this recommendation, the ATSDR has not released a revision to their 2018 draft MRL of 20 ng/kg-d based upon thyroid follicular cell damage in rats (ATSDR, 2018b). PFHxS showed similar associations with serological markers of liver function and inflammation as reported for PFOA, PFOS and PFNA (Nian et al., 2019; Jain and Ducatman, 2019; Bassler et al., 2019). Despite its legacy of widespread environmental occurrence associated primarily with AFFF use and growing regulatory interests, relatively little new toxicological information has emerged for PFHxS as of June 2019.

Studies published prior to 2019 were considered as a part of the initial PFAS MCL proposal put forward by NHDES (2019). This included re-evaluation of peer-reviewed evidence considered by ATSDR (2018b) including:

- thyroid toxicity including altered thyroid histology and reduced T_4 levels in rodent models (Butenhoff et al., 2008; Chang et al., 2018; Ramhøj et al., 2018), as well as epidemiology studies for altered T_4 levels (Ballesteros et al., 2017),
- immunomodulation in humans (Grandjean et al., 2012; Dong et al., 2013; Humblet et al., 2014; Okada et al., 2014; Buser and Scinicariello 2016; Stein et al., 2016; Zhu et al., 2016)
- reproductive and developmental toxicity in rodents (Butenhoff et al., 2008; Viberg et al., 2013; Chang et al., 2018; Ramhøj et al., 2018)
- hepatotoxicity or changes in lipid metabolism in rodents (Butenhoff et al., 2008; Bijland et al., 2011; Rosen et al., 2017; Chang et al., 2018; Ramhøj et al., 2018) and humans (Nelson et al., 2010; Starling et al., 2014; Mattsson et al. 2015).
- and human carcinogenicity (Hardell et al., 2010; Bonefel et al., 2014; Hurley et al., 2018).

To date, the carcinogenicity of PFHxS has not been reported in a rodent model. The human carcinogenicity of PFHxS has not been classified by the U.S. EPA, IARC or CDC (ATSDR). Therefore, NHDES did not conduct a cancer-based risk assessment for PFHxS. Should additional information become available that is adequate for consideration of a CSF for PFHxS, NHDES recommends consideration as to whether its development and application would be more protective than the proposed MCL.

Determination of a point of departure

As described in its initial MCL proposal (NHDES 2019), the principal study and point of departure (POD) was the same study (Chang et al., 2018) that has been adjusted primarily by use of benchmark dose modeling (Ali et al., *in review*). The critical health effect was reduced litter size in mice following a 14-d, prior to pregnancy, oral exposure to PFHxS (Chang et al., 2018). As mentioned above, the details and methodology for derivation of the POD for PFHxS are currently under review in Ali et al (*in review*). Benchmark dose (BMD) modeling was performed using Benchmark Dose Software (BMDS) (Version 3.1; USEPA, 2019). The critical effect endpoint was a change in the mean live litter size for adult CD-1 female mice, and due to the unavailability of litter-specific data was modeled based on PFHxS serum concentrations on study day 14 (reported in Chang et al., 2018). This resulted in a benchmark dose of 41,200 ng/mL and a 95% lower confidence limit on the benchmark dose (BMDL) of 13,900 ng/mL. NHDES determined that this is an appropriately cautious endpoint given the limited number of animal studies (reviewed in NHDES, 2019), considerably longer half-lives of PFHxS in humans when compared to other PFAS (Olsen et al., 2007; Zhang et al., 2013; Worley et al., 2017; Li et al., 2018), environmental occurrence and exposures (Daly et al., 2018), as well as suggestive associations of reproductive impacts in humans (Vélez et al., 2015; Zhou et al., 2017; Zhang et al., 2018).

Application of uncertainty factors

A total uncertainty factor of 300 was applied to the POD for PFHxS based on:

Intraspecies variability (10) × Interspecies variability (3) × Duration of exposure (3)
× Database limitations (3) = 300

For the non-risk assessor, the units of 3 and 10 are for partial (half) and full log units. So, a full log unit of 10 equals 10^1, but a half log unit of $10^{½}$ or $10^{0.5}$ is equal to 3.162. As a convention of risk assessment using EPA methodology (EPA 2002), the value of 3.162 is presented as 3. Thus, 10 × 3 × 3 × 3 is rounded to 300 from 316.14.

The full factor of 10 for intraspecies variability was deemed appropriate to protect for the poorly characterized differences in toxico-dynamics (× 3) and -kinetics (× 3) within the human population. As NHDES applied a DAF to convert the rodent serum concentration to an oral human dose, only a partial uncertainty factor (× 3) was applied for interspecies variability. As benchmark dose modeling was used to derive a POD, detailed in Ali et al. (*in review*), there was no need for any additional uncertainty factors to account for LOAEL to NOAEL conversion. After careful evaluation of technical comments and re-assessment of the literature and principal study, an additional but partial uncertainty factor (× 3) was applied to account for acute-to-chronic duration of exposure of female mice. In Chang et al. (2018), female mice received a less than chronic exposure (14 days) to PFHxS prior to the start of pregnancy. Because of the relatively limited number of studies on PFHxS and evidence for adverse impacts following longer exposure to similar compounds (i.e., PFOS), this was determined to be appropriate without being overly conservative (e.g., a full factor of × 10).

In its original proposal, NHDES applied a full database uncertainty factor (× 10) to account for the limited existing literature on PFHxS (× 3), as well as associations with thyroid hormone and transport interference (× 3; NHDES 2019). As a part of its revision to the proposed RfD and subsequent MCL,

NHDES determined the existing single-generation studies provide some basis for evaluating the reproductive and developmental toxicity of PFHxS. However, NHDES retained a partial uncertainty factor (× 3) to account for a lack of multigenerational rodent studies, as well as concern for potential immunotoxic impacts seen with other PFAS that have yet to be assessed (NTP 2016; DeWitt et al., 2019). The protracted human half-life of PFHxS relative to other PFAS underscores the need for additional research into biological impacts following chronic exposures.

Estimation of a human equivalent oral dose

The POD represents an internal animal serum level associated with the adverse health outcome of concern. Dividing the POD by the total uncertainty factor yields a protective target serum level equivalent for the human population. *This is not a clinical or diagnostic value, nor should it be interpreted as such*.

$$\text{Target serum level for PFHxS} = \frac{13{,}900\ \text{ng/mL}}{300} = 46.3\ \text{ng/mL}$$

To estimate how this internal blood level corresponds to an external oral dose of the specified compound, a dosimetric adjustment factor is applied by multiplication to identify a dose in ng of specific PFAS per kg of individual body weight per day (ng/kg-d). This step accounts for the highly-bioaccumulative nature and unique half-life estimates of each compound, and is consistent with prior risk assessment methods for derivation of RfDs for PFAS (USEPA 2016ab; NJDWQI 2017, 2018a; ATSDR 2018b; MDH 2019ab). The human equivalent oral dose is estimated by the following equations:

$$\text{Reference dose (RfD)} = \frac{\text{Point of departure (POD)}}{\text{Total uncertainty factors (UF)}} \times \text{Dosimetric adjustment factor (DAF)}$$

Where the DAF is equal to,

$$\text{DAF} = V_d \times \left(\frac{\text{Ln}(2)}{t_{1/2}}\right)$$

$$\text{DAF} = 213\ \text{mL/kg} \times \left(\frac{\text{Ln}(2)}{1{,}716\ \text{days}}\right) = 8.61\times10^{-2}\ \text{mL/kg-d}$$

In its revised MCL proposal for PFHxS, NHDES has changed both the V_d and half-life estimate for PFHxS to reflect the female-specific health impact utilized as the basis of the RfD. The V_d for PFHxS was reduced from 287 to 213 mL/kg which reflects a female-specific V_d value for PFHxS (Sundström et al., 2012). Sundström et al. (2012) reports the volume of distribution for cynomolgus monkeys, not humans, and no human V_d is currently available for PFHxS. Similar to ATSDR (ATSDR 2018b) and other agencies (MDH 2019b; MIDHHS 2019), NHDES used the non-human primate value as an estimate for the human volume of distribution. Similarly, NHDES adjusted the half-life value from 5.3 to the female-specific estimate of 4.7 years (average) based on a study of a community exposed to PFHxS through contaminated drinking water (Li et al. 2018; discussed in NHDES 2019). It is noted that use of this average half-life estimate for women is less conservative than longer average half-life estimates of 8.5 years (Olsen et al., 2007) or 7.4 years (Li et al., 2018) that rely on serum levels in men, or longer estimates of 7.7-35 years for women depending on age (Zhang et al., 2013). However, given the conservative nature and sex-specific effect selected for the POD of PFHxS, the use of a 4.7-year half-life in women was deemed appropriate without being overly-conservative.

