Development of Toxicity Values for GenX Chemicals

Briefing for North Carolina Secretaries' Science Advisory Board

US EPA

June 18, 2018

Purpose of this Briefing

- Provide North Carolina Secretaries' Science Advisory Board an overview of EPA's analysis and effects characterization of toxicity values for GenX chemicals
  - Assessment led by EPA Office of Water and Office of Pollution Prevention and Toxics

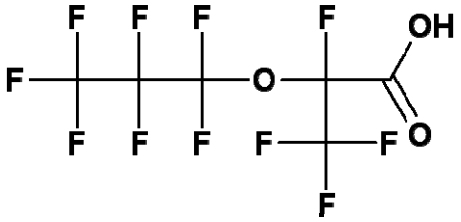
Overall Scientific Objectives

- Provide the health effects information for the development of toxicity values (e.g., oral reference doses) including the science-based decisions supported by relevant studies, effects, and estimated point(s) of departure (POD)

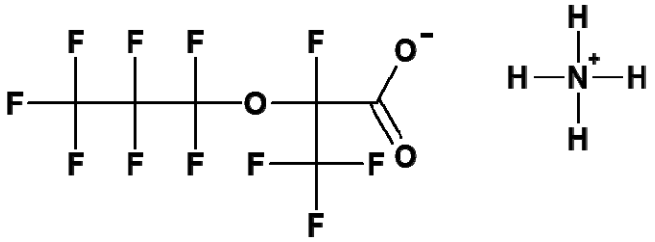
Document Structure

- Background
- Nature of the stressor including occurrence, chemical and physical properties and toxicokinetics
- Problem Formulation, including conceptual model and analysis plan
- Study Synthesis
- Summary of Hazard
- Dose response assessment including modeling, uncertainty factors and derivation of Reference Value(s)
- Characterization of Uncertainties

