GenX Health Studies and Health Advisories

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Public Health Role

- Determine whether compounds detected through environmental sampling could pose a risk to human health
- Provide health-based guidance on levels of exposure to such contaminants
- Conduct risk assessments and risk communication
Public Health Role – Drinking Water

• For private drinking water wells, PH provides
  – Information about the contaminant
  – Recommendations for use or treatment options
  – Recommendations for repeat sampling

• Guidance on public water supplies provided if requested from DEQ or local authorities
  – Assistance with health risk evaluations, use recommendations
Usual Sources for Health-Based Guidance

1. National regulatory standards (EPA)
2. State Standards (DEQ/Environmental Management Commission)
3. National health advisories or other health values (EPA, CDC)
4. Other governmental guidance
   - Standards from other states or countries
   - World Health Organization, European Union values
5. If guidance not available from 1–4, can consider establishing state-specific health goal
What is a Health Goal?

• Level of contamination below which no adverse health effects would be expected over a lifetime of exposure

• Calculated based on the most vulnerable population

• Non-regulatory, non-enforceable

• Change as new information becomes available
Health Goal: Requirements

• Must have sufficient health-related information
  – Animal studies *(required)*
  – Epidemiologic studies
  – Other laboratory studies

• Some health-related information not in public domain

• Health-related information often lacking for emerging compounds
GenX: Selected Sources of Health Data

• Oral toxicity studies conducted by Chemours and submitted for registration
• Peer-reviewed literature
Studies Submitted for Registration - 1

- Combined Chronic Toxicity/ Oncogenicity Study in Rats (Rae et al, Toxicol. Rep. 2015)

- Doses
  - Males: 0, 0.1, 1, and 50 mg/kg/day
  - Females: 0, 1, 50, and 500 mg/kg/day

- No Adverse Effect Level
  - NOAEL (male) = 1
  - NOAEL (female) = 50

- Basis for NOAEL
  - Males: Adverse liver effects; equivocal increases in pancreatic acinar and testicular interstitial tumors

Pod for initial DHHS calculations
Studies Submitted for Registration - 2

• Repeated Dose 28-Day Oral Toxicity Study in Mice (OECD Guideline 407)

• Doses
  – 0, 0.1, 3 and 30 mg/kg/day

• No Adverse Effect Level
  – **NOAEL (male) = 0.1**
  – NOAEL (female) = 3

• Basis for NOAEL
  – Adverse effects in the liver - single cell necrosis of hepatocytes and correlative increases in liver enzymes (male and female)

[POD for current DHHS provisional health goal](https://echa.europa.eu/registration-dossier/-/registered-dossier/2679/7/6/2/?documentUUID=7fde65ec-5187-42ef-8e05-58436035a555)
Studies Submitted for Registration - 3

• Reproduction/ Developmental Toxicity Screening Study in Mice (OECD Guideline 421)

• Doses
  – 0, 0.1, 0.5, and 5 mg/kg/day

• No Adverse Effect Levels
  – Reproductive Toxicity: Highest dose tested
  – Systemic Toxicity in Offspring: Body weight decrements in males and females in the 5 mg/kg/day group during the pre-weaning period
• Prenatal and Developmental Toxicity Study in Rats (OECD Guideline 414)

• Doses
  – 0, 10, 100, and 1000 mg/kg/day

• No Adverse Effect Level
  – NOAEL for maternal animals = 10
  – NOAEL for developmental toxicity = 10

• Basis for NOAEL
  – Maternal Animals: Maternal toxicity
  – Developmental Toxicity: Early deliveries and lower mean fetal weights
Peer-Reviewed Literature

• Evaluation of Immunomodulatory Effects in C57BL/6 Mice (Toxicological Sciences, 2017)

• Key findings:
  – T cell-dependent antibody response suppressed in females at 100 mg/kg
  – T lymphocyte numbers increased in males at 100 mg/kg
  – B lymphocyte numbers unchanged in both sexes
  – Females had less serum accumulation and higher clearance than males
  – Males had higher urine concentrations than females at all times and doses

Toxicity Studies of Other PFAS

• Considerable health data available regarding PFOA, PFOS, other legacy PFAS

• Limited toxicology data available for other emerging PFAS (PFECAs/PFESAs)

• Important to determine when and how inferences can be made based on data from other PFAS (i.e. “read-across”)
Health Goal: Calculations

