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

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

Studies Submitted for Registration - 4

- 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

https://echa.europa.eu/registration-dossier/-/registered-dossier/2679/7/9/3

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

https://academic.oup.com/toxsci/article-abstract/156/1/179/2938051?redirectedFrom=fulltext

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* x *Relative Source Contribution* x Body Weight) ÷ Intake Rate
- Reference dose = *No Adverse Effect Level* ÷ *Uncertainty Factors*
- Terms to define:
  - No Adverse Effect Level (NOAEL)
  - Reference dose (RfD)
  - Uncertainty Factors (UF)
  - Relative Source Contribution (RSC)

https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments

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

https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments

Definition: Uncertainty Factors (UF s)

- 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

https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments

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
- RfD = NOAEL ÷ UF

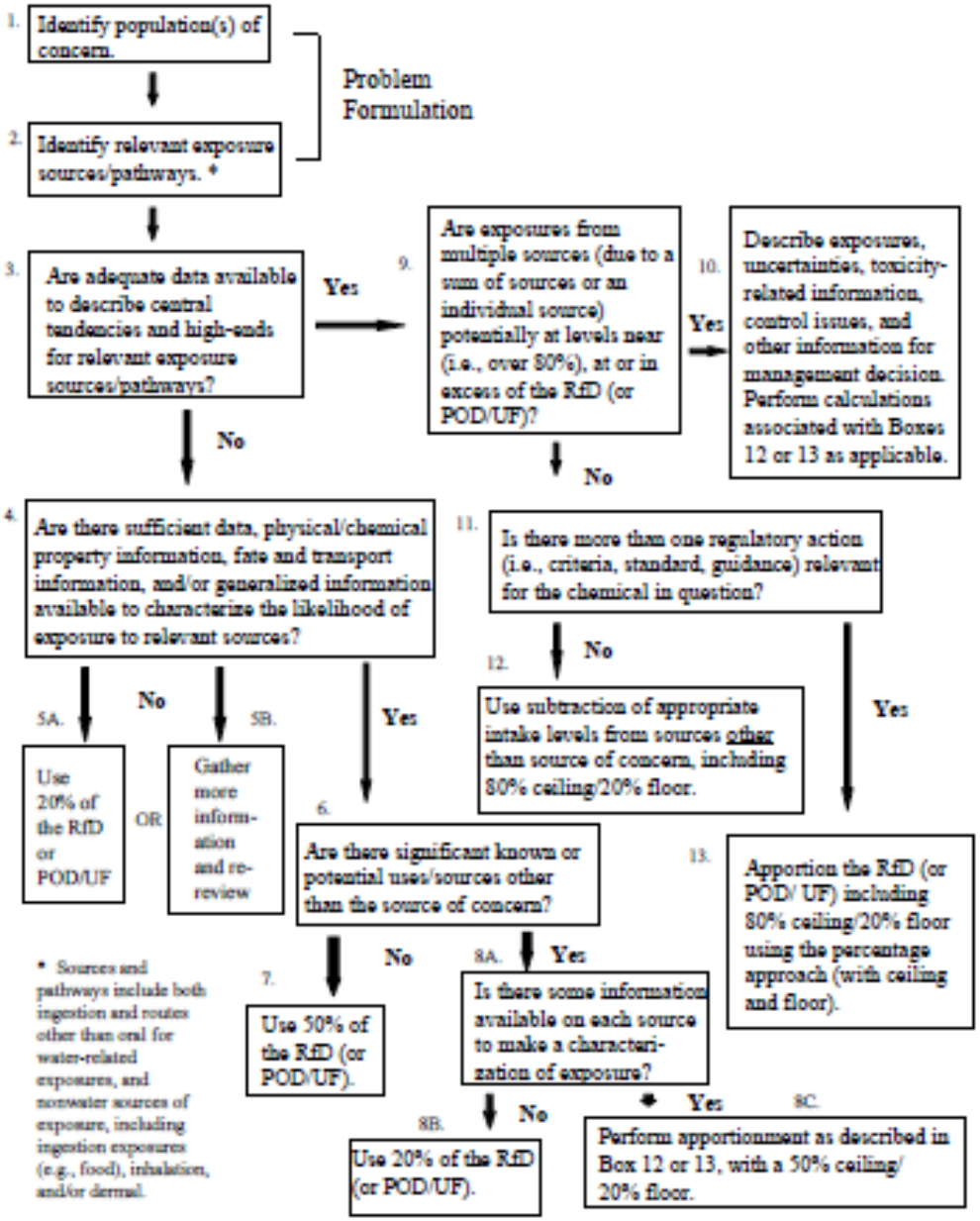
Definition: Relative Source Contribution (RSC)

- 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



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

Studies Submitted for Registration - 5

- 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)

Studies Submitted for Registration - 7

- 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

- Evaluation of chronic toxicity and carcinogenicity in Sprague–Dawley rats (Toxicol. Rep. 2015)
- 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