GenX Chemicals



HFPO dimer acid
CASRN 13252-13-6



HFPO dimer acid, ammonium salt
CASRN 62037-80-3

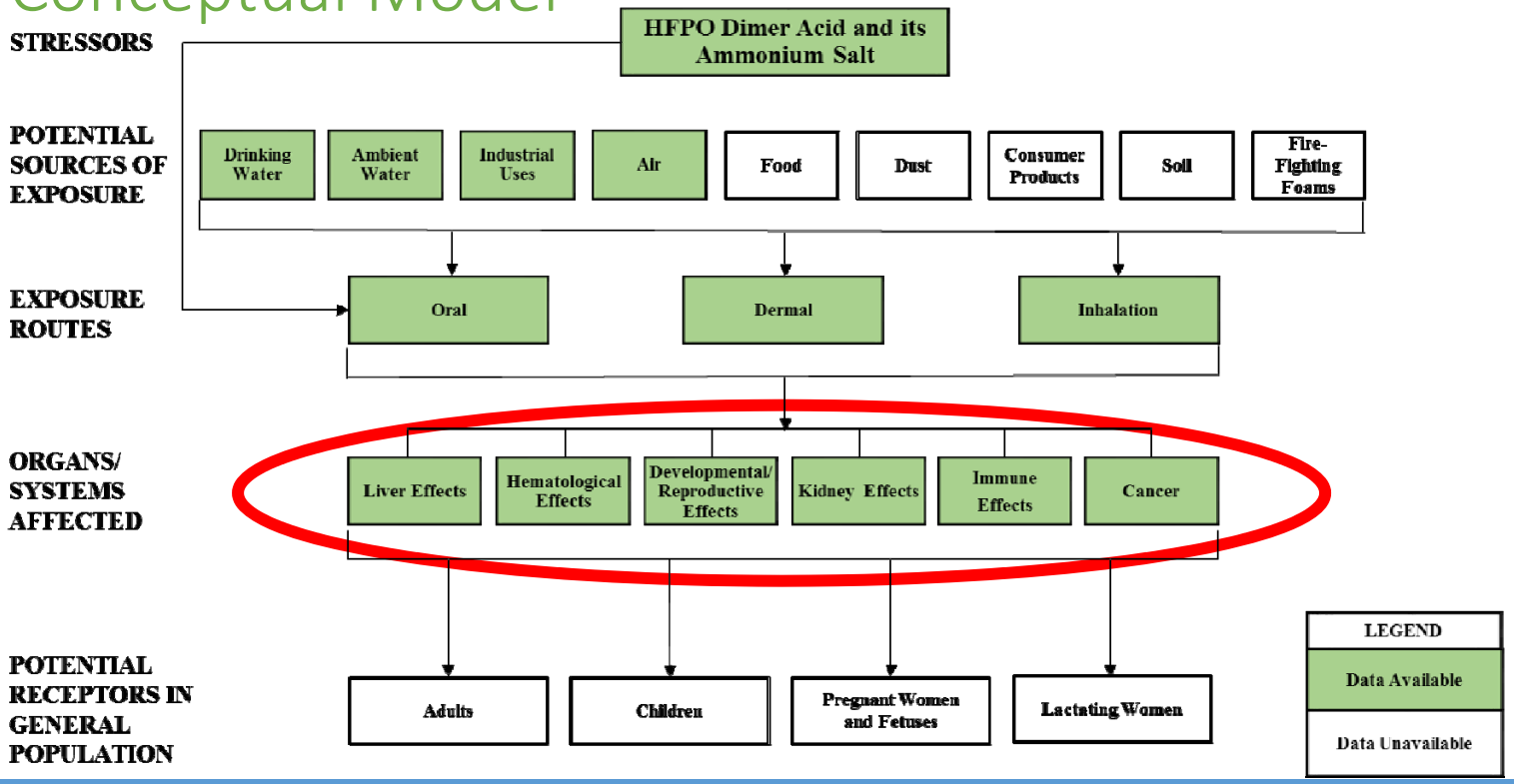
Environmental Fate

- GenX chemicals are stable to photolysis, hydrolysis and biodegradation and are persistent in air, water, soil and sediments.
- Highly soluble
- Low sorption to sediment and soil
  - Potential to rapidly leach to groundwater from soil and landfills.
- Partitioning from surface water to the vapor phase may occur.
  - They may undergo long range atmospheric transport in the vapor phase and be associated with particulate matter.
  - Removal from air may occur by scavenging by water droplets and attachment to particulates followed by precipitation and settling.
- They are not expected to be removed during wastewater treatment or conventional drinking water treatment.
- They have low potential to bioaccumulate in fish.

Occurrence

- Monitoring for GenX chemicals is limited.
  - GenX chemicals were first identified in North Carolina's Cape Fear River and its tributaries in the summer of 2012.
  - Sun et al. (2016) reported detections of GenX chemicals in three drinking water treatment plants treating surface water from the Cape Fear River watershed.
  - Subsequent monitoring by NCDEQ reported GenX chemicals in surface water, groundwater, and finished drinking water in the Cape Fear Watershed close to the Chemours facility where the chemicals were used and 100 miles downstream.
  - GenX chemicals have also been detected in three on-site production wells and one on-site drinking water well at Chemours' Washington Works facility in Parkersburg, West Virginia.
  - GenX chemicals were found in rainwater samples collected between February 28-March 2, 2018 up to 7 miles from the North Carolina plant.
  - EPA's ORD is providing monitoring assistance to North Carolina and New Jersey.

Problem Formulation
Conceptual Model



Study Evaluation for GenX Chemicals

- Many of the available studies were conducted by industry to support new uses and Pre-Manufacturing Notifications and were submitted to the Agency for review.
  - These studies are available through the HERO database: https://hero.epa.gov/hero/index.cfm/project/page/project_id/2627
- Studies were designed and implemented according to OECD Test Guidelines and followed Principles of Good Laboratory Practices.
- EPA evaluated the studies based on Agency Guidelines and criteria to determine if the studies:
  - Adequately describe study protocol and methods
  - Evaluate appropriate endpoints
    - Toxicity depends on the amount, duration, timing and pattern of exposure, and could range from frank effects (e.g., mortality) to subtler biochemical, physiological, pathological or functional changes in multiple organs and tissues.
  - Use appropriate statistical procedures to determine an effect
  - Establish a dose-response relationship (i.e., NOAEL) and/or lowest observed adverse effect level (LOAEL)
  - Have data to identify a POD for a change in the effect considered to be adverse (out of the range of normal biological variability).

