Development of Toxicity Values for GenX Chemicals and PFBS

Briefing #1 to States and Federal Agencies

US EPA

March 9, 2018

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Purpose of the Briefing:

- Provide States and federal agencies periodic updates on the status of EPA's development of toxicity values for two PFAS chemicals
  - GenX chemicals – assessment led by EPA Office of Water and Office of Pollution Prevention and Toxics
  - PFBS – assessment led by EPA Office of Research and Development

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Overall Scientific Objectives

- Provide the health effects information for the development of standard toxicity values (i.e., oral reference dose) including the science-based decisions providing the basis for estimating the point of departure (POD)

Plan for Engagement:

- States and Federal Agencies: Update # 1 – problem formulation and review of available information
- States and Federal Agencies: Update #2 – overview of analysis, including effects characterization and derivation of draft toxicity values
- External peer review
- States and Federal Agencies: Update #3 – Summary of external peer review comments, Agency response, and determination of final toxicity values
- Public meeting to present the final values and discuss risk communication

Proposed Document Structure

- Background
  - Nature of the stressor including occurrence, chemical and physical properties and toxicokinetics
- Problem Formulation
  - Conceptual model
  - Overall Scientific Objectives
  - Methods including the literature search strategy and study evaluation processes
  - Approach for Derivation of Reference Values (e.g., effect level identification; Benchmark Dose modeling)
- Study Synthesis and Health Effects Characterization
- Derivation of Reference Value(s)

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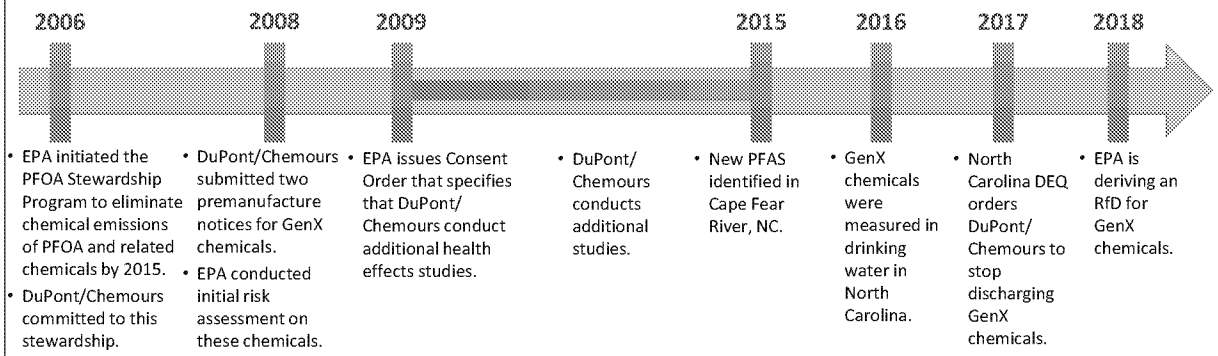
GenX Chemicals

Nature of the Stressor-GenX Chemicals

Background



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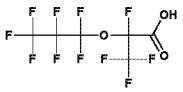
Nature of the Stressor-GenX Chemicals

Background

- GenX is a trade name for a processing aid technology developed by DuPont/Chemours
  - Enables the manufacture of fluoropolymers without the use of PFOA
    - Fluoropolymers are used in many applications including to make non-stick coatings for cookware, water repellent garments, and in other specialty agrochemical and pharmaceutical applications.
  - GenX chemicals have been detected in water in North Carolina and West Virginia; GenX was not included in national monitoring.

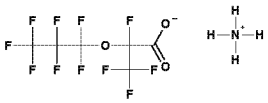
CAS# 13252-13-6



Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-

HFPO dimer acid

CAS# 62037-80-3



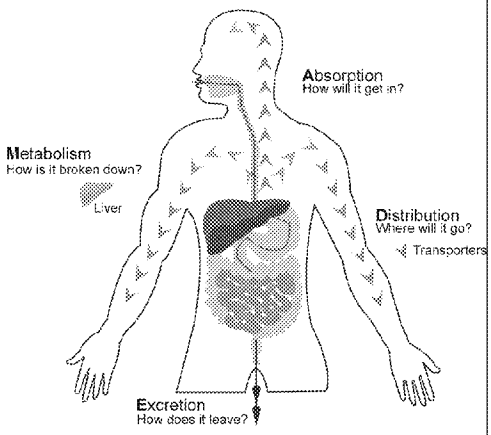
Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-, ammonium salt (1:1)

HFPO dimer acid ammonium salt

Nature of the Stressor-GenX Chemicals

Toxicokinetics

- Rapidly absorbed from the GI tract
- Little or no metabolism
- Available data indicate similar beta phase half-lives in rodents (23 – 89 **hours**) and monkeys (64 – 80 **hours**)
  - Elimination is more rapid compared to longer-chain PFAS
  - Clearance in female rodents is faster than males
- Cross placental transfer yields reduced fetal dose
- Mean blood concentrations did not increase after repeated doses



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A main point here is that elimination rates are the same in both rodents and monkeys and is in hours which is very different from PFOA

