Gen X and other Per- and Polyfluoroalkyl Substances (PFAS): A Look at Emerging and Legacy Contaminants and Human Health in NC’s Cape Fear River Basin

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Department of Pediatrics @ Brody School of Medicine
Liaison to NCSU’s Center for Human Health and the Environment
Per- and Polyfluoroalkyl substances (PFAS) the GenX Exposure Study

Objectives:

1. Describe what per- and polyfluoroalkyl substances (PFAS) are.
2. Identify health effects of PFAS exposure.
3. Describe East Carolina University’s role in, and the findings of, North Carolina State University’s GenX Study involving citizens in the Cape Fear River basin.
4. Apologies:
   - Alphabet soup
   - Unknowns
   - Disclosures/conflicts:
     - I have no conflicts to disclose

Fayetteville Works/Chemours facility
GenX Exposure Study Team

**NCSU**
- Jane Hoppin, PI
- Rob Smart
- Katy May
- Detlef Knappe
- Nadine Kotlarz

**ECU**
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**New Hanover County Health Department**
- Phillip Tarte
- Katelyn Matney

**Cape Fear River Watch**
- Kemp Burdette
- Madi Polera
- Amanda Boomershine
- Larry Cahoon

[Grant # 1R21ES029353](#)
[Grant # P30ES025128](#)
What are PFAS?

- **Per- and polyfluoroalkyl substances (PFAS)**
- A large family of compounds with ≥ carbon-fluorine bond
  - Man-made, first manufactured in 1940s
  - US EPA lists > 8,000 unique compounds
  - **Legacy**: PFAS with accumulating health data but may be phased out or use is decreasing
    - PFOA, PFOS
  - **Emerging**: PFAS which are being used as replacements but generally lack health data
    - **GenX** (Hexafluoropropylene oxide dimer acid)
      - May represent 70% of bioburden
  - **Long chain**: > 6 or 7 carbons
  - **Short chain**:
What are PFAS?

- Ubiquitous
  - US EPA estimates >600 are used in commercial & consumer products
  - “Forever Chemicals”
    - Carbon-fluorine bond very strong/resistant
    - Long half-lives
      - PFOA $t_{1/2}$ 3.8 yrs. humans
      - PFOS $t_{1/2}$ 5.4 yrs. humans > 41 yrs. in environment;
  - Measurable in virtually all people in developed countries
  - Found in wildlife and fish worldwide
    - Bioaccumulate/concentrate

Hexafluoropropylene oxide dimer acid HFPO-DA
Where are PFAS found?

- **Food**
  - Packaging, processing equipment, grown in contaminated soil and water
- **Commercial and household products**
  - Stain and water repellent fabrics, nonstick products (Teflon), polishes, waxes, paints, cleaning products
  - Pizza boxes, grease proof papers, air/dust
- **Drinking water**
  - Manufacturers, landfills, wastewater treatment plants
- **Workplace**
  - Fire-fighting foams (airports & military bases), various commercial processes
- **Living organisms**
  - Fish, mammals, humans, breast milk – accumulate up the food chain
Non-Occupational PFAS Exposure Pathways in Humans
Human Studies:
- Cross Sectional
- Longitudinal
- Interventional

Animal Studies
- Blinded Randomized Controlled Trials
- Longitudinal
- Cross Sectional

Evidence for Health Effects?
- Mechanistic Studies
Effects of 2X ↑ PFAS Concentration on Likelihood Non-Protective Antibody Titer (<0.1 IU/ml) vs. Diphtheria and Tetanus @ age 5 & 7.


<table>
<thead>
<tr>
<th>Td or Tdap or Tdap/IPV</th>
<th>DTaP</th>
<th>Blood for [PFAS]</th>
</tr>
</thead>
<tbody>
<tr>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

Gestation 3m 5m 12m 5y 5.2y 7.5 y

Blood for [PFAS]

| Maternal PFOS | /    | /    |
| Maternal PFOA | /    | /    |

PFOS at age 5 1.6* / 2.4 2.6

PFOA at age 5 / / 3.3* 4.2*

Antibody Specificity

Dip. Tet.
Response to Vaccination with Trivalent Influenza Vaccine by Quartile of Pefluorooctanoate (PFOA) Serum Concentration in Adults. Looker C et al. Tox Sciences 2014;138:76-88.