Available Studies

Published Peer Reviewed Literature

- 28 day oral toxicity study evaluating hepatotoxic effects in mice (Wang et al., 2016)
- 28 day oral toxicity study evaluating immunomodulatory effects in mice (Rushing et al., 2017)
- 2 studies that are published versions of DuPont/Chemours data:
  - The OECD 453 combined chronic toxicity/oncogenicity study (2 year) in rats (Rae et al., 2015)
  - An oral, single dose pharmacokinetic study describing absorption, distribution, metabolism, and elimination in rats, mice and cynomolgus monkeys (Gannon et al., 2016)

DuPont/Chemours Studies

- Acute oral, dermal, and inhalation toxicity studies
- Toxicokinetic studies
- Genotoxicity studies (in vivo and in vitro)
- Repeated-dose metabolism and pharmacokinetics in rats and mice (OPPTS 870.7485)
- 28 day oral toxicity study in mice and rats (OECD TG 407)
- 90-day toxicity study (OPPTS 870.3100; OECD 408)
- Chronic toxicity/carcinogenicity study in rats (OPPTS 870.4300; OECD 408)
- One-generation reproduction study in mice (OECD 421, modified)

EFFECTS CHARACTERIZATION

28-Day Oral Toxicity Studies (Chemours)

OECD Guideline 407

Mouse

- DuPont 24459
- Dose (gavage):
  - 0, 0, 0.1, 3 and 30 mg/kg/day
- Effects:
  - Liver effects (↑ relative liver weight in both sexes and ↑ hepatocellular hypertrophy in both sexes and single cell necrosis in males)
  - Hematological effects (↓ hemoglobin and hematocrit in males)
  - Immune effects (↓ globulin in females and ↑ A/G ratio in both sexes)
- NOAEL = 0.1 mg/kg/day

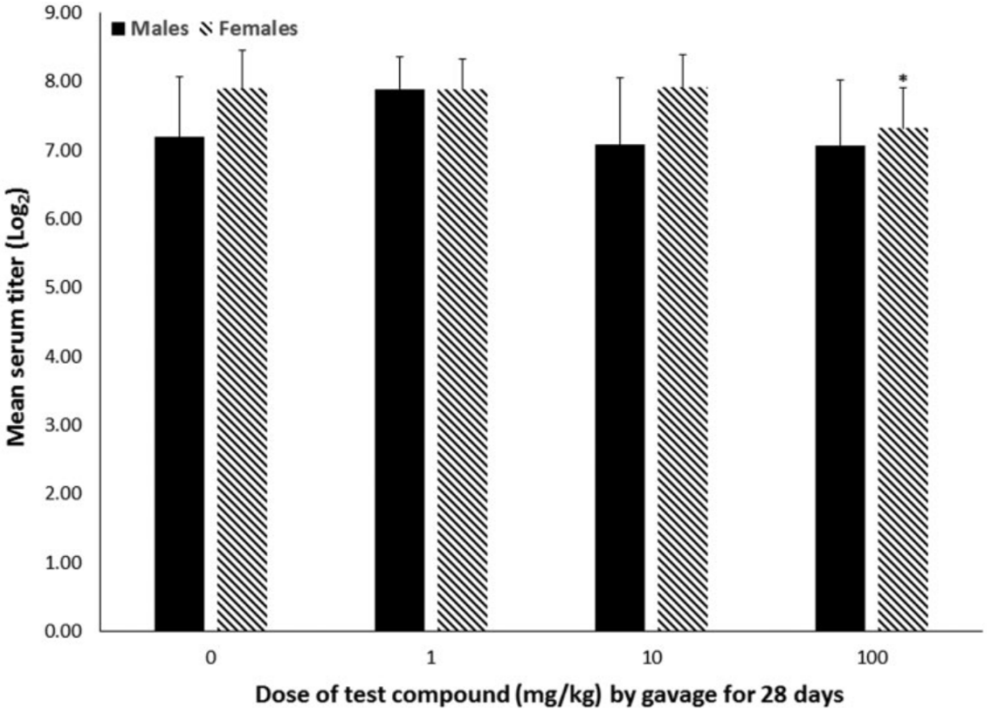
Rat

- DuPont 24447
- Dose (gavage):
  - 0, 0.3, 3 and 30 mg/kg/day (males)
  - 0, 3, 30 and 300 mg/kg/day (females)
- Effects:
  - Liver effects (↑ relative liver weight and hepatocellular hypertrophy in males)
  - Hematological effects (↓ erythrocyte count, hemoglobin, and hematocrit in males)
  - Immune effects (↓ globulin and ↑ A/G ratio in males)
- NOAEL = 0.3 mg/kg/day

