GenX Health Studies and Health Advisories

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Secretaries' Science Advisory Board Meeting
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Point of Departure for Provisional Health Goal

- No observed adverse effect level (NOAEL) of 0.1 mg/kg/day observed in two studies
  - 28-day oral toxicity study in mice
  - Reproductive/Developmental toxicity screen in mice
- Lowest NOAEL available
- Supported by other studies with similar or the same endpoints (toxicity to the liver)
- Consistent value:
  - EPA's 2008 Standard Review Risk Assessment
  - RIVM derivation of a chronic inhalation exposure limit
  - RIVM derivation of a lifetime drinking-water guideline

Repeated Oral Dose Studies ≥28 Days Submitted by Registrant

Study	Doses (mg/kg/day)	NOAEL (mg/kg/day)	BASIS FOR NOAEL
Repeated Dose 28-Day Oral Toxicity Study in Rats (OECD Guideline 407)	Males: 0, 0.3, 3 and 30 Females: 0, 3, 30 and 300	NOAEL (male) = 30 NOAEL (female) = 300	Highest dose tested
Repeated Dose 28-Day Oral Toxicity Study in Mice (OECD Guideline 407)	0, 0.1, 3 and 30	NOAEL (male) = 0.1 NOAEL (female) = 3	Males: Adverse effects in the liver at ≥3 mg/kg/day Females: Adverse effects in the liver at ≥30 mg/kg/day (Adverse effects included single cell necrosis of hepatocytes and correlative increases in liver enzymes)
Repeated Dose 90-Day Oral Toxicity Study in Rats (OECD Guideline 408)	Males: 0, 0.1, 10 and 100 Females: 0, 10, 100, and 1000	NOAEL (male) = 10 NOAEL (female) = 100	Males: Evidence of regenerative anemia at 100 mg/kg/day Females: Evidence of regenerative anemia and decreased survival in females at 1000 mg/kg/day
Repeated Dose 90-Day Oral Toxicity Study in Mice (OECD Guideline 408)	0, 0.1, 0.5, and 5	NOAEL (both sexes) = 0.5	Changes in clinical chemistry and histopathology indicative of liver toxicity at 5 mg/kg/day
Combined Chronic Toxicity/ Oncogenicity Study in Rats (OECD Guideline 453)	Males: 0, 0.1, 1, and 50 Females: 0, 1, 50, and 500	NOAEL (males) = 1 NOAEL (females) = 50	Males: Increases in focal cystic degeneration, focal necrosis, and centrilobular necrosis of the liver, and associated increases in cytotoxic liver enzymes, and equivocal increases in pancreatic acinar cell tumors and testicular interstitial (Leydig cell tumors) at 50 mg/kg/day Females: Reductions in body weight, body weight gain, and food efficiency; mild decreases in red cell mass; increases in individual cell necrosis in the liver; hyperplasia and/or inflammation in the nonglandular stomach and tongue; an increase in the incidence and severity of microscopic pathology in the kidneys; and an increase in hepatocellular adenomas and carcinomas, all observed at 500 mg/kg/day

*Adverse liver effects include single cell necrosis of hepatocytes, increases in liver enzymes, and histopathological changes

Repeated Oral Dose Studies ≥28 Days Submitted by Registrant

Study	Doses (mg/kg/day)	NOAEL (mg/kg/day)	BASIS FOR NOAEL
Reproduction/ Developmental Toxicity Screening Study in Mice (OECD Guideline 421)	0, 0.1, 0.5, and 5	NOAEL for reproductive toxicity = 5 NOAEL for systemic toxicity in F0 males = 0.1 NOAEL for systemic in F0 females = 0.5 NOAEL for offspring = 0.5	Reproductive Toxicity: Highest dose tested Systemic Toxicity in F0 Males: Single cell necrosis in the liver at 0.5 mg/kg/day Systemic Toxicity in F0 Females: Microscopic changes in the liver at 5 mg/kg/day 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)	0, 10, 100, and 1000	NOAEL for maternal animals = 10 NOAEL for developmental toxicity = 10	Maternal Animals: Maternal toxicity at ≥100 mg/kg/day Developmental Toxicity: Early deliveries and lower mean fetal weights at ≥100 mg/kg/day

*Adverse liver effects include single cell necrosis of hepatocytes, increases in liver enzymes, and histopathological changes

Intraspecies Uncertainty Factor

- Used to account for the variation in sensitivity to toxic effects among members of the human population

- Differences in sensitivity can be due to a variety of factors, including age, sex, disease status, nutrition, genetics, etc.