<table>
<thead>
<tr>
<th>PFOA Concentration</th>
<th>Titer rise post vaccination (GMT)</th>
<th>O.R. of seroprotection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type B</td>
<td>Type A H1N1</td>
</tr>
<tr>
<td>1st quartile (0.3 – 13.7 ng/ml)</td>
<td>49.5</td>
<td>476.2</td>
</tr>
<tr>
<td>2nd quartile (13.8 – 31.5 ng/ml)</td>
<td>46.0</td>
<td>352.2</td>
</tr>
<tr>
<td>3rd quartile (31.6 – 90 ng/ml)</td>
<td>43.6</td>
<td>306.3</td>
</tr>
<tr>
<td>4th quartile (90.4 – 2,140 ng/ml)</td>
<td>20.9</td>
<td>274.8</td>
</tr>
</tbody>
</table>

411 adults Mid Ohio C8 study. 2010/2011. Fluvirin (Novartis)
COVID-19 Severity in PFAS Exposure

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PFOA</td>
<td>0.99 (0.72 – 1.36)</td>
<td>0.90 (0.29 – 2.80)</td>
</tr>
<tr>
<td>PFOS</td>
<td>1.00 (0.96 – 1.04)</td>
<td>1.08 (0.94 – 1.24)</td>
</tr>
<tr>
<td>PFBA (Perfluorobutanoic Acid)</td>
<td>2.19 (1.39 - 3.46)</td>
<td>5.18 (1.29 – 20.72)</td>
</tr>
</tbody>
</table>

- N=323 adults in Denmark with PCR confirmed COVID-19 disease
- PFOA and PFOS found in 100% of subjects, PFBA detectable in 33% subjects
- PFBA (perfluorobutanoic acid) short chain (C4) short half life
- PFBA selectively accumulates in lungs
- Source?
  - Drinking water, seafood
  - Air pollution ... Chemours reported releasing **1,273 lbs. C4** and **11,276 lbs. C3** in 2016
# Effects of PFAS on Human Health

<table>
<thead>
<tr>
<th>Health Concern</th>
<th>C8 Study (n= 69,000)</th>
<th>Systematic Review 2018</th>
<th>Critical Review 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Hypercholesterolemia</td>
<td>Yes</td>
<td>Sufficient Evidence</td>
<td>Strong</td>
</tr>
<tr>
<td>*Thyroid disease/dysfunction</td>
<td>Yes</td>
<td>Inconsistent</td>
<td>Definitively</td>
</tr>
<tr>
<td>*NAFLD/NASH</td>
<td></td>
<td>Inconsistent</td>
<td>Emerging</td>
</tr>
<tr>
<td>*Suppressed immune response</td>
<td>(yes)</td>
<td>Limited Evidence</td>
<td>Strong</td>
</tr>
<tr>
<td>*Ulcerative colitis</td>
<td>Yes</td>
<td>Inconsistent</td>
<td>Probable</td>
</tr>
<tr>
<td>*Increased uric acid</td>
<td></td>
<td>Limited Evidence</td>
<td>Effect underestimated</td>
</tr>
<tr>
<td>*Decreased GFR</td>
<td></td>
<td>Limited Evidence</td>
<td>Likely causes</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td></td>
<td>Limited Evidence</td>
<td>Accumulating evidence</td>
</tr>
<tr>
<td>Impaired sperm motility &amp; no.</td>
<td></td>
<td>Inconsistent</td>
<td>Ample evidence</td>
</tr>
<tr>
<td>Time-to-pregnancy</td>
<td></td>
<td>Inconsistent</td>
<td>Increased (reversible)</td>
</tr>
<tr>
<td>Preeclampsia/PIH</td>
<td>Yes</td>
<td>No</td>
<td>Probably linked</td>
</tr>
<tr>
<td>*Lower birthweight</td>
<td>PFOS only</td>
<td>Prospective (reversible)</td>
<td></td>
</tr>
<tr>
<td>Kidney cancer</td>
<td></td>
<td>Limited Evidence</td>
<td>Accumulating evidence</td>
</tr>
<tr>
<td>Testicular cancer</td>
<td></td>
<td>Limited Evidence</td>
<td>Evidence</td>
</tr>
</tbody>
</table>

**Bold = widely accepted effect**,  * Effects can be seen in adults and children.
Legacy and Emerging Perfluorooalkyl Substances Are Important Drinking Water Contaminants in the Cape Fear River Watershed of North Carolina

Mei Sun, Elisa Arevalo, Mark Strynar, Andrew Lindstrom, Michael Richardson, Ben Kears, Adam Pickett, Chris Smith, and Detlef R. U. Knappe

