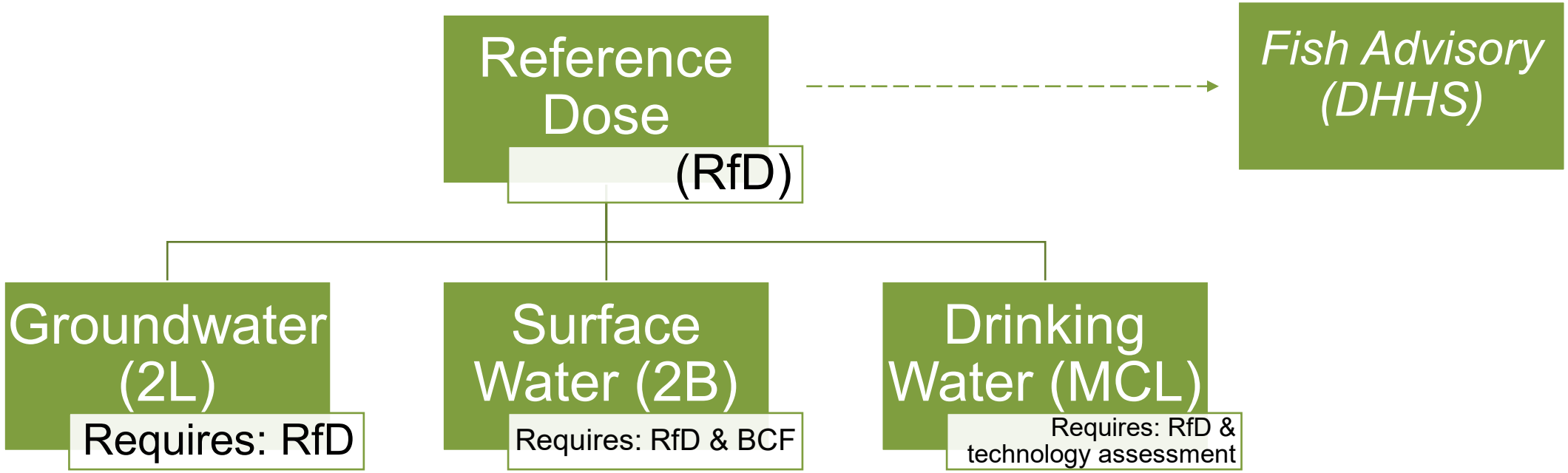
April 6, 2023

PFAS in NC – Next PFAS for Toxicological Evaluation

Frannie Nilsen, PhD
DEQ Environmental Toxicologist

The Important of Reference Doses in NC Standard Development



PFAS in North Carolina

PFBS	PFHxS	PFHpA	PFMOAA	PMPA	PFOS
PFOA	PFO2HxA	PFBA	PEPA	PFO3OA	PFHxA
PFNA	GenX	PFO4DA	PFO5DA	HydroEVE	PFDA
		PFPeA	Nafion BPs		