Thus, using this chemical-specific DAF and the aforementioned point of departure and uncertainty factors, NHDES derived an oral reference dose for PFHxS of 4.0 ng/kg-d.

$$\text{Reference dose (RfD)} = \frac{13{,}900 \text{ ng/mL}}{300} \times 8.61\times10^{-2} \text{ mL/kg-d} = 4.0 \text{ ng/kg-d}$$

Summary of Recommended RfDs for PFOA, PFOS, PFNA and PFHxS

Recommended RfDs

NHDES recommends the following chronic oral RfDs for PFOA, PFOS, PFNA and PFHxS:

- PFOA, 6.1 ng/kg-d
- PFOS, 3.0 ng/kg-d
- PFNA, 4.3 ng/kg-d
- PFHxS, 4.0 ng/kg-d

These RfDs are for protection from the primary health effects of liver toxicity (PFOA and PFNA), immune suppression of antibody responses (PFOS) and reduced female fertility (PFHxS) based on evidence from animal studies. In addition to these primary health outcomes, these RfDs are expected to be reasonably protective for associated and secondary (less sensitive) health outcomes that occur at similar or higher serum concentrations in rodents. Secondary health effects for these and other PFAS include disruption of thyroid and sex hormone levels and their signaling, teratogenic effects, early-life growth delays, changes in cholesterol levels, neurobehavioral effects, renal toxicity and fertility in rodent models. NHDES believes its selection of PODs, uncertainty factors and DAFs for each RfD provides adequate protection of human health from appreciable risk of these primary and secondary health effects during a lifetime.

Table 2 presents the NHDES recommended RfDs or MRLs, along with their applied uncertainty factors those selected by other agencies that have evaluated these same PFAS. The application of uncertainty factors follows EPA guidance (EPA 2002), and is dependent on the principal study selected and consideration of other available studies. However, it is not uncommon for different risk assessors and toxicologists to arrive at different applications of uncertainty factors when considering where reasonable and health-protective conservatism is being applied in the risk assessment process.

Discussion of scientific uncertainties

While the human health effects of PFAS is a rapidly growing area of scientific research, the exact nature of their associated health effects in humans remains uncertain (ATSDR, 2018b; Michigan Panel, 2018). The cross-sectional nature of most epidemiological studies precludes proof of causality between measured PFAS serum concentrations and the reported associated health outcomes. This is especially problematic as the extraordinarily long half-lives of PFAS (years) make it difficult to disentangle the associated health effects in these studies from co-exposure to other environmental contaminants with relatively shorter half-lives (days to weeks). Additionally, there is a general lack of true control groups for comparison as various combinations of PFAS are detectable in the blood of virtually all populations from around the world. There is concern for the implications of reverse causation with certain health outcomes associated to PFAS. As an evolving area of scientific research, NHDES anticipates new findings will improve the understanding of PFAS-related health effects in humans.

Due to the limitations of epidemiological studies, RfDs were derived using animal data. There are inherent uncertainties associated with RfDs derived from animal studies (EPA 2002), specifically related

to considerations of human health relevance (e.g., biological plausibility) and translation of animal findings to human equivalent values (i.e., uncertainty factors and DAFs).

As a part of its initial proposal (NHDES, 2019), NHDES considered the contentious issue of peroxisome proliferator-activated receptor subtype α (PPARα) activation in rodents and its relevance to human health. The activation of PPARα is a contributing pathway for several of the reported toxic responses in rodent models evidenced by genetic knockout studies and gene expression profiling studies (reviewed by ATSDR 2018b and NHDES 2019). This is especially true for hepatotoxicity and changes in lipid metabolism in rodents following exposure to PFAS due to upregulation of rodent specific pathways leading to oxidative stress (Perkins et al., 2004; Loveless et al., 2006; Rosen et al., 2007, 2008, 2017; Das et al., 2017; reviewed by ATSDR, 2018b). *In vitro* testing demonstrates that PFAS show a stronger binding affinity for rodent PPARα when compared to human PPARα (Wolf et al., 2008). These and other studies reviewed by NHDES (2019) suggest qualitative and quantitative differences in toxicity between species for PPARα-dependent effects.

Such qualitative and quantitative differences raise concern for selection of critical health effects such as liver toxicity based on rodent studies (reviewed by Klaunig et al., 2012), and have been a major criticism of the half-lives derived by NHDES and other agencies for RfDs for PFOA, PFOS, PFNA and PFHxS. Based on existing toxicological information, NHDES contends that selected critical effects from animal studies are appropriate for the protection of human health. While the physiological roles of PPARs (i.e., PPARα, β and γ) in humans are less defined than those of the other nuclear receptors like the estrogen or androgen receptor, there is evidence that they are involved in lipid metabolism (Issemann and Green, 1990; Lee et al., 1995) and function of muscle, adipose and immune cells throughout the body (Tyagi et al., 2011). Independent of PPARα activation, there is evidence for other mechanisms for rodent toxicity (e.g. mitochondrial dysfunction) that are potentially relevant to humans and other organisms (Hagenaars et al., 2013; Cui et al., 2015; reviewed by Li et al., 2017; Li et al., 2018; NHDES, 2019). Furthermore, evidence from non-human primates further suggest that effects on the liver, cholesterol levels, thyroid hormones and the immune system are relevant to humans and not isolated to rodent studies (Griffith and Long 1980; Thomford 2001; Butenhoff et al., 2002; Seacat et al., 2002). Taken collectively, this supports the NHDES risk assessment and derivation of RfDs using the selected critical health effects.

With respect to uncertainty factors, NHDES received multiple comments regarding its application of uncertainty factors in the initially proposed MCLs (NHDES, 2019). Table 2 presents the uncertainty factors used by other state or federal agencies for the derivation of RfDs for PFOA, PFOS, PFNA or PFHxS, and demonstrates that NHDES's selections are within the norms of the professional practice. As previously explained for each compound, NHDES considered available information from human and animal studies to arrive at the total uncertainty factors applied for each RfD. Difference in principal study selection and consideration of available data results in differences in the selection and application of total uncertainty factors (EPA 2002). Given the selection of principal studies and considerations of exposure assumptions described in Section IV, NHDES remains confident that its application of uncertainty factors is appropriate without being overly conservative.

Table 2. Interagency Differences in Uncertainty Factors. Summary of uncertainty factor allocations, RfDs and MRLs by government risk assessment groups.

Specific Uncertainty Factors	ATSDR[a] (MRLs)	US EPA[b,c] (RfD)	TX CEQ[d] (RfD)	MN DOH[e-g] (RfD)	NJ DWQI[h-j] (RfD)	NH DES (RfD)	NY DOH[k] (RfD)
PFOA							
Principal Study	Koskela et al. 2016	Lau et al. 2006	Macon et al. 2011	Lau et al. 2006	Loveless et al. 2006	Loveless et al. 2006	Macon et al. 2011
Human Variability	10	10	10	10	10	10	10
Interspecies Differences	3	3	1	3	3	3	3
Duration of Exposure	1	1	1	1	1	1	1
LOAEL to NOAEL	10	10	30	1	1	1	1
Database Insufficiency	1	1	1	3	10	3	3
Total Uncertainty Factor	300	300	300	100	300	100	100
RfD (ng/kg-d)	3.0	20.0	12.0	18.0	2.0	6.1	1.5
PFOS							
Principal Study	Luebker et al. 2005	Luebker et al. 2005	Zeng et al. 2011	Dong et al. 2011	Dong et al. 2009	Dong et al. 2011	Dong et al. 2009
Human Variability	10	10	10	10	10	10	10
Interspecies Differences	3	3	1	3	3	3	3
Duration of Exposure	1	1	1	1	1	1	1
LOAEL to NOAEL	1	1	10	1	1	1	1
Database Insufficiency	10	10	1	3	1	3	1
Total Uncertainty Factor	300	300	100	100	30	100	30
RfD (ng/kg-d)	2.0	20.0	23.0	3.0	1.8	3.0	1.8
PFNA							
Principal Study	Das et al. 2015	n.a.	Fang et al. 2010	n.a.	Das et al. 2015	Das et al. 2015	n.a.
Human Variability	10	-	10	-	10	10	-
Interspecies Differences	3	-	1	-	3	3	-
Duration of Exposure	1	-	10	-	10	1	-
LOAEL to NOAEL	1	-	1	-	1	1	-
Database Insufficiency	10	-	10	-	3	3	-
Total Uncertainty Factor	300	-	1,000	-	1,000	100	-
RfD (ng/kg-d)	3.0		12.0		0.73	4.3	
PFHxS							
Principal Study	Butenhoff et al. 2009	n.a.	Hoberman & York 2003	Unpublished NTP data	n.a.	Chang et al. 2018	n.a.
Human Variability	10	-	10	10	-	10	-
Interspecies Differences	3	-	1	3	-	3	-
Duration of Exposure	1	-	1	1	-	3	-
LOAEL to NOAEL	1	-	3	1	-	1	-
Database Insufficiency	10	-	10	10	-	3	-
Total Uncertainty Factor	300	-	300	300	-	300	-
RfD (ng/kg-d)	20.0		3.8	9.7		4.0	

n.a. indicates the specific compound was not assessed or reported on by the specific agency.