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National Exposure Research Laboratory, U.S. Environmental Protection Agency Research Triangle Park, North Carolina 27711, United States
Cape Fear Public Utility Authority, Wilmington, North Carolina 28403, United States
Town of Pittsboro, Pittsboro, North Carolina 27312, United States
Fayetteville Public Works Commission, Fayetteville, North Carolina 28301, United States

Supporting Information

ABSTRACT: Long-chain per- and polyfluorooalkyl substances (PFASs) are being replaced by short-chain PFASs and fluorinated alternatives. For ten legacy PFASs and seven recently discovered perfluoroalkyl ether carboxylic acids (PFEEAs), we report (1) their occurrence in the Cape Fear River (CFR) watershed, (2) their fate in water treatment processes, and (3) their adsorbability on powdered activated carbon (PAC). In the headwater region of the CFR basin, PFEEAs were not detected in raw water of a drinking water treatment plant (DWTP), but concentrations of legacy PFASs were high. The U.S. Environmental Protection Agency’s lifetime health advisory level (70 ng/L) for perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) was exceeded in the inflow to the DWTP.
• Largest watershed in NC
• Supplies ~1.5M people with drinking water
Exposure to newly identified PFAS in drinking water

Fluorochemical Plant, Fayetteville, NC

Cape Fear River

upper

lower

Wilmington, NC

GenX
Utility can’t filter out chemical produced upriver at Fayetteville plant

By Vaughn Hagerly StarNews Correspondent

A 2000 aerial photo of Fayetteville Works on the Cumberland-Bladen county line. The site, home to several plants, one of which makes GenX, is about 100 miles upstream from Wilmington. [COURTESY OF THE FAYETTEVILLE OBSERVER]
What are perfluoroalkyl ether acids?

2002 PFOA (C8)...

2009 was replaced by GenX...

To manufacture Teflon products

Ether oxygen atom introduced into perfluorinated carbon chain
Not just GenX:

Family of Per- and Polyfluorinated Chemicals
GenX only a small fraction of contaminants in finished drinking water (Knappe et al).....
Public Response

Citizen Outrage led DEQ to respond
Forced the company to cease discharge to the Cape Fear River
NC DHHS Set a Health Goal
  71,000 ppt (ng/L)
  lowered to 140 ppt 3 weeks later

Late June 2017
GenX concentrations after fluorochemical manufacturer announced on 6/21/2017 that it stopped discharging GenX

![Graph showing GenX concentrations over time](image)

- **NC Health Goal**: 140 ng/L

The graph illustrates the GenX concentration over time in ng/L, with a notable decrease starting from 6/21/2017, indicating the manufacturer's discontinuation of discharging GenX.
CHHE hosts a Community Meeting

Meet the Scientists

Detlef Knappe, Engineer
Jamie DeWitt, Toxicologist

Announce the plan to submit a grant to NIEHS to answer:

Am I exposed?
What predicts exposure?
What are the health effects?

Late July 2017
GenX Exposure Study

Grant (time sensitive R21) submitted to NIEHS August 1, 2017
  Coordinating with Community Partners
  Developing IRB protocol – ECU reliance agreement with NCSU
  Hiring a Post-doc – Nadine Kotlarz (NCSU)

Funded November 1, 2017

Sample Collection November 10-12, 2017
Responding to Community Concerns

People want to know:
- Am I exposed?
- Is the chemical in my body?
- What are the health effects?

Challenges:
- What chemicals to look for?
- No analytical standards
- No half life information
- Little or no toxicology data
- No comparison populations
Research Questions

What chemicals will be present?
- Water
- Blood
- Urine

Biological half lives
- How long do these chemicals stay in the body?

How to best share results in a timely and community focused fashion?
Study Design

Enroll Wilmington residents on CFPUA water
Collect blood, urine, and drinking water
Analyze for GenX and other PFAS
Analyze serum for thyroid function, liver function, lipids
Report back results to community, individuals
Publish scientific results
Two CFPUA water treatment plants serve New Hanover County.

Sweeney water treatment plant (Cape Fear River)

Richardson water treatment plant (groundwater)
Eligibility

Served by Cape Fear Public Utility Authority for at least a year (since July 1, 2016)
>5 years old
Up to 4 people/household
English or Spanish speaking

Exclusions
  Pregnant
  HIV+, HepC+
Home and Clinic Visit

Home visit
collected tap water

Clinic visit
blood draw
urine sample collection
questionnaire
height and weight measurement

Nov 2017 at New Hanover County Health Department

May 2018 at MLK Center
Who Participated?