Problem Formulation-GenX Chemicals

Conceptual Model

- Provides useful information to characterize and communicate the potential health risks related to exposure
  - Sources of exposure to the contaminant
  - Routes of exposure
  - Potential endpoints for the assessment (liver toxicity, developmental effects, etc.)
  - Population and life stages potentially at risk

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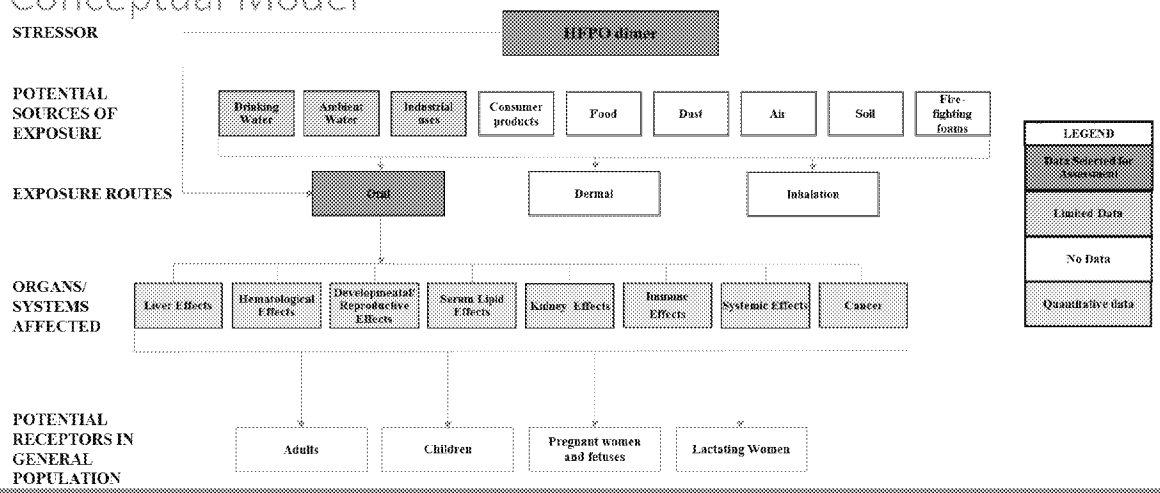
Problem Formulation-GenX Chemicals

Conceptual Model



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Methods-GenX Chemicals

Publically available peer reviewed studies

- Conducted a comprehensive contractor-led search of information available in the public domain
  - Searched 4 major databases (PubMed, Toxline, WOS, TSCATS)
  - Supplemented by searching 20 other databases for health effects, toxicokinetic, and mechanistic information
- Determined potential relevance based primarily on a title and abstract screen

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Literature Search Results- GenX Chemicals

Publically available peer reviewed studies

- No human epidemiological studies identified
- 4 in vivo studies from the peer-reviewed primary 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 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)
- 1 *in vitro* study evaluating cytotoxicity in human liver cells (Sheng et al., 2018)

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Methods-GenX Chemicals

Data Submitted from DuPont/Chemours

- Original Premanufacture Notices (PMN) was submitted in 2008 and included health data such as:
  - Acute and 7 day oral and dermal toxicity studies
  - 28 day oral toxicity study in mice and rats (OECD TG 407)
  - Toxicokinetic studies
  - Genotoxicity studies (*in vivo* and *in vitro*)
- EPA concluded that additional testing was required in a 2009 Consent Order:
  - One-generation reproduction study in mice (OECD 421, modified)
  - Repeated-dose metabolism and pharmacokinetics in rats and mice (OPPTS 870.7485)
  - 90-day toxicity study (OPPTS 870.3100; OECD 408)
  - Chronic toxicity/carcinogenicity study in rats (OPPTS 870.4300; OECD 408)
- Additional data was submitted as required under TSCA reporting requirements

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Methods-GenX Chemicals

Screening and Evaluation of DuPont/Chemours Data

EPA

EPA/OPPT's 2008 Review:

- Many of the studies submitted were conducted according to OECD Test Guidelines and Principles of Good Laboratory Practices (GLP), and full study reports were submitted to EPA by Dupont/Chemours.
- The studies formed the primary basis of OPPT's 2008 assessment of potential health hazards.

Additional Data Submitted Under TSCA:

- Under the 2009 Consent Order EPA required additional testing according to OECD Test Guidelines and/or EPA Health Effects Test Guidelines for Pesticides and Toxic Substances
  - For the one-generation reproduction study in mice (OECD 421, modified), EPA included specific modifications to the test based on information for PFAS chemicals.
  - For the chronic toxicity/carcinogenicity study in rats (OPPTS 870.4300; OECD 408) , EPA reviewed and concurred with the study protocol.
- The submitter consulted with EPA on study findings to determine the need for additional data (e.g., the need for further toxicokinetic testing based on results of the first study)
- Upon receipt, EPA review of the studies indicated they were acceptable for their intended purpose for use in assessing risks under TSCA.