PFAS in North Carolina

EPA PFAS RoadMap Compounds

PFBS	PFHxS	PFOS
PFOA	PFBA	PFHxA
PFNA	GenX	PFDA

Non-EPA PFAS RoadMap Compounds

PFHpA	PFMOAA	PMPA
PFO2HxA	PEPA	PFO3OA
PFO4DA	PFO5DA	HydroEVE
PFPeA	Nafion BPs	

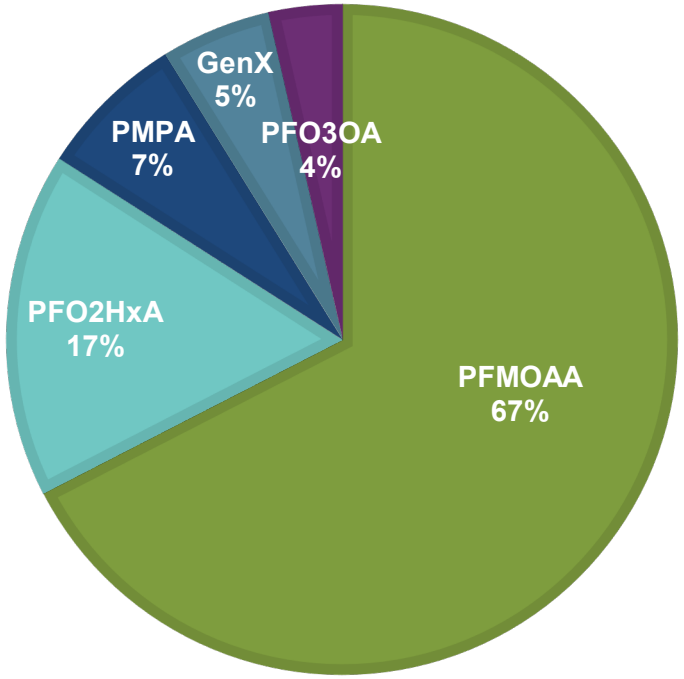
Department of Environmental Quality

DEQ's Regulatory Priorities – Chemours PFAS

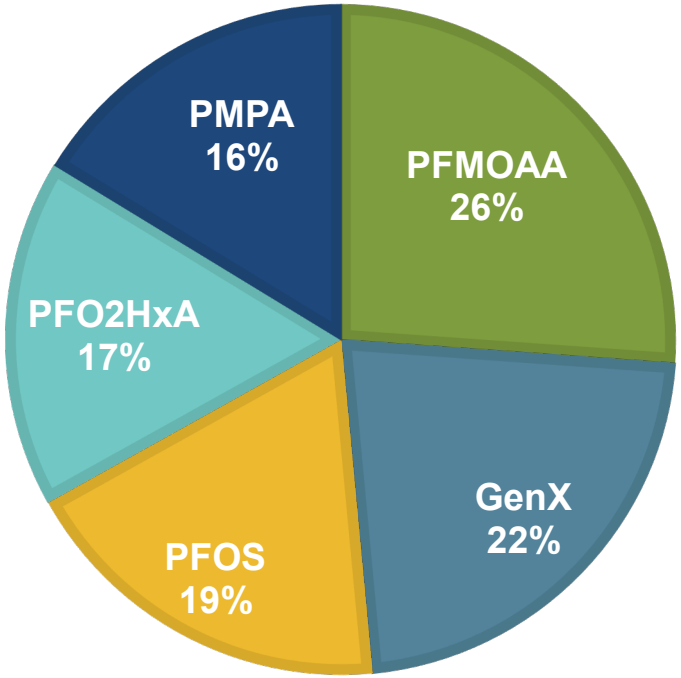
The Consent Order PFAS Compounds are unique to NC & EPA is not evaluating them.