[a] ATSDR, 2018b. Draft Toxicological Profile for Perfluoroalkyls

[b] U.S. EPA, 2016a. Health Effects Support Document for Perfluorooctanic Acid (PFOA)

[c] U.S. EPA, 2016b. Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)

[d] TX Commission on Environmental Quality (TXCEQ), 2016. Perfluoro Compounds (PFCs): available at: https://www.tceq.texas.gov/assets/public/implementation/tox/evaluations/pfcs.pdf

[e] Minnesota Department of Health (MDH), 2018. Toxicological Summary for: Perfluorooctanoate.

[f] Minnesota Department of Health (MDH), 2019a. Toxicological Summary for: Perfluorooctane sulfonate.

[g] Minnesota Department of Health (MDH), 2019b. Toxicological Summary for: Perfluorohexane sulfonate.

[h] New Jersey Drinking Water Quality Institute (NJDWQI), 2017. Appendix A: Health-Based Maximum Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA)

[i] New Jersey Drinking Water Quality Institute (NJDWQI), 2018a. Appendix A: Health-Based Maximum Contaminant Level Support Document: Perfluorooctane Sulfonate (PFOS)

[j] New Jersey Drinking Water Quality Institute (NJDWQI), 2018b. Appendix A: Health-Based Maximum Contaminant Level Support Document: Perfluorononanoic Acid (PFNA)

[k] New York Department of Health (NYDOH), 2018 and personal communications. Presentation available at: https://www.health.ny.gov/environmental/water/drinking/dwqc/

Section IV. Drinking Water Exposure Assumptions, Modeling and Resulting MCLs

Using the reference dose (RfD) derived in Section III, the MCL considers the estimated daily intake of water from a specific source and how much drinking water contributes to the total exposure from all other sources of a specified contaminant. Specific methodologies for deriving health protective water criteria are detailed by the EPA (USEPA 1989, 2004, 2017, 2018). Although NHDES chose a different approach, the conventional method for deriving drinking water values utilizes the following equation:

$$\text{Maximum contaminant level (ng/L)} = \frac{\text{Reference dose (ng/kg-d)}}{\text{Daily water ingestion rate (L/kg-d)}} \times \text{Relative source contribution (unitless)}$$

For a simple example, a drinking water value for PFOA using the currently recommended RfD, 95th percentile ingestion rate of lactating women and a relative source contribution of 0.5 (meaning 50%) is shown below. This approach was used in the initially proposed MCL, but is not being applied following consideration of breastfeeding (Goeden et al., 2019).

$$\text{Example for PFOA (not an actual MCL recommendation by NHDES)} = \frac{6.1 \text{ ng/kg-d}}{0.055 \text{ L/kg-d}} \times 0.5 = 55 \text{ ng/L}$$

The daily water ingestion rate is a body-weight adjusted factor specific to certain age groups, to gender, and to lactation or pregnancy status. In its initial proposal, NHDES selected the water ingestion rate of the 95th percentile of lactating women, an estimated value of 0.055 L/kg-d (EPA, 2011; NHDES, 2019). While lower estimates are more reflective of the central tendencies of the general population, especially non-lactating women, they were deemed inadequately protective for the larger population. The values are selected from the Exposure Factors Handbook (EPA 2011), which was recently updated specifically for these ingestion rates (see Chapter 3 of EPA, 2019). These updated values were used by NHDES.

Instead of applying a fixed daily water ingestion rate that is assumed to be protective across a lifespan, NHDES applied the toxicokinetic model described by Goeden et al. (2019) to consider how changes in water ingestion at a given MCL are predicted to influence internal blood levels of each PFAS. This is due to the prolonged and elevated internal doses (i.e., serum levels) predicted across infancy and childhood resulting from PFAS in breastmilk. NHDES acknowledges that this is a departure from typical methodology for deriving such a standard, but the unique properties of PFAS (i.e., long half-lives) merit its application to be truly protective across all life stages for the chronic health impacts associated with these chemicals.

The relative source contribution (RSC) is an estimate of how much of the typical daily exposure will be allowed to come from drinking water. EPA recommends an RSC floor of 20% of the RfD and a ceiling of 80% of the RfD. The intention of an RSC ceiling of 80% is to ensure that total exposure from all sources does not exceed 100% of the RfD with a margin of safety for potential unknown or underestimated exposures. PFAS are present in a wide variety of environmental media (Moriwaki et al., 2003; Trudel et al., 2008; Haug 2011; Haug et al., 2011; Winkens et al., 2017, 2018) and consumer products (Haug 2011; Carpet and Textile Treatment - Washburn et al., 2005; Winkens et al. 2017; Cosmetics - Kang et al., 2016; Fast Food Packaging – Schaider et al., 2017), with an ever-growing number of potential sources identified (Boronow et al., 2019; Kim et al., 2019; Nakayama et al., 2019). Thus, for the typical person, it is unlikely that drinking water is responsible for 100% of their exposure. However, an exact profile for the proportions of exposure from various sources remains poorly characterized. The latter part of this section details how this was evaluated by NHDES to arrive at a RSC of 50% for PFOA, PFOS, PFNA and PFHxS.

Application of Goeden et al. (2019) for exposure modeling

As a part of the evaluation of published research and technical comments on the initially proposed MCLs (NHDES, 2019), NHDES has adopted the use of the transgenerational toxicokinetic model (detailed in Goeden et al., 2019), for the determination of appropriately protective health-based MCLs. This is a toxicokinetic model that predicts the serum concentration of PFAS due to drinking water exposure and consumption of breastmilk or formula across a lifespan starting at birth (Goeden et al., 2019). It does not predict an effect (health outcome) due to exposure from drinking water, only the blood concentration for an individual in a reasonable maximum exposure (RME) scenario. The tolerable blood concentration in the RME scenario, or threshold, is determined by the chemical-specific RfD and RSC. This Excel-based model is available upon request from the MN Department of Health.

After review of the model and studies on the placental transfer (Fei et al., 2007; Midasch et al., 2007; Monroy et al., 2008; Fromme et al., 2010; Beesoon et al., 2011; Kim et al., 2011; Liu et al., 2011; Needham et al., 2011; Lee et al., 2013; Porpora et al., 2013; Zhang et al., 2013; Kato et al., 2014; Cariou et al., 2015; Manzano-Salgado et al., 2015; Fisher et al., 2016; Yang et al., 2016; Chen et al., 2017; Mamsen et al., 2019) and breastmilk transfer (Karrman et al., 2007; Haug et al., 2011; Kim et al., 2011; Liu et al., 2011; Cariou et al., 2015; Gyllenhammer et al., 2018) of PFOA, PFOS, PFNA and PFHxS, NHDES determined this novel and "fit-for-purpose" tool (Goeden et al., 2019) was necessary to evaluate exposure outcomes from the proposed MCLs. Specifically, the transfer of PFAS into breastmilk combined with the relatively high breastmilk and water ingestion rates of infants results in a prolonged elevation of serum levels throughout childhood. Under RME assumptions, the serum levels are predicted to be drastically higher than background serum levels seen in the general population, which is assumed to be free of widespread PFAS contamination in drinking water. Furthermore, this elevation throughout childhood into late adolescence limits the RSC allotment for exposure to other sources of PFAS in the environment that, to date, are not regulated.

The following subsections describe the inputs selected by NHDES for RME modeling using Goeden et al. (2019). A summary of model inputs, and associated references, used by NHDES for selection of the proposed MCLs are provided in Table 3.