28-Day Oral Immunotoxicity Study

Rushing et al., 2017

- C57BL/6 mice
- 0, 1, 10, and 100 mg/kg/day HFPO dimer acid
- Effects:
  - TDAR suppression in females
  - ↑ lymphocytes in males
- NOAEL = 10 mg/kg/day



90-Day Oral Toxicity Studies (Chemours)

OECD Guideline 408

Mouse

- DuPont 18405-1307
- 0, 0.1, 0.5, and 5 mg/kg/day
- Effects:
  - Liver enzyme level changes (↑aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase) in both sexes
  - ↑ relative liver weight in both sexes
  - ↑ hepatocellular hypertrophy and single cell necrosis in males
- NOAEL = 0.5 mg/kg/day

Rat

- DuPont 17751-1026
- 0, 0.1, 10 and 100 mg/kg/day (males) and 0, 10, 100, and 1000 mg/kg/day (females)
- Effects:
  - ↓ erythrocyte count, hemoglobin, and hematocrit in males
- NOAEL = 0.1 mg/kg/day

2-Year Oral Toxicity/Carcinogenicity Study

OECD Guideline 453

- DuPont 18405-1238
- Crl:CD(SD) rats
- 0, 0.1, 1, and 50 mg/kg/day (males) and 0, 1, 50, and 500 mg/kg/day (females)
- Effects:
  - ↑ liver enzyme levels (alkaline phosphatase, ALT, and SDH) in males
  - ↑ centrilobular hepatocellular hypertrophy and cystic focal degeneration in males
  - ↑ centrilobular necrosis in both sexes
- NOAEL = 1 mg/kg/day

Oral Reproductive/Developmental Toxicity Study

Modified OECD Guideline 421

- DuPont 18405-1037
- Crl:CD1(ICR) mice
- 0, 0.1, 0.5, and 5 mg/kg/day
- Effects:
  - F0- ↑ relative liver weight in both sexes and single cell necrosis in males
  - Offspring- ↓ pup weights and delays in the attainment of balanopreputial separation and vaginal patency
- NOAEL = 0.1 mg/kg/day (F0) and 0.5 mg/kg/day (offspring)

Oral Prenatal and Developmental Screening Study

OECD Guideline 414

- DuPont 18405-841
- 0, 10, 100, and 1000 mg/kg/day
- Effects:
  - ↑ early deliveries and↓ gravid uterine weight
  - ↓fetal weights in both sexes
- NOAEL = 10 mg/kg/day (maternal and offspring)

Study	NOAEL (mg/kg/day)	Effects
DuPont 24447: 28-Day Oral (Gavage) Toxicity Study in Rats	NOAEL = 0.3	• Liver effects • Hematological effects • Immune effects
DuPont 24459: 28-Day Oral (Gavage) Toxicity Study in Mice	NOAEL = 0.1	• Liver effects • Hematological effects • Immune effects
Rushing et al. (2017): 28-day Oral (Gavage) Immunotoxicity Study in Mice	NOAEL = 10	• Immune effects
DuPont 17751-1026: 90-Day Oral (Gavage) Toxicity Study in Rats	NOAEL = 0.1	• Hematological effects
DuPont 18405-1307: 90-Day Oral (Gavage) Toxicity Study in Mice	NOAEL = 0.5	• Liver effects
DuPont 18405-1238: Combined Chronic Toxicity/ Oncogenicity Study in Rats	NOAEL = 1	• Liver effects
DuPont 18405-1037 Oral (Gavage) Reproduction/ Developmental Toxicity Screening Study in Mice	NOAEL (F0) = 0.1 NOAEL (offspring) = 0.5	• Liver effects • Developmental effects
DuPont 18405-841 Prenatal and Developmental Toxicity Study in Rats	NOAEL (maternal and offspring) = 10	• Developmental effects

Weight of Evidence for Hazard

- Adverse effects are observed in the liver, developing fetus, and hematological and immune systems.
- The single cancer bioassay show increased liver tumors (females) and combined adenomas and carcinomas pancreatic acinar (males) in rats at the high doses only.
  - There was an increased incidence of testicular interstitial cell adenoma in males, but this increase was not statistically significant.
  - There are no studies measuring cancer endpoints in mice.
- Liver is primary target of toxicity. Effects are observed in both male and female mice and rats at varying durations of exposures and doses and are the endpoints that are observed at the lowest doses of exposure to these chemicals.
  - Use of Hall et al. (2012) criteria for adversity of liver endpoints.
    - Hepatocellular hypertrophy and an increased liver weight are common findings in rodents, but are often considered non-adverse if there is evidence for PPARα activation.
    - These effects were considered adverse when accompanied by necrosis, fibrosis, inflammation, and/or steatosis.