Top 5 PFAS in Surface water bodies

HUSKE DAM BOAT RAMP

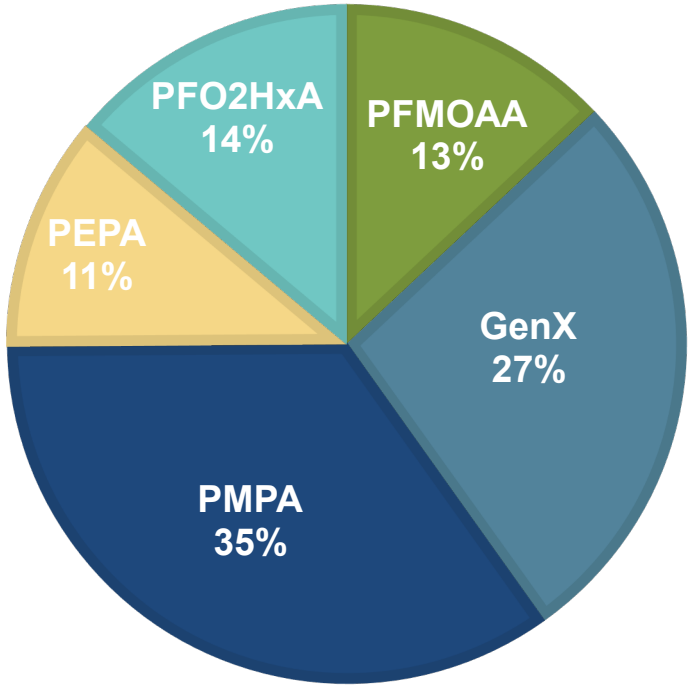


DOWNSTREAM CFR



Top 5 PFAS in well water

RESIDENTIAL WELL WATER



DEQ's Priority PFAS Group 1

Non-EPA PFAS RoadMap Compounds

PFHpA	PFMOAA	PMPA
PFO2HxA	PEPA	PFO3OA
PFO4DA	PFO5DA	HydroEVE
PFPeA	Nafion BPs	

DEQ's Priority PFAS Group 1

- PFMOAA
- PMPA
- PFO2HxA
- PEPA
- PFO3OA

- These are PFAS that are specific to NC and the waterbodies sampled in the lower Cape Fear region.
- There is not much existing toxicity information for these PFAS.

Priority PFAS – Group 1 – June 2022

- There is not much existing toxicity information for these PFAS.

PFAS Compound	Exposure Data	Toxicology References	Human Biomonitoring Studies
PFMOAA	DEQ, NCSU	2 (1,2)	3 (3,4,5)
PMPA	DEQ, NCSU	0	2 (4,5)
PF02HxA	DEQ, NCSU	0	2 (4,5)
PEPA	DEQ, NCSU	0	2 (4,5)
PFO3OA	DEQ, NCSU	0	2 (4,5)

Priority PFAS – Group 1 – April 2023

PFAS Compound	Exposure Data	Toxicology References	Human Biomonitoring Studies
PFMOAA	DEQ, NCSU	2 (1,2)	3 (3,4,5)
PMPA	DEQ, NCSU	0	2 (4,5)
PFO2HxA	DEQ, NCSU	1 (7)	2 (4,5)
PEPA	DEQ, NCSU	0	2 (4,5)
PFO3OA	DEQ, NCSU	3 (6-8)	2 (4,5)

- Automating DEQ's PFAS-specific searches has yielded more comprehensive retrieval of publications than manual searches

PFO3OA Toxicology Publications

1. Comparative Hepatotoxicity of Novel PFOA Alternatives (Perfluoropolyether Carboxylic Acids) on Male Mice

2. Perfluoropolyether carboxylic acids (novel alternatives to PFOA) impair zebrafish posterior swim bladder development via thyroid hormone disruption

3. Drinking Water-Associated PFAS and Fluoroethers and Lipid Outcomes in the GenX Exposure Study.

PFO3OA – Toxicology Studies' Review Plan

- Review publications in detail and summarize the key findings
- Evaluate methodology and rank quality of data following published quality metric
- Present key findings and quality ranking to the Board for feedback and recommendations moving forward

PFO3OA Toxicology Publication #1 – Guo et al. 2019

Environmental Science & Technology

Article

Cite This: *Environ. Sci. Technol.* 2019, 53, 3929–3937

pubs.acs.org/est

Comparative Hepatotoxicity of Novel PFOA Alternatives (Perfluoropolyether Carboxylic Acids) on Male Mice

Hua Guo,[†] Jinghua Wang,[†] Jingzhi Yao,[†] Sujie Sun,[†] Nan Sheng,[†] Xiaowen Zhang,[†] Xuejiang Guo,[§] Yong Guo,[‡] Yan Sun,[‡] and Jiayin Dai*[,†]

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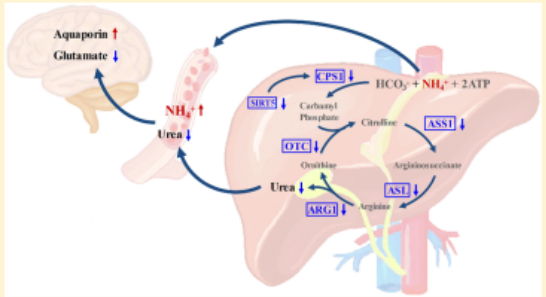
Supporting Information