Human half-life and V_d assumptions

Explanations of the selected half-lives for PFOA, PFOS, PFNA and PFHxS are described in the discussions of DAFs in Section III of this report. For PFOA, an average serum-based half-life was selected from Bartell et al. (2010), which was estimated from a sample population of 200 individuals from the Mid-Ohio valley who were exposed to PFOA from their drinking water supply due to contamination from a DuPont facility. NHDES selected the half-life estimates from Li et al. (2018) for PFOS and PFHxS. These serum-derived half-life estimates were determined to be more representative of the general population, and were obtained from a Swedish community (n = 106 participants) exposed to PFAS, namely PFOS and PFHxS, from drinking water contaminated by AFFF use at a nearby airbase (Li et al., 2018). Finally, the half-life estimate for PFNA was selected from Zhang et al. (2013) which reports urine-based values from a Chinese population (n = 86 participants).

Similar to the half-life values, the volume of distribution (V_d) estimates were identical to those selected by NHDES to derive RfDs for PFOA, PFOS, PFNA and PFHxS (Section III, and references therein).

Table 3. Exposure Model Parameters. Summary of parameters utilized in the transgenerational model (Goeden et al., 2019) by NHDES for derivation of proposed MCLs.

Model Parameter	Central or Upper Tendency of Parameter	PFOA	PFOS	PFHxS	PFNA
Half-Life, years (yrs)	Central	2.3 [a]	3.4 [b]	4.7 [b]	4.3 [c]
Placental Transfer Ratio	Central	0.72 [d]	0.40 [d]	0.70 [d]	0.69 [e]
Breastmilk Transfer Ratio	Central	0.050 [d]	0.017 [d]	0.014 [d]	0.032 [e]
Volume of Distribution (V_d), L/kg	Central	0.170 [f]	0.230 [f]	0.213 [g]	0.200 [e,h]
Relative Source Contribution (RSC), %	Central	50	50	50	50
		Same for All 4 PFAS Exposure Scenario Models			
Duration of Exclusive Breastfeeding, months	Upper	12			
Water Ingestion Rates, mL/kg-d [i] (EPA Exposure Factors Handbook, 2019 Update)					
Birth to <1 mon	Upper	224			
1 to <3 mons	Upper	267			
3 to <6 mons	Upper	158			
6 to <11 mons	Upper	133			
1 to <2 yrs	Upper	57			
2 to <3 yrs	Upper	67			
3 to <6 yrs	Upper	45			
6 to <11 yrs	Upper	41			
11 to <16 yrs	Upper	31			
16 to <18 yrs	Upper	31			
18 to <21 yrs	Upper	31			
21+ yrs	Upper	44			
Lactating Woman	Upper	47			
Breastmilk Ingestion Rates, mL/kg-d (EPA Exposure Factors Handbook, 2011)					
Birth to <1 mon	Upper	220			
1 to <3 mons	Upper	190			
3 to <6 mons	Upper	150			
6 to <12 mons	Upper	130			

[a] Bartell et al., 2010; [b] Li et al., 2018; [c] Zhang et al., 2013; [d] MDH, 2018, 2019ab
[e] MIDHHS, 2019; [f] Thompson et al., 2010; [g] Sundström et al., 2012; Ali et al., *in review*
[h] ATSDR, 2018b;
[i] Body weight and age-specific adjustments to the V_d were maintained the same as described in Goeden et al., 2019.

Placental & breastmilk transfer ratios

NHDES applied previously selected placental and breastmilk transfer ratios for PFOA (MDH 2018), PFOS (MDH 2019), PFNA (MIDHHS 2019) and PFHxS (MDH 2019). In line with the MDH and MIDHHS, NHDES opted to use central tendency values for each PFAS versus the upper or 95th percentile estimate for transfer in the RME scenarios (Table 3).

The exact quantitative nature of PFAS transfer across the placenta remains an active area of research. For example, Mamsen et al. (2019) demonstrated that the accumulation of PFAS in fetal tissues begins early in pregnancy and continues throughout gestation as specific PFAS are taken up by the forming organs with slightly different efficiencies. Several studies of cord blood compared to maternal serum levels of PFAS have been used to estimate placental transfer ratios and are used in the model to predict the "at birth" serum level (Fei et al., 2007; Midasch et al., 2007; Monroy et al., 2008; Fromme et al., 2010; Beesoon et al., 2011; Kim et al., 2011; Liu et al., 2011; Needham et al., 2011; Lee et al., 2013; Porpora et al., 2013; Kato et al., 2014; Cariou et al., 2015; Manzano-Salgado et al., 2015; Fisher et al., 2016; Yang et al., 2016; Chen et al., 2017; Mamsen et al., 2019). The average maternal-to-cord blood or placenta ratios ranged from 0.20 (Mamsen et al., 2019) to 1.24 (Midasch et al., 2007) for PFOA, 0.14 (Fisher et al., 2014) to 0.60 (Midasch et al., 2007) for PFOS, 0.24 (Mamsen et al., 2019) to 1.18 (Monroy et al., 2008) for PFNA, and 0.23 (Fisher et al., 2016) to 1.25 (Monroy et al., 2008) for PFHxS. A point of caution in interpreting placental transfer ratios in these studies is the trimester of pregnancy that data are collected. Changes in blood volume over the coruse of pregnancy are expected to affect the maternal blood concentration, thereby influences cord blood to maternal blood concentration ratios for various PFAS. Collectively, these studies provide valuable and reliable information for estimating the transfer from mother to newborn. This model does not predict fetal blood or tissue concentrations of PFAS as this compartmentalization is poorly understood, although recent work, such as Mamsen et al. (2019) may lead to the development of such models.

Compared to placental transfer efficiencies that are well-documented for PFAS, a small body of literature informs our understanding of the PFAS in breastmilk. As a part of its review of the technical documents described by MDH (2018, 2019ab) and MIDHHS (2019), NHDES reviewed the source papers for the breastmilk transfer ratios (Karrman et al., 2007; Haug et al., 2011; Kim et al., 2011; Liu et al., 2011; Cariou et al., 2015; Gyllenhammer et al., 2018). These studies demonstrate that the small average percentage (0.6-11% across various PFAS) transferred from a mother's serum, which is typically at concentrations of ng/mL or ppb, results in breastmilk at concentration ranges well above most existing drinking water advisories. Combined with relatively high ingestion rates of breastmilk relative to the infant's body weight, this results in a spike of infant blood concentrations that the model predicts will remain high through childhood.

Duration of breastfeeding

A major assumption for the breastfeeding component of this model is the duration of exclusive breastfeeding. Consistent with the RME scenarios selected by other states (MDH, 2018, 2019ab; MIDHHS, 2019), NHDES used a 12-month duration of *exclusive breastfeeding* for all four RME scenarios. Similar to the CDC, the World Health Organization (WHO) defines exclusive breastfeeding as:

> "Exclusive breastfeeding means that the infant receives only breast milk. No other liquids or solids are given – not even water – with the exception of oral rehydration solution, or drops/syrups of vitamins, minerals or medicines." – WHO eLENA (2019)

A central tendency assumption for the duration of exclusive breastfeeding would be 6 months, but NHDES selected a more conservative modeling parameter of 12 months of exclusive breastfeeding. A 12-month exclusive breastfeeding duration is a conservative assumption because the CDC recommends 6 months of exclusive breastfeeding and some continuation through infancy given the clear benefits to an infant's health and their long-term development. After 6 months of age, the recommendation is that other food items are introduced and breastfeeding continues for up to 2 years of age.

This assumption has been argued by some to be overly conservative relative to the RME scenarios as 1) CDC recommended exclusive breastfeeding for up to 6 months of age and 2) if an infant were exclusively breastfeeding at or after 12 months of age, it is unlikely they are not ingesting other fluids or foods. NHDES contends that this is a reasonable assumption given 1) the role that the duration of exclusive breastfeeding plays in the MN model and 2) the high rates of breastfeeding in New Hampshire and breastfeeding trends across the nation.

MDH notes that the duration of breastfeeding, along with breastmilk intake rates and water concentration, are the most sensitive parameters of the model (MDH 2017). The duration of exclusive breastfeeding and breastfeeding with complimentary foods varies, but the CDC recommends up to 2 years of breastfeeding with the addition of complimentary foods. The transgenerational model does not contain parameters for apportionment of exposure from breastmilk versus complimentary foods, or formula, across the first two years of life. Given this uncertainty for mixed exposures for breastfed infants, NHDES agreed that the assumption of a 12-month exclusive breastfeeding duration was appropriate for estimate for the purpose of the model.