- Health Goal = \( (Reference\ Dose \times Relative\ Source\ Contribution \times Body\ Weight) \div Intake\ Rate \)

- Reference dose = \( No\ Adverse\ Effect\ Level \div Uncertainty\ Factors \)

- Terms to define:
  - No Adverse Effect Level (NOAEL)
  - Reference dose (RfD)
  - Uncertainty Factors (UF)
  - Relative Source Contribution (RSC)

Definitions: No Adverse Effect Level (NOAEL)

• Used as Point of Departure for calculations
• Experimentally determined dose at which there is no statistically or biologically significant indication of the toxic effect of concern
• Usually based on laboratory animal studies

Definition: Uncertainty Factors (UFs)

- Factors used in calculations to represent specific areas of uncertainty in the available data

- Standard UFs include
  - **Intraspecies UF**: Accounts for variation in sensitivity among the members of the human population
  - **Interspecies UF**: Accounts for uncertainty involved in extrapolating from animal data to humans
  - **Subchronic to chronic UF**: Accounts for uncertainty involved in extrapolating from less-than-chronic NOAELs to chronic NOAELs

EPA Guidance for Use of Uncertainty Factors

- Use a 10-fold factor when extrapolating from valid experimental results in studies using prolonged exposure to average healthy humans.
- Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals.
- Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there are no useful long-term human data.

Definition: Reference Dose (RfD)

- Daily dose below which health effects are not expected in human populations (mg/kg/day)
- Derived from the NOAEL by consistent application of generally order-of-magnitude uncertainty factors that reflect various types of data sets used to estimate RfDs
- \( \text{RfD} = \frac{\text{NOAEL}}{\text{UF}} \)

Definition: Relative Source Contribution (RSC)

- Percentage of reference dose exposure attributed drinking water
- Accounts for possibility of non-water sources of exposure, such as
  - Foods
  - Inhalation
  - Skin absorption
- Guidelines available from EPA for compounds with limited data
- 20% RSC used for GenX health goal calculations

https://nepis.epa.gov/Exe/ZyPDF.cgi/20003D2R.PDF?Dockey=20003D2R.PDF
Figure 4-1
Exposure Decision Tree for Defining Proposed RfD (or POD/UF) Apportionment

1. Identify population(s) of concern.

2. Identify relevant exposure sources/pathways.

3. Are adequate data available to describe central tendencies and high-ends for relevant exposure sources/pathways? *

4. Are there sufficient data, physical/chemical property information, fate and transport information, and/or generalized information available to characterize the likelihood of exposure to relevant sources?

5A. Use 20% of the RfD or POD/UF

5B. Gather more information and re-review

6. Are there significant known or potential uses/sources other than the source of concern?

7. Use 50% of the RfD (or POD/UF).

8A. Is there some information available on each source to make a characterization of exposure?

8B. Use 20% of the RfD (or POD/UF).

8C. Perform apportionment as described in Box 12 or Box 13, with a 50% ceiling/20% floor.

9. Are exposures from multiple sources (due to a sum of sources or an individual source) potentially at levels near (i.e., over 80%) or in excess of the RfD (or POD/UF)?

9A. Yes

10. Describe exposures, uncertainties, toxicity-related information, control issues, and other information for management decision. Perform calculations associated with Boxes 12 or 13 as applicable.

10A. Yes

11. Is there more than one regulatory action (i.e., criteria, standard, guidance) relevant for the chemical in question?

11A. No

12. Use subtraction of appropriate intake levels from sources other than source of concern, including 80% ceiling/20% floor.

13. Apportion the RfD (or POD/UF) including 80% ceiling/20% floor using the percentage approach (with ceiling and floor).