ABSTRACT: As novel alternatives to perfluorooctanoic acid (PFOA), perfluoropolyether carboxylic acids (multiether PFECAs, $CF_3(OCF_2)_nCOO^-$, n = 2–4) have been detected in various environmental matrices; however, public information regarding their toxicities remains unavailable. To compare the hepatotoxicity of multiether PFECAs (e.g., PFO2HxA, PFO3OA, and PFO4DA) with PFOA, male mice were exposed to 0.4, 2, or 10 mg/kg/d of each chemical for 28 d, respectively. Results demonstrated that PFO2HxA and PFO3OA exposure did not induce marked increases in relative liver weight; whereas 2 and 10 mg/kg/d of PFO4DA significantly increased relative liver weight. Furthermore, PFO2HxA and PFO3OA demonstrated almost no accumulation in the liver or serum; whereas PFO4DA was accumulated but with weaker potential than PFOA. Exposure to 10 mg/kg/d of PFO4DA led to 198 differentially expressed liver genes (56 down-regulated, 142 up-regulated), with bioinformatics analysis highlighting the urea cycle disorder. Like PFOA, 10 mg/kg/d of PFO4DA decreased the urea cycle-related enzyme protein levels (e.g., carbamoyl phosphate synthetase 1) and serum ammonia content in a dose-dependent manner. Both PFOA and PFO4DA treatment (highest concentration) caused a decrease in glutamate content and increase in both glutamine synthetase activity and aquaporin protein levels in the brain. Thus, we concluded that PFO4DA caused hepatotoxicity, as indicated by hepatomegaly and karyolysis, though to a lesser degree than PFOA, and induced urea cycle disorder, which may contribute to the observed toxic effects.



Brief Summary:

- Male mice were exposed to 0.4, 2, or 10 mg/kg/d of PFO3OA for 28 days.
- Results demonstrated that PFO2HxA and PFO3OA exposure did not induce marked increases in relative liver weight;
  - whereas 2 and 10 mg/kg/d of PFO4DA significantly increased relative liver weight.

NORTH CAROLINA Department of Environmental Quality

PFO3OA Toxicology Publication #2 – Wang et al. 2020

Environment International 134 (2020) 105317

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Perfluoropolyether carboxylic acids (novel alternatives to PFOA) impair zebrafish posterior swim bladder development via thyroid hormone disruption

Jinxing Wang[a,1], Guohui Shi[a,1], Jingzhi Yao[a], Nan Sheng[a], Ruina Cui[a], Zhaoben Su[b], Yong Guo[b], Jiayin Dai[a,*]

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ARTICLE INFO

Keywords:
Perfluoropolyether carboxylic acids
Swim bladders
Thyroid disruptors
Developmental toxicity
Zebrafish
Perfluorooctanoic acid

ABSTRACT

Perfluoropolyether carboxylic acids (PFECAs, $CF_3(OCF_2)_nCOO^-$, n = 2–5) are novel alternatives to perfluorooctanoic acid (PFOA) and are widely used in industrial production. However, although they have been detected in surface water and human blood, their toxicities on aquatic organisms remain unknown. We used zebrafish embryos to compare the developmental toxicities of various PFECAs (e.g., perfluoro (3,5,7-trioxaoctanoic) acid (PFO3OA), perfluoro (3,5,7,9-tetraoxadecanoic) acid (PFO4DA), and perfluoro (3,5,7,9,11-pentaoxadodecanoic) acid (PFO5DoDA)) with that of PFOA and to further reveal the key events related to toxicity caused by these chemicals. Results showed that, based on half maximal effective concentrations (EC_{50}), toxicity increased in the order: PFO5DoDA > PFO4DA > PFOA > PFO3OA, with uninflated posterior swim bladders the most frequently observed malformation. Similar to PFOA, PFECA exposure significantly lowered thyroid hormone (TH) levels (e.g., T3 (3,5,3′-L-triiodothyronine) and T4 (L-thyroxine)) in the whole body of larvae at 5 d post-fertilization following disrupted TH metabolism. In addition, the transcription of UDP glucuronosyltransferase 1 family a, b (*ugt1ab*), a gene related to TH metabolism, increased dose-dependently. Exogeneous T3 or T4 supplementation partly rescued PFECA-induced posterior swim bladder malformation. Our results further suggested that PFECAs primarily damaged the swim bladder mesothelium during early development. This study is the first to report on novel emerging PFECAs as thyroid disruptors causing swim bladder malformation. Furthermore, given that PFECA toxicity increased with backbone OCF_2 moieties, they may not be safer alternatives to PFOA.