Results from the National Immunization Survey (NIS) indicate that, in the general U.S. population of newborns, approximately 24.9% ± 1.2 (± half 95% CI) of infants are exclusively breastfed at 6 months of age. By 12 months, 35.9% ± 1.3 of infants consume breastmilk along with complimentary foods and liquids (CDC, 2018a). New Hampshire specific estimates from this same dataset are that 30.2% ± 5.8 of infants exclusively breastfeed at 6 months of age, while 45.6% ± 6.5 breastfeed at 12 months of age in addition to complimentary foods (CDC, 2018a). Based on the historical trends, the 2018 Breastfeeding Report Card (CDC, 2018b) indicates more women nationwide are breastfeeding or want to breastfeed their children, giving weight to the consideration of breastfeeding and selecting a conservative window of 12 months.

Breastmilk and drinking water ingestion rate assumptions

This transgenerational model evaluates the impact of changing water ingestion rates across a lifespan. These ingestion rates are expressed as liters of water per kilogram of an individual's body weight per day (L/kg-d). As a person grows, their physiological demand for water changes and this is reflected by age-specific ingestion rates, or life-process specific rates in the case of pregnant and lactating women. To put this in context of historical practice, the EPA typically assumed a drinking water ingestion rate of 2 L/d

for adults and 1 L/d for infants and children under 10 years of age (U.S. EPA, 2000). After adjusting for body weight, these typical rates would underestimate the water consumption of infants, children and lactating and pregnant women. Thus, consideration of these life-stage specific values is prudent for a persistent and highly-bioaccumulative class of drinking water contaminants.

To be protective of the general population including high-end water consumers, NHDES applied the 95th percentile water and breastmilk ingestion rates throughout life in the RME scenarios for PFOA, PFOS, PFHxS and PFNA. The use of the 95th percentile for water ingestion rates is consistent with the initial proposal, and this is simply an extension to other life stages. Recently updated values in 2019 Updated Chapter 3 of the Exposure Factors Handbook (EPA, 2019) were combined with estimated breastmilk ingestion rates from Chapter 15 of the 2011 Edition (EPA, 2011). As these changes were specific to water ingestion, not breastmilk, the difference between the 2011 and 2019 estimates for infants, a change of -9% to +3% for those <1 year of age, was determined to be a minor and tolerable change to the RME scenarios. The breastfed RME exposure was the driver of the MCL for all evaluated PFAS, and therefore protective of an individual in the formula-fed RME scenario.

Consideration of the Relative Source Contribution (RSC)

Exposure to PFAS is not solely due to drinking water, so in order for the MCL to be health protective NHDES needs to account for the contribution of other sources towards the reference dose (RfD). The proportion of exposure attributed to a specific source is accounted for through the relative source contribution (RSC). With respect to a MCL, the RSC is the percentage of total exposure typically accounted for by drinking water (EPA 2000). This value can be referred to as a proportion or percentage, and EPA recommends a ceiling of 80% and a floor of 20%. A smaller RSC for drinking water exposure results in a lower regulatory standard, but implies that sources other than water contribute more significantly to exposure.

Presently, there is no inventory of all relevant sources of PFAS exposure to determine what proportion each source shares in an RSC for the general population. Several studies have characterized specific media such as dust, food (Kowalczyk et al., 2013; reviewed by EFSA, 2018) and breastmilk (previously discussed) and estimated the percentages of total exposure attributable to these sources; but no single study has merged these findings to estimate the reasonable and realistic RSC for drinking water.

In the absence of such data, the EPA provides a decision tree for identifying an appropriate RSC (replicated in Figure 1; EPA 2000). Following this process, NHDES determined:

- (Box 6 to 8a) *Yes, there are significant known sources of these PFAS other than drinking water*. As a result of their dispersion into the environment and lack of adequate removal from waste streams, there are known sources of PFAS that contribute to environmental exposures. This includes release into surface water and implications for fish and shellfish consumption (Fair et al., 2019), and the impacts of PFAS contamination of soil (Filipovic et al., 2015; Scher et al., 2018), dust (Fu et al., 2015; Winkens et al., 2018) and agriculture-related exposures (Nascimento et al., 2018; reviewed by Ghisi et al., 2019).

- (Box 8a to 8c) *Yes, there is some information to make a characterization of exposure*. As mentioned above, there is some data on environmental sources to make rough characterizations. Additionally, there is blood data from the National Health and Nutrition Examination Survey (NHANES) to estimate the general exposure of the U.S. population to PFAS. The NHANES data for blood levels of PFAS is assumed to reflect general exposure to all sources in the U.S. population, and is presumed to not reflect the results of excessively high exposures, relative to the proposed MCLs, due to contaminated drinking water as seen in the communities of Southern New Hampshire Pease Tradeport and Southern New Hampshire.
- (Box 8c to 13) *NHDES performed apportionment with a 50% ceiling and 20% floor for each of the assessed PFAS*. This apportionment was achieved using the EPA subtraction method (EPA 2000).

The subtraction method (EPA 2000) estimates an apportionment of the RSC is based on assumed knowledge of the background exposure. For PFAS, the subtraction method has been mathematically applied as follows (NJDWQI 2018; MDH 2018, 2019ab):

$$\text{Relative Source Contribution} = \frac{\text{Target serum level } \left(\frac{\text{ng}}{\text{mL}}\right) - \text{Reference or background population level } \left(\frac{\text{ng}}{\text{mL}}\right)}{\text{Target serum level } \left(\frac{\text{ng}}{\text{mL}}\right)} \times 100\%$$

The difference between the target serum level and the RfD is that the former is an internal blood concentration while the latter is the external amount of the chemical that could come from multiple sources. For each of the compounds, the target serum levels were: PFOA – 43.5 ng/mL, PFOS – 23.6 ng/mL, PFNA – 49.0 ng/mL and PFHxS – 46.3 ng/mL. The reference population serum level is meant to reflect a background level of exposure from the general population, not one that is highly exposed due to a specific environmental source such as drinking water. Using the NHANES average serum values, subtracting this background level from the target serum level (the maximum allowable level) results in a proportion that is presumably permissible for drinking water alone. Other sources including food, dust, treated consumer products (e.g., carpeting, cookware, food packaging, etc.) are assumed to be included in the reference or background population blood concentrations.

Using this approach with the NHANES 2013-2014 data for children ranging in age from 3 to 19 years (as reported in Daly et al., 2018), NHDES arrived at RSCs of 50% for PFOA, PFOS, PFNA and PFHxS. Unlike its initial proposal, NHDES selected the NHANES dataset over the use of NH-specific estimates. The NH-specific blood data was focused on communities whose primary exposure was associated with drinking water, and would therefore overestimate non-drinking water exposure sources if used to establish an RSC as initially proposed in January (NHDES, 2019). Thus, the NHANES dataset was deemed more appropriate to account for other non-drinking water sources of exposure. For an understanding of how the NHANES data compares to that collected from one of the highly-exposed communities in New Hampshire and the limitations of interpreting these findings, readers are referred to Daly et al. (2018).

Instead of using the general population (i.e., all ages), NHDES estimated RSCs based on the serum concentrations from those younger than 19 years of age (Table 4). As emphasized in several comments made to NHDES on its initial proposal, the risk assessment needs to consider current information for children. Since the phase out of certain PFAS, but not all, the national average serum levels have declined suggesting some reduction of background exposure. Given the emphasis of the RME on infancy

and early childhood, NHDES determined it was appropriate to derive the RSC with specific consideration of this group. All of the values for PFOA, PFOS, PFNA and PFHxS were at or above 48.3%, therefore NHDES opted for an RSC of 50%.

NHDES acknowledges that the use of the general NHANES estimates that includes adults with historically high exposures results in similar or more restrictive RSC values; especially for PFOS. However, the RME scenarios for the proposed MCLs indicate that the predicted serum level for the 95th percentile of adult water consumers is approximately equal to or below the 20% RSC and therefore sufficiently protective after considering the context of the national dataset. Furthermore, the cap of 50% despite calculated higher RSCs for each of these accounts for the unknown and novel sources of PFAS exposure, as well as the higher serum levels of PFAS found in New Hampshire's highly-exposed communities.

Table 4. Relative Source Contribution Estimates. Various relative source contribution (RSC) values resulting from use of the EPA subtraction method (EPA 2002) in combination with available serum data for the geometric mean (GM) and 95th percentile from the NHANES 2013-2014 dataset, as reported in Daly et al. (2018).