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Perfluorobutane sulfonate (PFBS)

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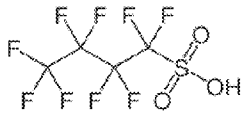
Nature of the Stressor-PFBS

Background

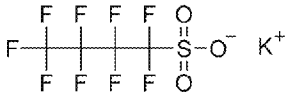
1-Perfluorobutanesulfonic Acid (PFBS) (CASRN 375-73-5) and its related salt called potassium perfluorobutane sulfonate (K+PFBS) (CASRN 29420-49-3) are manufactured for use in paints, cleaning agents, and water-impermeable products

PFBS has been detected at or above the minimum reporting level (0.09 ug/L) in public water systems in Alabama, Colorado, Georgia, and the North Mariana Islands

1-Perfluorobutanesulfonic Acid



Potassium Perfluorobutane Sulfonate



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Nature of the Stressor-PFBS

Toxicokinetics

Exposure regimen	Serum half-life
Varied; occupational exposure (5 male; 1 female); followed for 180 days after cessation of PFBS exposure	25.8 days (95% confidence interval = 16.6-40.2)
Cynomolgus monkey I.V. (10mg/kg)	95.2±27.1 hours (males) 83.2±41.0 hours (females)
Rat I.V. (30 mg/kg)	4.51±2.22 hours (males) 3.96±0.21 hours (females)
Rat Oral	4.68±0.43 hours (males) 7.42±0.79 hours (females)

TK information based on Olsen et al. (2009)

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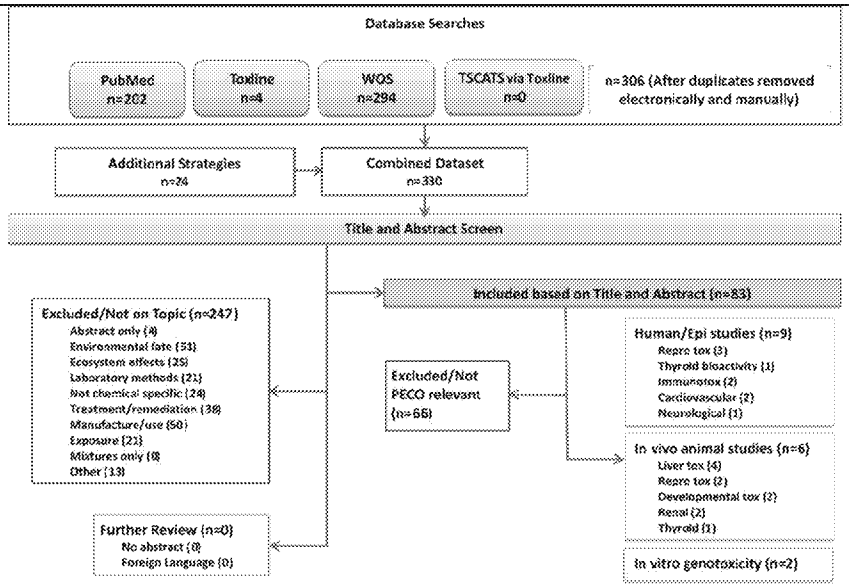
Methods-PFBS

Publically available peer reviewed studies



(Note: Some of the included studies were assigned more than one tag, so the sum of the references in boxes below "Title and Abstract screen" does not match exactly the total number of references in the "Combined Dataset")

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Literature Search Results-PFBS

Publically available peer reviewed studies

Summary of Available Toxicity Information																	
	Hepatic		Repro		Dev		Neuro		Thyroid		Immune		Renal		Cardio		Cancer
Perflourobutanesulfonate (PFBS)		4		2		2				1				2			

= human study(ies) available = mammalian animal study(ies) available

- **A 2014 Provisional Peer Reviewed Toxicity Value (PPRTV) assessment already exists; the information provided here includes the studies from the PPRTV and the literature update**
  - https://hhpprtv.ornl.gov/issue_papers/PerfluorobutanesulfonicacidPFBS.pdf
- There are 9 human epidemiological studies that provide data on potential reproductive, neurological, thyroid, cardiovascular or immunological effects

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Literature Search Results-PFBS

Publically available peer reviewed studies

EPA

Summary of Available Toxicity Information	Hepatic	Renal	Dev	Neuro	Thyroid	Immune	Renal	Cardio	Cancer
Perflourobutanesulfonate (PFBS)	4	2	2			1	2		

= human study(ies) available = mammalian animal study(ies) available

- Six *in vivo* animal studies provide potentially relevant data on various adverse effects, including liver and kidney toxicity, reproductive/developmental toxicity, and thyroid effects
  - Acute exposure study in rats (Bomhard and Löser, 1982)
  - 90 day oral gavage study in rats (Lieder et al., 2009)
  - 2-generation oral gavage reproduction study in rats (Lieder et al., 2009)
  - 4 week study in transgenic mice (3M, 2010)
  - Subchronic exposure study in rats evaluating lipoprotein metabolism (Bijland et al., 2011)
  - Gestational exposure study in rats (Feng et al., 2017)

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Next Steps

- Review and evaluate data
- Develop draft analysis including POD(s), uncertainty factors, RfD derivation
- Update States and Federal Agencies and present draft decisions prior to external peer review

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