Technical Fact Sheet: Draft Toxicity Assessments for GenX Chemicals and PFBS

EPA is releasing draft toxicity assessments for public comment for hexafluoropropylene oxide (HFPO) dimer acid and its ammonium salt (referred to as GenX chemicals) and perfluorobutane sulfonic acid (PFBS) and its potassium compound salt, perfluorobutane sulfonate (K+PFBS) based on the Agency's analysis of the best available science on the health effects of these chemicals. The values included in these draft assessments are not final and may change following the public comment period. The EPA is issuing the draft toxicity assessments for PFBS and GenX chemicals for public comment to give the public an opportunity to provide input to the Agency. When final, these toxicity assessments can be used by EPA and other federal agencies, and state, tribal, and local communities, along with specific exposure and other relevant information, to determine, under appropriate regulations and statutes, if and when it is necessary to take action to address potential risk associated with human exposure to PFAS. Following closure of the 60-day public comment period, the EPA will consider the comments, revise the draft documents, as appropriate, and publish final toxicity assessments.

Background on GenX Chemicals and PFBS

GenX chemicals and PFBS are man-made, fluorinated organic chemicals that are part of a larger group referred to as per- and polyfluoroalkyl substances (PFAS). PFAS are used in many applications because of their unique physical properties such as resistance to high and low temperatures, resistance to degradation, and nonstick characteristics.

GenX is a trade name for a processing aid technology used to make high-performance fluoropolymers without the use of perfluorooctanoic acid (PFOA). HFPO dimer acid and its ammonium salt are the major chemicals associated with GenX processing aid technology. GenX chemicals have been found in surface water, groundwater, finished drinking water, rainwater, and air emissions in some areas.

PFBS is a four-carbon PFAS that was developed as a replacement for perfluorooctane sulfonic acid (PFOS), a chemical that was voluntarily phased out by its U.S. manufacturers. PFBS has been identified in the environment and consumer products, including surface water, wastewater, drinking water, dust, carpeting and carpet cleaners, floor wax, and food packaging.

PFBS and GenX chemicals are persistent in the environment and mobile in groundwater and surface water.

EPA's Draft Toxicity Assessments

In the risk assessment/risk management paradigm, a toxicity assessment is on the risk assessment side of the paradigm. The GenX chemicals and PFBS toxicity assessments cover the first two steps (Step 1. Hazard Identification and Step 2. Dose-Response) of the four-step risk assessment process, described by the National Academy of Science in 1983 as "the characterization of the potential adverse health effects of human exposures to environmental hazards." Characterizing risk, which is not done in these toxicity assessments, would require additional consideration of exposure. For further details about risk assessment see: https://www.epa.gov/risk/conducting-human-health-risk-assessment.

EPA's draft toxicity assessments for GenX chemicals and PFBS include the first two steps of the risk assessment paradigm described above, including developing oral references doses (RfDs). An RfD is a type of toxicity value specifically for non-cancer effects associated with the oral (ingested) route of exposure. A reference dose is 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. It can be derived from a no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. The higher the RfD, the higher the chemical dose needed to elicit potential adverse health effects.

EPA followed the general guidelines for risk assessment set by the National Research Council (1983) and characterized in a variety of EPA risk assessment guidance and recommendations[1] in identifying the hazards and determining the points of departure (PODs) for the derivation of the RfDs for these chemicals. Consistent with the recommendations presented in EPA Guidelines, EPA considered and applied uncertainty factors to the POD to address, where applicable, intraspecies variability, interspecies variability, extrapolating from the LOAELs to the NOAELs, deficiencies in the database, and extrapolation of study data from a subchronic to a chronic exposure duration.

When final, the toxicity values from the GenX chemicals and PFBS assessments can be combined with specific exposure information (Step 3. Exposure Assessment) by government and private entities to help characterize (Step 4. Risk Characterization) public health risks of these chemicals. Thus, once the GenX chemicals and PFBS assessments are final, EPA will work with our state, tribal, and local partners to provide technical assistance, including information about appropriate regulations and statutes, as they begin considering the final values in relevant exposure scenarios. It is the risk management part of the risk assessment/risk management paradigm where the supporting science, as well as statutory and legal considerations, risk management options, public health considerations, cost/benefit considerations, economic factors, social factors, and other considerations are weighed.

The draft toxicity assessments underwent independent, external expert peer review in June and July 2018. EPA considered the peer reviewers' comments and revised the draft assessments accordingly. External peer review comments and EPA's responses can be viewed at: www.epa.gov/pfas.