Reference Population	Reference Serum level (ng/mL)	Target Serum Level (ng/mL)	Resulting RSC Allotment for Drinking Water (%)
PFOA			
3-5 year olds (GM)	2.00	43.5	95.4
6-11 year olds (GM)	1.89	43.5	95.7
12-19 year olds (GM)	1.66	43.5	96.2
3-5 year olds (95th percentile)	5.58	43.5	87.2
6-11 year olds (95th percentile)	3.84	43.5	91.2
12-19 year olds (95th percentile)	3.47	43.5	92.0
PFOS			
3-5 year olds (GM)	3.38	24.0	85.9
6-11 year olds (GM)	4.15	24.0	82.7
12-19 year olds (GM)	3.54	24.0	85.3
3-5 year olds (95th percentile)	8.82	24.0	63.3
6-11 year olds (95th percentile)	12.40	24.0	48.3
12-19 year olds (95th percentile)	9.30	24.0	61.3
PFNA			
3-5 year olds (GM)	0.76	49.0	98.4
6-11 year olds (GM)	0.81	49.0	98.3
12-19 year olds (GM)	0.60	49.0	98.8
3-5 year olds (95th percentile)	3.49	49.0	92.9
6-11 year olds (95th percentile)	3.19	49.0	93.5
12-19 year olds (95th percentile)	2.00	49.0	95.9
PFHxS			
3-5 year olds (GM)	0.72	46.3	98.4
6-11 year olds (GM)	0.91	46.3	98.0
12-19 year olds (GM)	1.27	46.3	97.3
3-5 year olds (95th percentile)	1.62	46.3	96.5
6-11 year olds (95th percentile)	4.14	46.3	91.1
12-19 year olds (95th percentile)	6.30	46.3	86.4

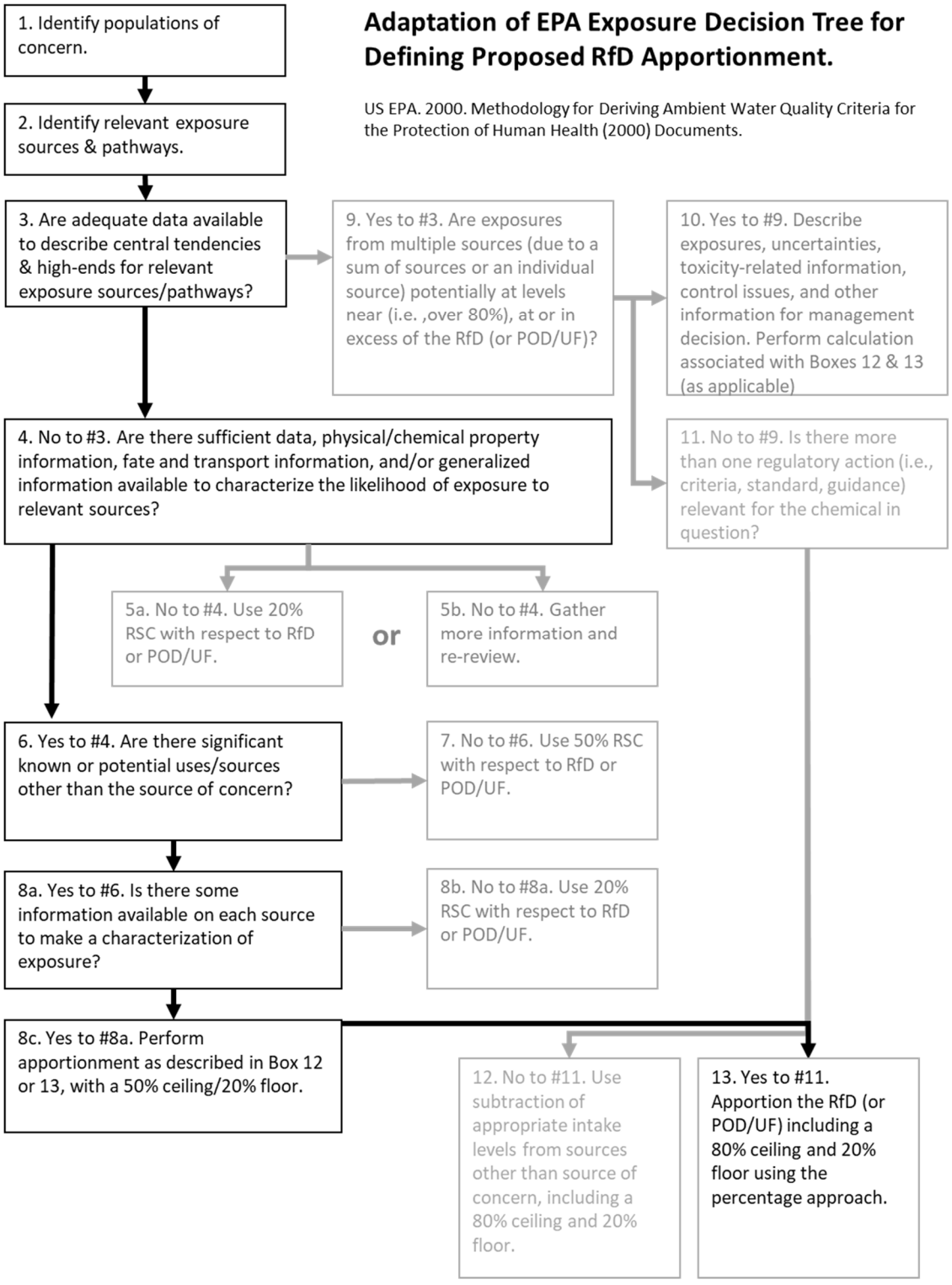

Figure 1. Adaptation of EPA decision tree (EPA, 2000) for determining the RSC. Black boxes, text and arrows outline the decision process used by NHDES to arrive at the subtraction method for PFAS with a 50% ceiling. The target serum level is a population assessment value, *not clinical*, from the derivation of the RfDs, detailed in Section III.

Section V. Discussion of the MCLs proposed by NHDES

Based on the previously described RfDs, exposure considerations and application of the transgenerational model (Figure 2), the proposed maximum contaminant levels (MCLs) are:

- **12 ng/L for Perfluorooctanoic acid, or perfluorooctanoate (PFOA)**
- **15 ng/L for Perfluorooctane sulfonic acid, or perfluorooctane sulfonate (PFOS)**
- **11 ng/L for Perfluorononanoic acid, or perfluorononanoate (PFNA)**
- **18 ng/L for Perfluorohexane sulfonic acid, or perfluorohexane sulfonate (PFHxS)**

These health-based values are intended as health-protective limits against the chronic health effects for a through-life exposure. The primary associated health outcomes are hepatotoxicity and changes in lipid metabolism (PFOA and PFNA), suppressed immune response to vaccines (PFOS) and impaired female fertility (PFHxS). Secondary associated health effects that are expected to be less sensitive are changes in thyroid and sex hormone levels, early-life growth delays, changes in cholesterol levels and biomarkers of liver function, neurobehavioral effects, and a possible risk for certain cancers (i.e., testicular and kidney).

Modeled Exposure Results

Figure 2 shows the model result for predicted serum concentrations at the proposed MCL for each PFAS. The exposure starts at birth with the assumption that the mother is at a steady-state serum level from consumption of water at the modeled drinking water concentration. The solid blue line represents the highest exposure in the RME model, showing the predicted serum level for a breastfed infant who consumes breastmilk and water at the 95th percentile ingestion rates throughout life and is born to and breastfeeds from a mother with a similar water consumption rate. The solid green line represents the predicted serum level for a formula-fed infant who consumes formula (reconstituted with water at the MCL) and water at the 95th percentile ingestion rates throughout life and is born to a mother with a similar water consumption rate. The dashed lines represent the predicted serum concentrations for individuals at the central tendency or average breastmilk, formula and water ingestion rates.

There is a clear spike in predicted serum levels of breastfed infants due to the aforementioned transfer efficiencies of PFAS into breastmilk. For infants, this is concerning due to the potential for hand-to-mouth behaviors in later infancy that have been shown to contribute to PFAS exposure in children of this age (Trudel et al., 2008). Because of these potential exposures and the suspected health impacts on early development, NHDES selected an MCL value that does not allow the predicted infant serum level to exceed the 50% RSC of the RfD or target serum level. It is true that the central tendency consumers fall well below this threshold. However, it has been shown that when considering variants on the RME scenarios the use of the 95th percentile ingestion rate is adequately protective for other factors (e.g., higher breastmilk transfer efficiencies or longer half-life estimates) (Goeden et al., 2019).

The long half-lives of these compounds result in significantly elevated serum levels peaking at the cessation of breastfeeding and continuing through the remainder of childhood. While the predicted steady-state concentrations for adults or formula-fed infants would allow less restrictive MCLs, breastfed children could potentially exceed the RfD due to other sources such as dust (Winkens et al., 2018) or foods and food packaging (D'eon et al., 2009; reviewed by EFSA, 2018). This point further emphasizes the appropriateness of the 50% cap on the RSC as selected by NHDES.