Sample Collection in November 2017 May 2018

344 individuals
289 adults
55 children (6-17 years)

Racially diverse
76% White
10% Black
9% Hispanic
5% Other
Community Involvement

Partnered with Cape Fear River Watch and New Hanover County Health Department

Community Science Advisory Panel

Provide input on community concerns
 Feedback on report back materials

Report back of study results to participants first

Community meetings to discuss results

Working with community to respond to results
What’s in the Water?
PFAS we tested for
(tinyurl.com/GenXstudy)

December 2017 – February 2018

“Legacy”
1. PFBA
2. PFPeA
3. PFHxA
4. PFHpA
5. PFOA
6. PFNA
7. PFDA
8. PFBS
9. PFHS
10. PFOS

Newly identified
11. GenX
12. Nafion byproduct 2
13. PFMOAA
14. PFO4DA
15. PFO3OA
16. PFO2HxA
17. 6:2 FTS
Water source for 198 participating households

194 households on CFPUA’s Cape Fear River water plant
Similar GenX concentrations in Sweeney treated water

GenX (ng/L)

- Groundwater source
- Cape Fear River source
- Treated water from Sweeney plant, Oct 2-Dec 5, 2017

NC health value (140 ng/L)
Individualized results

Average concentration (45 parts per trillion)

Participant’s sample

Health value

“Non-detect” Concentration (parts per trillion – ng/L)

April 2018
PFOA and PFOS in Nov 2017

Water Health Goals
- EPA: 70 ng/L
- NH – PFOS: 38 ng/L
- NH – PFOA: 70 ng/L
- NJ – PFOA: 14 ng/L
- NJ – PFOS: 13 ng/L
Other fluorochemicals were present

No pure chemicals were available (semi-quantitative)
Water Analysis Results

Provided information about what was happening at the tap for PFAS

Helped identify what chemicals to look for in blood.
Are PFAS in my body?
Half-life for PFAS in blood

<table>
<thead>
<tr>
<th>PFOA</th>
<th>8 Human</th>
<th>3.8 years</th>
</tr>
</thead>
</table>

Formula of PFOA: \( \text{C}_2\text{F}_7\text{O} = \text{OH} \)
# Half-life for PFAS in blood

<table>
<thead>
<tr>
<th>CFAS</th>
<th>Species</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFOA</td>
<td>Humans</td>
<td>3.8 years</td>
</tr>
<tr>
<td>PFOS</td>
<td>Humans</td>
<td>5.4 years</td>
</tr>
<tr>
<td>PFHxA</td>
<td>Humans</td>
<td>32 days</td>
</tr>
<tr>
<td>GenX</td>
<td>Monkeys</td>
<td>64-80 hours</td>
</tr>
<tr>
<td>GenX</td>
<td>Rats</td>
<td>23-90 hours</td>
</tr>
<tr>
<td>GenX</td>
<td>Mice</td>
<td>24-37 hours</td>
</tr>
</tbody>
</table>

*Best guess for GenX*
Liquid chromatography, high resolution mass spectrometry

May 2018-August 2018
# Standards for 23 PFAS

<table>
<thead>
<tr>
<th>Newly identified PFAS</th>
<th>Legacy PFAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GenX</td>
<td>PFBA</td>
</tr>
<tr>
<td>PFMOAA</td>
<td>PFPeA</td>
</tr>
<tr>
<td>PMPA</td>
<td>PFHxA</td>
</tr>
<tr>
<td>PEPA</td>
<td>PFHpA</td>
</tr>
<tr>
<td>PFO2HxA</td>
<td>PFOA</td>
</tr>
<tr>
<td>PFO3OA</td>
<td>PFNA</td>
</tr>
<tr>
<td>PFO4DA</td>
<td>PFDA</td>
</tr>
<tr>
<td>PFO5DoDA</td>
<td>PFBS</td>
</tr>
<tr>
<td>NVHOS</td>
<td>PFHxS</td>
</tr>
<tr>
<td>Nafion byproduct 1</td>
<td>PFOS</td>
</tr>
<tr>
<td>Nafion byproduct 2</td>
<td>6:2 FTS</td>
</tr>
<tr>
<td>Nafion byproduct 4</td>
<td></td>
</tr>
</tbody>
</table>
# Results for 14 PFAS

## Newly identified PFAS
- GenX
- PMPA
- PEPA
- PFO4DA
- PFO5DoDA
- Nafion byproduct 1
- Nafion byproduct 2

## Legacy PFAS
- PFHxA
- PFOA
- PFNA
- PFDA
- PFHxS
- PFOS
- 6:2 FTS

Nov 2018
Did we find GenX in blood?