Brief Summary:

- Zebrafish embryos were used to compare the developmental toxicities of PFO3OA with PFOA
- Results showed that at [EC50], toxicity increased in the order:

  PFO5DoDA > PFO4DA > PFOA > PFO3OA,
  - uninflated posterior swim bladders the most frequently observed malformation.
- Exposure significantly lowered thyroid hormone (TH) levels and T4 in the whole body of larvae following disrupted TH metabolism.

PFO3OA Toxicology Publication #3 – Rosen et al. 2022

Research

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP11033.

Drinking Water–Associated PFAS and Fluoroethers and Lipid Outcomes in the GenX Exposure Study

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[5]Department of Public Health, East Carolina University (ECU), Greenville, North Carolina, USA
[6]Department of Pediatrics, Brody School of Medicine, ECU, Greenville, North Carolina, USA
[7]Department of Environmental and Occupational Health, University of California Irvine Public Health, University of California, Irvine, Irvine, California, USA

Background: Residents of Wilmington, North, Carolina, were exposed to drinking water contaminated by fluoroethers and legacy per- and polyfluoroalkyl substances (PFAS), such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), with fluoroether exposure occurring from 1980 to 2017. PFOA and PFOS have previously been associated with metabolic dysfunction; however, few prior studies have examined associations between other PFAS and lipid levels.

Objectives: We measured the association between serum fluoroether and legacy PFAS levels and various cholesterol outcomes.

Methods: Participants in the GenX Exposure Study contributed nonfasting blood samples in November 2017 and May 2018 that were analyzed for 20 PFAS (10 legacy, 10 fluoroethers) and serum lipids [total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides] and calculated non-HDL cholesterol. We estimated covariate-adjusted associations between quartiles of exposure to each of the PFAS measures (as well as the summed concentrations of legacy PFAS, fluoroethers, and all 10 targeted PFAS) and lipid outcomes by fitting inverse probability of treatment weighted linear regressions.

Results: In this cross-sectional study of 326 participants (age range 6–86 y), eight PFAS were detected in >50% of the population. For PFOS and perfluorononanoic acid (PFNA), non-HDL cholesterol was approximately 5 mg/dL higher per exposure quartile increase: [PFOS: 4.89; 95% confidence interval (CI): 0.10, 9.68 and PFNA: 5.25 (95% CI: 0.39, 10.1)], whereas total cholesterol was approximately 6 mg/dL higher per quartile [PFOS: 5.71 (95% CI: 0.38, 11.0), PFNA: 5.92 (95% CI: 0.19, 11.7)]. In age-stratified analyses, associations were strongest among the oldest participants. Two fluoroethers were associated with higher HDL, whereas other fluoroether compounds were not associated with serum lipid levels.

Discussion: PFNA and PFOS were associated with higher levels of total and non-HDL cholesterol, with associations larger in magnitude among older adults. In the presence of these legacy PFAS, fluoroethers appeared to be associated with HDL but not non-HDL lipid measures. https://doi.org/10.1289/EHP11033

Brief Summary:

- GenX Exposure Study blood samples analyzed for 20 PFAS and serum lipids.
- PFO3OA was one of the least frequently detected PFAS at 28% detection human samples
  - Was not evaluated further statistically.

PFO3OA – Toxicology Studies' Review Plan / Next Steps

- Review publications in detail and summarize the key findings
- Evaluate methodology and rank quality of data following published quality metric
- Present key findings and quality ranking to the Board for feedback and recommendations moving forward
  - **Planned for June 2023 meeting.**