- Value used = 10 (default)

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

Interspecies Uncertainty Factor

- Used to account for uncertainty involved in extrapolating from animal data to humans
- Differences in sensitivity can be due to a variety of factors such as difference in metabolism and kinetics
- Some PFAS show vast differences in interspecies kinetics, longer human half-lives for PFOA and PFOS
- Not enough information to determine interspecies variability for GenX
  - No human data on GenX pharmacokinetics and half-life
  - Study with rodents & primates indicates shorter half-life compared to PFOA*
- Value used = 10 (default)

*Beekman et al 2016

Sub-Chronic–to–Chronic Uncertainty Factors

- Used to account for uncertainty involved in extrapolating from less-than-chronic NOAELs to chronic NOAELs
- Generally assumed that longer exposure times would result in adverse effects at lower concentrations due to accumulation of the toxicant or inability to repair injury from the substance
- Lowest NOAELs for GenX were from sub-chronic studies
- Value used = 10 (default)

LOAEL–to–NOAEL Uncertainty Factor

- Used to account for uncertainty involved in extrapolating from a LOAEL to a NOAEL if there is not a NOAEL available as the POD

- Not used in calculation of the Provisional Health Goal for GenX in drinking water due to availability of NOAELs

Modifying Factor

- Additional uncertainty factor of 0–10
- Depends on the professional assessment of scientific uncertainties of the data base not explicitly treated above- e.g., completeness of the overall database and the number of species tested
- Not used in calculation of the Provisional Health Goal for GenX in drinking water
  - NOAELs from several studies identical or within same order of magnitude with identical or similar health endpoints (i.e. liver toxicity)
  - Uncertainty factors adequately address uncertainties of the database

Reference Dose (RfD) Calculations

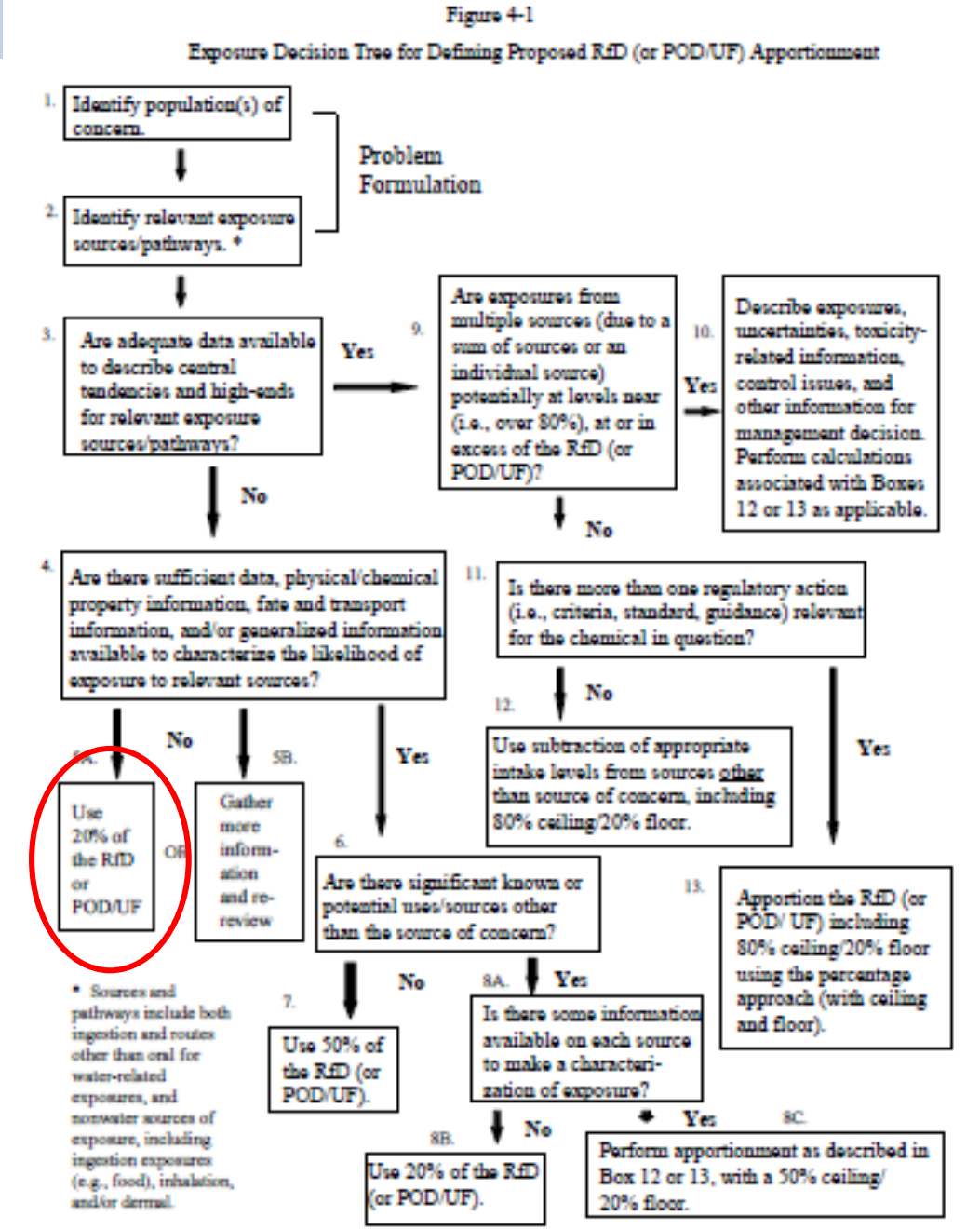
- "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime."
- Applies to non-cancer endpoints
- Applies to total exposure from multiple sources
- RfD = NOAEL or POD ÷ Uncertainty Factors
- RfD for provisional health goal for GenX in drinking water:

  0.1 mg/kg/day ÷ (10 x 10 x 10) = 0.0001 mg/kg/day

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

Relative Source Contribution

- Used to account for potential other sources of the contaminant
- For GenX, little to no information currently available about other exposure routes
- Assumes 80% of exposure is from other sources besides drinking water



Health Goal Calculations

- Provisional 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
  - Generally infants are considered a potentially vulnerable population due to physiology and development
  - Bottle fed infants have the highest intake rate to body weight ratio of any age group = highest dose received by the drinking water route
- Provisional Health Goal = (0.0001 mg/kg/day x 0.20 x 7.8 kg*) ÷ 1.113 L/day**
- Provisional Health Goal = 0.00014 mg/L = 140 ng/L (ppt)
- Subject to change based on new information

* 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]

Questions?

Suggested charges for SAB

- Review the GenX provisional health goal as calculated by DHHS to determine if the SAB recommends any modifications. Recommendations regarding the Reference Dose will be considered by DEQ in its development of groundwater and surface water standard proposals to be presented to the Environmental Management Commission (EMC) for rulemaking.
- Perform a similar review for health goal calculated for hexavalent chromium.
- Review available information to determine whether an acceptable ambient level should be considered/recommended to address potential inhalation risks associated with GenX and other related emerging contaminants.
- Provide guidance regarding use of the EPA health risk assessment processes for the preliminary calculation of health goals. Is this a reasonable and sufficient approach for providing health information for emerging contaminants?

Roy Cooper, Governor

Michael S. Regan, Secretary
N.C. Department of Environmental Quality

Mandy K. Cohen, Secretary
N.C. Department of Health and Human Services

Secretaries' Science Advisory Board

January 29, 2018
10:00 am
Ground Floor Hearing Room – Archdale Building

I. Call to Order

II. Approval of December 4, 2017 SAB Meeting Minutes

III. Ethics Statement

IV. Presentation by Representatives from the Netherlands on their Established Drinking Water Target Value followed by Question and Answer Session

V. Follow-up from December 4, 2017 Meeting on GenX Health Studies

a. Reference Dose (RfD) and Point of Departure (POD) selection

b. Review of Uncertainty Factors (UF) and rationale for use

c. Relative Source Contribution (RSC) estimates

VI. Discussion of SAB Deliverable Expectations by DEQ and DHHS

VII. SAB Principles and Practices

VIII. Discussion of Precautionary Principle

IX. Public Comment Forum

X. Next Meetings

(i) March 19, 2018

(ii) April 30, 2018

(iii) June __, 2018