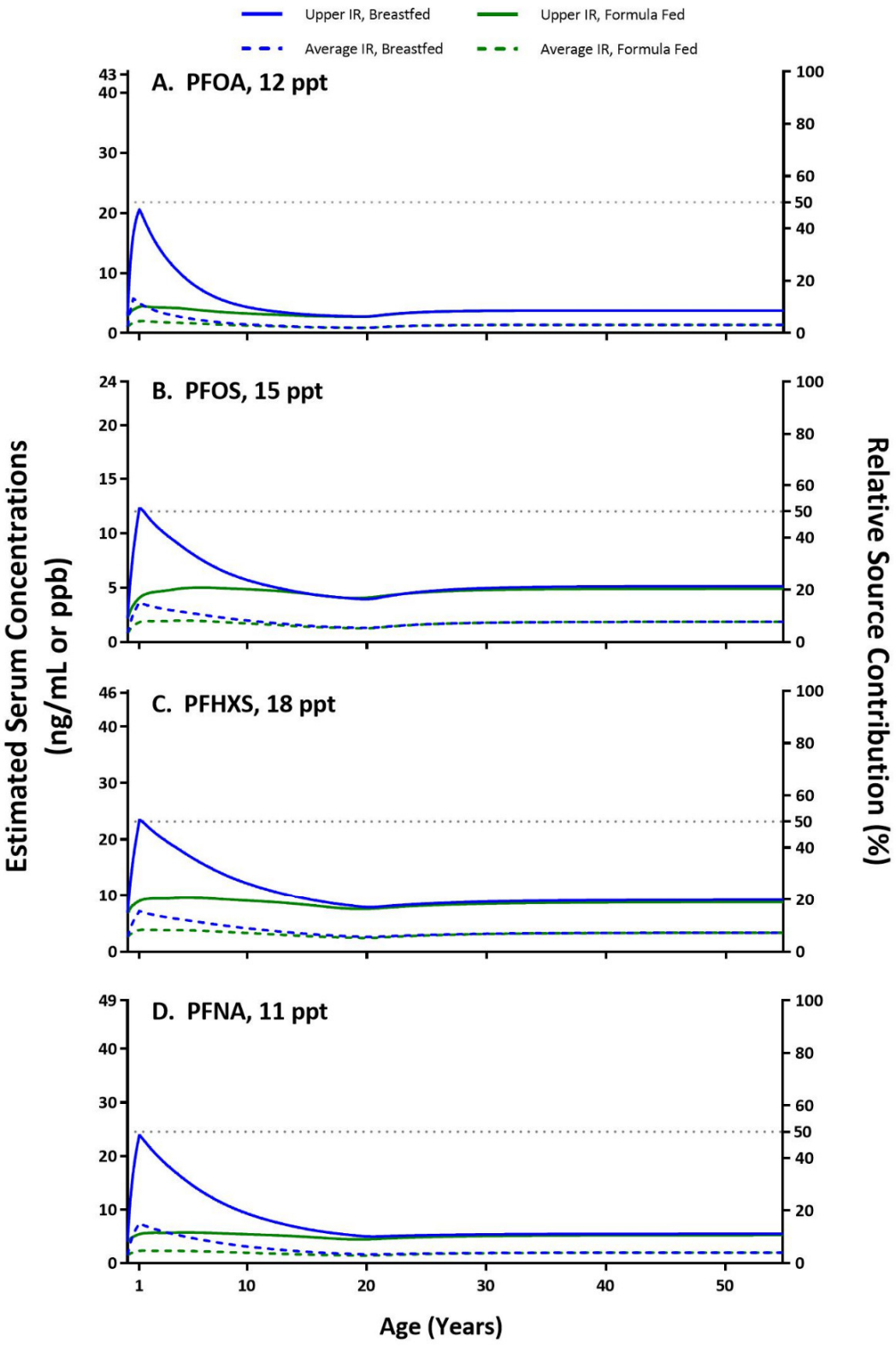

Figure 2. Predicted serum PFAS concentrations in response to upper (95th percentile) and average (mean) water ingestion rates (IR) at the proposed MCLs. Blue lines indicate results for breastfed infants with 12 months exclusive breastfeeding, and green lines indicate results for formula-fed infants. Solid lines represent upper IRs and dashed lines indicate average (mean) IRs. Estimates made using the model described in Goeden et al. (2019).

Using the proposed MCL values for each compound, serum concentrations attributable to drinking water can be estimated for an individual across various life stages (adapted from Figure 2). For newborns (at birth), the estimated drinking water contribution to serum concentrations for the 95th percentile consumer would be: 2.9 ng/mL for PFOA, 2.2 ng/mL for PFOS, 4.0 ng/mL for PFNA and 6.9 ng/mL for PFHxS. The model does not predict fetal tissue concentrations, so the predicted at-birth values represent the aforementioned placental transfer efficiencies. The predicted drinking water contribution to serum concentrations for the 95th percentile breastmilk consumer (at the end of 1 year of exclusive breastfeeding) would be: 20.6 ng/mL for PFOA, 12.4 ng/mL for PFOS, 25.1 ng/mL for PFNA and 23.5 ng/mL for PFHxS. Adults at steady state following constant water consumption at the 95th percentile are predicted to have drinking water contributions of PFAS equal to or less than: 3.8 ng/mL for PFOA, 5.1 ng/mL for PFOS, 5.7 ng/mL for PFNA and 9.2 ng/mL for PFHxS.

As a point of caution in interpretation, the previously described results assume no fluctuation from the 95th percentile drinking water consumption rate across an individual lifespan. That is to say, the 95th percentile consumer remains the 95th percentile consumer every day. These estimates include several conservative and protective assumptions, such as the use of the 95th percentile of drinking water ingestion rates (adjusted for body weight) throughout life, not the average water consumer or fluctuations between these tendencies. Additionally, the modeled outputs may not reflect individual variations in biology throughout life (Fàbrega et al., 2014; Worley et al., 2017) and are intended for population-level exposure assessment. However, as described by Goeden et al. (2019), this fit-for-purpose tool provides important insight into exposures during critical life stages of development. Further development and refinement of multi-compartment models will certainly prove useful for future risk assessments of these and other PFAS.

The proposed MCLs are predicted to result in a modest increase of serum concentrations due to drinking water levels; but, as argued by Post et al. (2017), such increases relative to background are preferred over the significantly larger serum levels that are predicted for the previously proposed MCLs (NHDES, 2019) or the EPA lifetime health advisories (EPA, 2016ab). Based on current evidence, this level of exposure is expected to be sufficiently health protective relative to current background levels reported in populations of concern, such as children and adolescents (Table 4).

Limitations and uncertainties

As with any risk assessment, this process was subject to uncertainty and limitations. Limitations included recommendation of individual versus group-based MCLs for PFAS, and consideration of background exposure using the RME scenarios described in Section IV. A major uncertainty was quantifying the exact risks of disease incidence for each compound, which is also a significant challenge for quantifying, or monetizing, the benefits of the proposed MCLs.

A limitation to the present assessment is that the transgenerational model's RME scenarios focus on the predicted impact of drinking water exposure, not other background sources of exposure. In general, there is a downward trend for the background levels of most measured PFAS based on the NHANES data. NHDES considered this with its use of the NHANES data to derive and apply a 50% RSC for each compound. Although PFOA and PFOS were recently phased out by most U.S. manufacturers, there remains potential for exposure to these and other PFAS from imported products or the degradation of

precursors into PFOA or PFOS in the environment. Nevertheless, the appropriate level of conservatism applied in the assumptions of drinking water ingestion rates and RSC provide reasonable protection.

At this time, NHDES is not recommending a class-based approach to regulation of these compounds. This is a limitation of the present risk assessment given the considerable number of PFAS detected in the environment and used in commerce. However, individual assessment of each compound found each one to have relatively unique toxico-dynamic and –kinetic properties based on consideration of existing animal toxicity and human data. Despite similarity in the range of the proposed MCLs for these 4 PFAS, it is likely that future individual assessments, using current EPA methodology, of shorter carbon chain PFAS will result in higher drinking water values for shorter carbon chain compounds as a result of shorter half-lives. Given these considerations, it was determined that a class based approach was not advisable at this time. Should other state agencies or the U.S. EPA identify science-based methods for group regulation that account for some of the unique properties of these compounds, NHDES will consider this approach.