[1] www.epa.gov/risk/risk-assessment-guidelines#tab-1

GenX Chemicals: Health Effects Summary

Oral animal (rat, mouse) toxicity studies for HFPO dimer acid and its ammonium salt conducted according to test guidelines (i.e., Organisation for Economic Co-operation and Development (OECD) and EPA Office of Pollution Prevention and Toxics (OPPT)) were available for acute, short-term, subchronic, and chronic durations of exposure. Additionally, oral animal studies reported liver toxicity (increased relative liver weight, hepatocellular hypertrophy, and single cell necrosis), kidney toxicity (increased relative kidney weight), immune effects (antibody suppression), developmental effects (increased early deliveries and delays in genital development), and cancer (liver and pancreatic tumors) at doses ranging from 0.5 mg/kg-day to 1000 mg/kg-day. Overall, the toxicity studies available demonstrate that the liver is particularly sensitive to HFPO dimer acid- and HFPO dimer acid ammonium salt-induced toxicity. Currently, there are not enough data to determine the mode of action GenX chemicals are operating under to illicit these effects in animals.

GenX Chemicals: Reference Dose

The critical study chosen for determining the subchronic and chronic RfDs for HFPO dimer acid and its ammonium salt is the oral reproductive/developmental toxicity study in mice and the critical effect is in the liver (single cell necrosis in males) (DuPont-18405-1037, 2010). While other effects were observed (kidney toxicity, immunological effects, developmental effects, and cancer), effects on liver were observed consistently across all studies which supported selection of this endpoint and critical study. Liver effects were observed in both male and female mice and rats at varying durations of exposures and doses. Because liver effects such as increases in liver weight and hypertrophy can be associated with activation of cellular peroxisome proliferator-activated receptor (PPAR)-α, a process unique to rodents, the EPA assessed the relevance of the liver effects to humans using established criteria (Hall et al., 2012). Based on these criteria, only those doses associated with effects classified as adverse in humans (e.g., histologic or clinical pathology indicative of liver toxicity such as changes in liver enzyme concentrations in the serum, necrosis, inflammation, and degeneration) were used for the point of departure (POD) quantification.

Using EPA's *Benchmark Dose Technical Guidance Document* (2012), benchmark dose modeling was used to empirically model the dose-response relationship in the range of observed data. Consistent with the EPA's Benchmark Dose Technical Guidance (USEPA, 2012), the BMD and the BMDL were estimated using a BMR of 10% extra risk for dichotomous data to facilitate a consistent basis of comparison across endpoints, studies, and assessments. The best fitting model was the Multistage 2 model based on adequate p values (>0.1), the BMDLs are sufficiently close, and the Multistage 2 model had the lowest Akaike information criterion (AIC). Additionally, EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (2011) was used to allometrically scale a toxicologically equivalent dose of orally administered agents from adult laboratory animals to adult humans. The use of allometric scaling addresses some aspects of cross-species extrapolation of toxicokinetic and toxicodynamic processes (i.e., interspecies UF). The resulting $BMDL_{10}$ POD human equivalent dose (HED) is 0.023 mg/kg-day. UFs applied include a 10 for intraspecies variability (UF_H), 1 because the POD is a BMDL (UF_L), 3 for interspecies differences (UF_A), 1 for extrapolation from a subchronic to a chronic duration (UF_S), and 3 for database deficiencies (UF_D) in immune effect studies and additional developmental studies, to yield a subchronic RfD of 0.0002 mg/kg-day (Table 1). For the chronic RfD, the same UFs were applied with the addition of a UF_S of 3, which resulted in a chronic RfD of 0.00008 mg/kg-day (Table 1).

Table 1. Summary of Draft Reference Doses for GenX Chemicals

	Critical Study	Critical Effect	POD HED*	Total UF	Draft RfD
Draft Subchronic RfD	Reproductive/ developmental toxicity study; DuPont-18405-1037 (2010)	Single cell necrosis in the liver	$BMDL_{10}$ = 0.023 mg/kg-day	UF_H-10 UF_A-3 UF_L-1 UF_S-1 UF_D-3 Total UF-100	**0.0002 mg/kg-day**
Draft Chronic RfD	Reproductive/ developmental toxicity study; DuPont-18405-1037 (2010)	Single cell necrosis in the liver	$BMDL_{10}$ = 0.023 mg/kg-day	UF_H-10 UF_A-3 UF_L-1 UF_S-3 UF_D-3 Total UF-300	**0.00008 mg/kg-day**