APPROACH FOR DERIVATION OF REFERENCE DOSE

Approach for Dose-Response Assessment

- Follow the general guidelines for risk assessment set forth by the National Research Council (1983) and EPA's *Framework for Human Health Risk Assessment to Inform Decision Making* (2014)
- EPA's *A Review of the Reference Dose and Reference Concentration* (2002) document describes a multi-step approach to dose–response assessment including analysis in the range of observation followed by extrapolation to lower levels.

Selection of Critical Study and Effect

- Studies were evaluated based on duration of exposure, use of a control and two or more doses, and provision of NOAEL and/or LOAEL values.
  - Given the availability of subchronic, chronic and reproductive and developmental toxicity studies indicating effects at lower doses, the 28-day studies were not considered quantitatively.
- From the available subchronic (90 day), chronic (2-year cancer bioassay) and reproductive and developmental toxicity studies, the studies that observed adverse effects at the lowest doses tested are considered in the selection of the critical study for derivation of the RfD.
  - NOAELs for liver effects range from 0.1-1 mg/kg/day
  - NOAEL for hematological effects is 0.1 mg/kg/day

Determination of Point of Departure

Benchmark Dose Modeling

- Use of EPA's *Benchmark Dose Technical Guidance Document* (2012).
  - No biologically based dose-response models are available
- Considerations influencing selection of BMD model endpoints include: available data with dose-response, percent change from controls, adversity of effect, and consistency in effect observed across studies.

Determination of Point of Departure

Allometric scaling

- Use *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (2011) when applicable.
  - Use of a body weight scaling applied to extrapolate toxicologically equivalent doses of oral doses from adult laboratory animals to adult humans.
  - Addresses some aspects of cross-species extrapolation of toxicokinetic and toxicodynamic processes and affects interspecies uncertainty factor.

Characterization of Uncertainty

Uncertainty factors will be selected in accordance with EPA guidelines considering the following:

- Variations in sensitivity among humans (UF_H)
  - No information to is available to characterize interindividual and age-related variability in the toxicokinetics or toxicodynamics.
- Differences between animals and humans (UF_A)
  - Use of allometric scaling will address some of the toxicokinetic and toxicodynamic aspects
- Duration of exposure in the key study compared to a lifetime of the species studied (UF_S)
- Extrapolation from a LOAEL to a NOAEL (UF_L)
  - When the POD type is a BMDL, the current approach is to address this factor as one of the considerations in selecting a BMR for BMD modeling.

Characterization of Uncertainty (Cont'd)

Completeness of the toxicology database (UF_D)

- There are no data from epidemiological studies in the general population or worker cohorts available for use in evaluating human health effects.
- The database available to EPA assesses numerous endpoints: acute toxicity, metabolism and toxicokinetics, genotoxicity, and systemic toxicity in mice and rats with dosing durations of up to 2 years.
  - Deficiencies in the database include limited developmental toxicity testing and immune studies.

Derivation of RfDs

EPA will use the information described above to derive both a subchronic and a chronic toxicity value, or RfD:

$$\text{Subchronic RfD} = \frac{POD_{HED}}{Total\ UF}$$

$$\text{Chronic RfD} = \frac{POD_{HED}}{Total\ UF}$$

Total Uncertainty Factor ($Total\ UF$) will be different for subchronic and chronic RfD calculations

Next Steps

- Independent External Peer Review (June 2018)

Contacts

- Elizabeth (Betsy) Behl, EPA/OW, Director Health and Ecological Criteria Division in the Office of Science and Technology

  Phone: 202-566-0788

  Email: behl.betsy@epa.gov
- Jamie Strong, Ph.D., EPA/OW, Chief, Human Health Risk Assessment Branch in the Health and Ecological Criteria Division in the Office of Science and Technology

  Phone: 202-566-0056

  Email: strong.jamie@epa.gov