* Sources and pathways include both ingestion and routes other than oral for water-related exposures, and nonwater sources of exposure, including ingestion exposures (e.g., food), inhalation, and/or dermal.
Calculation of GenX Reference Dose

- Reference dose (RfD) = NOAEL ÷ UF
  - NOAEL = 0.1 mg/kg/day
  - UF = 1,000
    - 10 intraspecies
    - 10 interspecies
    - 10 subchronic to chronic

- RfD = 0.1 mg/kg/day ÷ 1,000
- RfD = 0.0001 mg/kg/day
Calculation of GenX Health Goal

• Health Goal = (Reference Dose (mg/kg/day) x RSC x body weight (kg)) ÷ intake rate (L/day)

• Used body weight and intake rate values for bottle fed infants to calculate the most health protective goal to protect the most vulnerable

• Health Goal = (0.0001 mg/kg/day x 0.20 x 7.8 kg*) ÷ 1.113 L/day**

• Health Goal = 0.00014 mg/L = 140 ppt

* EPA EFH Table 8-1: Weighted average of mean body weight from 0-12 months [EPA 2011, ATSDR 2016a]
** EPA EFH Table 3-1: Weighted average of 95th percentile for consumers from 0-12 months [EPA 2011, ATSDR 2016b]
Provisional Health Goal: Considerations

• Applies only to GenX, not related compounds
  – Sufficient information not available to calculate health goals for other emerging per- and polyfluorinated compounds
  – Sufficient information not available to assess additive risk of all per- and polyfluorinated compounds in combination

• Represents level of chronic exposure which is not likely to result in adverse effects to humans

• Subject to change based on new information
Use Recommendations: GenX >140ppt

- Do not use well water for drinking, cooking, or preparing baby formula
- Can continue to use well water for bathing, washing dishes and laundry
  - Per CDC, only a very small amount can get into the body through the skin
  - Little exposure expected during swimming, bathing, or showering
Ongoing DHHS Activities and Next Steps

• Review new and ongoing environmental testing results

• Work with local partners to review updated information and identify new or ongoing concerns

• Ongoing coordination with CDC, EPA, and NIEHS to review new and updated health and toxicology information

• Monitor and respond to results of epidemiologic studies and testing of clinical specimens (such as blood or urine)

• Provide communities with information and assist with outreach and health education
Questions?
Extra Slides
• Repeated Dose 28-Day Oral Toxicity Study in Rats (OECD Guideline 407)

• Doses
  – Males: 0, 0.3, 3 and 30 mg/kg/day
  – Females: 0, 3, 30 and 300 mg/kg/day

• No Adverse Effect Level
  – NOAEL (male) = 30
  – NOAEL (female) = 300

• Basis for NOAEL
  – Highest dose tested
Studies Submitted for Registration - 6

• Repeated Dose 90-Day Oral Toxicity Study in Rats (OECD Guideline 408)

• Doses
  – Males: 0, 0.1, 10 and 100 mg/kg/day
  – Females: 0, 10, 100, and 1000 mg/kg/day

• No Adverse Effect Level
  – NOAEL (male) = 10
  – NOAEL (female) = 100

• Basis for NOAEL
  – Evidence of regenerative anemia (male and female)
  – Decreased survival (female)
• Repeated Dose 90-Day Oral Toxicity Study in Mice (OECD Guideline 408)

• Doses
  – 0, 0.1, 0.5, and 5 mg/kg.day

• No Adverse Effect Level
  – NOAEL (male and female) = 0.5

• Basis for NOAEL
  – Changes in clinical chemistry and histopathology indicative of liver toxicity
Point of Departure for GenX Health Goal

• NOAEL = 0.1 mg/kg/day

• Based on 28-day oral ingestion mouse study conducted by Chemours (2008)
  – 0 mg/kg/day......(20 male, 20 female)
  – 0.1 mg/kg/day...(10 male, 10 female)
  – 3 mg/kg/day.......(10 male, 10 female)
  – 30 mg/kg/day.....(20 male, 20 female)

• NOAEL based on liver effects in male mice

https://echa.europa.eu/registration-dossier/-/registered-dossier/2679/7/6/2/?documentUUID=7fde65ec-5187-42ef-8e05-58436035a555
Future of Emerging Compounds

• Rapid advances in environmental testing
  – Identification of “non-targeted” compounds
  – Able to identify lower concentrations
  – Outpacing advances in toxicology, health knowledge

• Likely to detect more compounds with limited (or no) health data in Cape Fear River and elsewhere
Peer-Reviewed Literature


• Key findings:
  − NOAEL of 0.1 mg/kg (males) and 1 mg/kg (females) based on liver and kidney effects
  − Reductions in body weight, weight gain, and food efficiency in females given 500mg/kg
  − 9% of females exposed to 500mg/kg died prior to the end of the study and had test compound-related papillary necrosis and kidney inflammation
  − Overall survivorship not reported as being associated with the test compound