Currently, there is uncertainty to quantifying the health risks associated with exposure to PFOA, PFOS, PFNA, PFHxS and other PFAS. A growing number of epidemiological and animal toxicity studies are adding to the body of evidence for the biological activity and health outcomes associated with these contaminants. However, the exact nature of PFAS-related health hazards remains elusive due to a variety of factors including, but not limited to: a limited understanding of the toxicological mechanism of action, their occurrence world-wide and lack of control (i.e., PFAS-free) populations to compare health outcomes against, lack of long-term studies despite decades of use, and co-exposure with other PFAS and other environmental contaminants. Additional research is critically needed to address this issue and better characterize and quantify the risks associated with PFAS.

Conclusions

The lower MCLs proposed in this report are primarily due to consideration of the elevated serum levels predicted for infants and young children under a reasonable maximum exposure scenario. At the initially proposed values, these spikes in infant blood levels of PFAS would result in unacceptable reductions in the margin of exposure from infancy through childhood due to the unique properties of PFAS. Their capacity to transfer through breastmilk combined with relatively long half-lives of each compound merits the use of novel methods (i.e., Goeden et al., 2019) to provide a more accurate assessment of exposure. This is not a recommendation against breastfeeding for women who are currently breastfeeding or plan to breastfeed as the benefits of breastfeeding are very well-defined relative to the potential risk associated with PFAS. NHDES recommends these MCLs to afford adequate long-term health protection of the population based on its assessment of these four PFAS.

The human health impacts of PFAS is a continuously evolving area of scientific research, and is expected to continue changing in the future. The assessments made by NHDES are based on currently available information but recognizes that science is a process, not an outcome. Future assessments of these and other PFAS compounds may result in higher or lower health protective values based on the best available science at the time. NHDES will continue to review emerging information as a part of its ongoing efforts to understand the impacts of PFAS contamination across New Hampshire.

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June 25, 2019

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Concord, NH 03302

Dear Mr. Freise:

I have reviewed at your request the *New Hampshire Department of Environmental Services Technical Background for the June 2019 Proposed Maximum Contaminant Levels (MCLs) for Perfluorooctanoate (PFOA), Perfluorooctane sulfonate (PFOS), Perfluorononanoate (PFNA) and Perfluorohexane Sulfonate (PFHxS).* This document was prepared by Jonathan Ali, Ph.D., Mary Butow, M.S., and David Gordon, M.S., of the Permitting & Environmental Health Bureau and is dated June 7, 2019. This document updates drinking water standards for PFOA, PFOS, PFNA, and PFHxS originally proposed by the Department on December 31, 2018, taking into consideration recently published studies, as well as public comments on the original proposed Maximum Contaminant Levels (MCLs). Because the updated analysis is intended to be responsive to public comments, I have also read the public comments on the original proposed MCLs as part of my review.

All of the proposed MCLs are risk-based, meaning that the numerical value of the MCL is determined solely by what is determined to be a safe dose limit for the chemical in drinking water. Typically, risk-based criteria (i.e., concentration limits) for drinking water are derived using rather simplistic equations that combine some expression of the safe dose of the chemical with assumptions regarding drinking water consumption rate. The drinking water consumption rate is usually derived from an upper percentile value for a segment of the population [often, all adults]. Poly- and perfluoroalkyl substances (PFAS) are among the few environmental contaminants for which significant data are available regarding blood concentrations associated with adverse health effects, both in humans and animal models used in toxicity studies. This information, combined with information on the toxicokinetics of PFAS in humans and animals, allows safe levels of exposure to be based on blood concentrations and drinking water consumption that would produce those blood concentrations. Although this requires a more complex analysis than traditional methods for deriving MCLs, it provides a more rigorous and scientifically defensible basis for extrapolating dose-response relationships for toxicity observed in animals to humans.

The New Hampshire Department of Environmental Services (NHDES) and others have taken this approach for development of risk-based standards for PFAS in drinking water, but NHDES has taken it a step further. There is concern for PFAS exposure in infants, not only because some PFAS have been shown to produce adverse developmental effects in animals, but also because infants may have the highest blood concentrations of any life stage due to their small body weight and intake from

breastmilk or from formula made from PFAS contaminated water. This means that infants may be more susceptible to not only developmental effects from PFAS, but to other PFAS effects as well. To address explicitly potential risks from early life exposure to the four PFAS for which MCLs are proposed, NHDES has used a model recently developed by the Minnesota Department of Health (Goeden et al. 2019) that predicts blood concentrations of PFAS beginning at birth and extending into adulthood. The predicted blood concentrations of PFOA, PFOS, PFNA, and PFHxS using this model show clearly the importance of considering early life drinking water exposures, both direct and indirect, and allow demonstration that the proposed MCLs are protective at all life stages. This is a significant advance over the previous derivation of PFAS MCLs by the Department, and over most of the drinking water standards for PFAS developed elsewhere.

A critical aspect of the calculation of risk-based MCLs for PFAS is the derivation of safe dose limits, or reference doses. Development of these reference doses requires identification of a critical effect and study that provides dose-response information for that effect, determining a no-effect level from the data, selection of uncertainty factors to insure a health protective value in the face of limitations in the available data, and identifying a human equivalent dose based upon the toxicokinetics of the chemical in humans. The proposed MCLs in the June 2019 document include refinements in the reference doses for PFOA, PFOS, PFNA, and PFHxS presented in the January 2019 report based on consideration of new information, new analyses, and public comments. These include a change in critical effect (PFOS), total uncertainty factor (PFNA), modeling of toxicity data (PFHxS), and Dosimetric Adjustment Factor (PFOA, PFNA, PFHxS) to estimate a human equivalent oral dose. The rationale for each of the changes is clearly articulated in the report and all are well justified scientifically, in my opinion. I should note that a colleague, Dr. Leah Stuchal, and I collaborated with Dr. Ali of NHDES on the dose-response analysis for PFHxS presented in this report.

A number of public commenters took issue with one or more of the uncertainty factors selected for the derivation of initial reference doses for PFOA, PFOS, PFNA, and PFHxS in the January 2019 document. The selection of uncertainty factors for these and other chemicals is undoubtedly important as they have a direct impact on the risk-based drinking water standards that are derived. I have served as a peer reviewer for the U.S. EPA for many years on topics including proposed reference doses for several chemicals, primary through service on the Chartered Science Advisory Board and the Chemical Assessment Advisory Committee. Selection of uncertainty factors involves a good deal of scientific judgment, and despite guidance from the U.S. EPA on how uncertainty factor values should be selected in a given situation, it is often difficult to get complete agreement among objective scientists. So the number, and sometimes contradictory nature, of suggestions among public commenters regarding choices of uncertainty factors is not surprising. As with other aspects of reference dose development, I found the rationale for selection of uncertainty factors presented in the current document to be clear and consistent with U.S. EPA guidance. The comparison in Table 2 of uncertainty factors selected by NHDES with those chosen by other agencies that have developed reference doses for these chemicals shows that they are in line with judgments made by other regulatory scientists.

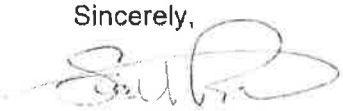
Another issue raised by public commenters is the overall level of conservatism inherent in the originally proposed MCL values, with comments offered in both directions — too conservative or not conservative enough. Concern that the initial MCLs were not

sufficiently conservative in that they were not clearly protective of infants has been addressed by NHDES through use of modeling that includes breastfed and formula-fed infants. For other, more general aspects of MCL derivation, NHDES is reasonably transparent in its attempts to strike the right balance of conservatism — conservative enough to provide confidence that the proposed MCLs are health protective without excessive conservatism that undermines the credibility of the results. Conservative choices are identified as such, and are used in combination with central tendency values for other inputs in an effort to create upper end, but not unrealistic estimates of risk. In my opinion, the level of conservatism achieved is entirely consistent with current risk assessment practice by state and federal environmental agencies.

As noted in the report, study of the potential health impacts of PFAS exposure is a rapidly changing field, and new information is becoming available almost continuously. Nevertheless, environmental regulatory agencies must often capture existing science as best they can and move forward with environmental criteria. Overall, I found the derivation of the MCLs proposed in the Technical Background document to be clearly described and scientifically sound, taking advantage of the most recent data and technical approaches.

The opinions expressed in this review are solely my own and do not necessarily reflect those of my employer, the University of Florida.

Sincerely,



Stephen M. Roberts, Ph.D.

Reference cited:

Goeden; HM, Greene CW, Jacobus JA. A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance. J. Expos. Sci. Environ. Epi. 29:183-195, 2019.