No, we did NOT find GenX in blood
Method reporting limit: 2 ng/mL GenX

Sampled ~5 months after discharge stopped
50 ng/L GenX in water in Nov 2017
<10 ng/L GenX in water in May 2018

NC Dept of Health and Human Services
GenX NOT in blood from 30 people living near Chemours plant
Newly identified PFAS in Wilmington blood

1. Nafion byproduct 2 (99%)

2. PFO4DA (98%)

3. PFO5DoDA (87%)
Blood concentration (ng/mL)

How much was found?
Newly identified PFAS in Wilmington blood

1. Nafion byproduct 2 (99%)
2. PFO4DA (98%)
3. PFO5DoDA (87%)
4. Hydro-EVE (76%)
Analyzed archived blood samples for comparison

20 samples

Women, 30-44 years old

Raleigh, Durham, Chapel Hill

Collected 2008-2009
Newly identified PFAS are unique to Wilmington blood

In blood from our comparison group:

No Nafion byproduct 2
No PFO4DA
No PFO5DoDA
No Hydro-EVE
Compare Wilmington with US residents for legacy PFAS
How do we know about legacy PFAS in US residents?

Centers for Disease Control and Prevention’s National Health and Nutrition Examination Survey (NHANES)

PFOA, PFOS, PFHxS, PFNA, PFDA results are publicly available

1999-2000 survey (higher exposure)
2015-2016 survey (lower exposure)
PFOA in US residents’ blood

PFOA concentration (ng/mL)

US 1999 (n=1,591)

US 2015 (n=2,170)

Wilmington, NC (n=344)

PFOA concentration

54
PFOA in US residents’ blood

PFOA concentration (ng/mL)

US 1999 (n=1,591)  US 2015 (n=2,170)

- US 1999
  - 95%
  - 75%
  - 50%
  - 25%
  - 5%

- US 2015
  - 95%
  - 75%
  - 50%
  - 25%
  - 5%
Elevated PFOA in Wilmington blood, 2017

PFOA concentration (ng/mL)

US 1999 (n=1,591)  US 2015 (n=2,170)  Wilmington, NC 2017 (n=344)
Why is there elevated PFOA in Wilmington blood?

Historical exposure to high PFOA?
Limited data in lower Cape Fear, 2002-2009

2002 – Chemours began producing PFOA
2009 – Chemours replaced PFOA with GenX

8 years = 2 half lives = ¼ bioburden remaining

Continued exposure to low PFOA?
18 ng/L PFOA in Wilmington tap water
Upstream sources
Other elevated legacy PFAS in Wilmington
Do PFAS persist in blood?
Blood concentrations of newly identified PFAS decreased after six months

Median blood concentration for 44 participants (ng/mL)

- November 2017: Nafion byproduct 2 (4 ng/mL)
- May 2018: PFO4DA (5 ng/mL)
- May 2018: PFO5DoDA (1 ng/mL)
Legacy PFAS levels didn’t change over six months

Median blood concentration for 44 participants (ng/mL)
What does this all mean?

Wilmington residents exposed to poorly-understood PFAS from Chemours plant legacy PFAS with known health effects
Key findings in blood

Majority of blood samples had:
- Nafion byproduct 2
- PFO4DA
- PFO5DoDA
- Hydro-EVE

Higher legacy PFAS in Wilmington blood than US residents

Newly identified PFAS decreased in six months; legacy PFAS didn’t
Next steps

• Analyzing PFAS in urine
• Recruited 153 people who live around the chemical plant (Feb 2019)
  • Wristbands and dust samples, well water and tap water
• Resampled Wilmington Residents (Nov 2020)
• Health Outcome Analyses (lab analysis at VMC/ECU)
  • Lipid, BMI, Liver Function, Thyroid
    o Very high prevalence hypothyroidism in women in study cohort
    o Highest risk is in highest PFAS quartile
• Resample people around chemical plant 2021
• Move up-river to Pittsboro 2021
• Add assessment of PFAS on COVID-19 vaccine response
• Target total 1,200-1,400 subjects followed for 3-8 years with repeat sampling
Thank you:

GenX Exposure Study participants
Community Science Advisory Panel Members
Drs Hoppin, Knappe, Kotlarz and NCSU’s CHHE
Melissa Johnson ECU

Kotlarz N. et al. Measurement of Novel, Drinking Water-Associated PFAS in Blood from Adults and Children in Wilmington, North Carolina. *Environmental Health Perspectives* 2020;128:0770051-12. available @ [https://doi.org/10.1289/EHP6837](https://doi.org/10.1289/EHP6837)