** Allometric scaling adjustment according to EPA guidance using default body weight ¾ scaling*

PFBS: Health Effects Summary

High and medium confidence animal (rat and mouse) toxicity studies from oral exposure to PFBS and its potassium salt were available for acute, short-term, subchronic, and gestational exposure durations, as well as a two-generation reproductive toxicity study. A group of low and medium confidence observational human studies of PFBS exposure and health effects were identified, but their ability to inform conclusions was limited. Health outcomes evaluated across available studies included effects on the thyroid, reproductive organs and tissues, developing offspring, liver, lipids and lipoproteins, immune system, and kidneys following oral exposure to PFBS. Overall, from the identified targets of PFBS toxicity, the thyroid and kidney are particularly sensitive targets of PFBS-induced toxicity.

PFBS: Candidate Reference Doses

Candidate subchronic and chronic RfDs were derived for both thyroid and kidney effects associated with PFBS. For thyroid effects, the critical study chosen for determining the candidate subchronic and chronic RfDs for PFBS and its potassium salt is the oral gestational exposure study in mice (Feng et al., 2017) and the critical effect is on the thyroid (decreased serum total thyroxine) in offspring. Using EPA's Benchmark Dose Technical Guidance Document (2012), benchmark dose modeling was used to empirically model the dose-response relationship in the range of observed data. Additionally, EPA's Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose (2011) was used to allometrically scale a toxicologically equivalent dose of orally administered agents from animals to humans. The use of allometric scaling addresses some aspects of cross-species extrapolation of toxicokinetic and toxicodynamic processes (i.e., interspecies UF). The resulting point of departure (POD) human equivalent dose (HED) is 4.2 mg/kg-day. Uncertainty factors applied include a 10 for intraspecies variability (UF_H), 3 for interspecies differences (UF_A), 1 because the POD is a BMDL (UF_L), 1 because the POD comes from a developmental study (UF_S), and 3 for database deficiencies (UF_D), including the lack of developmental neurotoxicity and immune effect studies, to yield a candidate subchronic RfD of 0.04 mg/kg-day (Table 2). In the derivation of the chronic RfD, in addition to the

uncertainty factors above, the UF_D was increased to 10 to account for the lack of chronic duration studies, to yield a candidate chronic RfD of 0.01 mg/kg-day (Table 2).

For kidney effects, the critical study chosen for determining the candidate subchronic and chronic RfDs for PFBS and its potassium salt is the two-generation reproductive toxicity study in rats (Lieder et al., 2009b) and the critical effect is kidney histopathology, specifically papillary epithelial tubular/ductal hyperplasia in adult female rats. Using EPA's Benchmark Dose Technical Guidance Document (2012), benchmark dose modeling was used to empirically model the dose-response relationship in the range of observed data. Additionally, EPA's Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose (2011) was used to allometrically scale a toxicologically equivalent dose of orally administered agents from animals to humans. The use of allometric scaling addresses some aspects of cross-species extrapolation of toxicokinetic and toxicodynamic processes (i.e., interspecies UF). The resulting point of departure (POD) human equivalent dose (HED) is 11.5 mg/kg-day. Uncertainty factors applied include a 10 for intraspecies variability (UF_H), 3 for interspecies differences (UF_A), 1 because the POD is a BMDL (UF_L), 1 because the POD comes from a study of subchronic duration (UF_S), and 3 for database deficiencies (UF_D), including the lack of developmental neurotoxicity and immune effect studies, to yield a candidate subchronic RfD of 0.1 mg/kg-day (Table 2). In the derivation of the chronic RfD, in addition to the uncertainty factors above, the UF_S was increased to 10 to account for the lack of chronic duration studies, to yield a candidate chronic RfD of 0.01 mg/kg-day (Table 2).

In light of the consistent observation of the thyroid effects across life stages and the greater dose response sensitivity, relative to the kidney effects, EPA is proposing to base the overall subchronic and chronic RfDs on the thyroid effects. See the Federal Register Notice announcing the availability of the draft assessment for PFBS and requesting public review and comment on this proposal in addition to the approaches and conclusions in the PFBS assessment.

Table 2. Summary of Draft Reference Doses for PFBS

	Critical Study	**Critical Effect**	**POD (HED)***	**Total UF**	**Draft Candidate RfD**
Draft Candidate Subchronic RfD (thyroid effects)	Gestational exposure study (GD1-20); Feng et al. (2017)	Decreased serum total T4 in newborn (PND1) mice	$BMDL_{20}$ = 4.2 mg/kg-day	UF_H-10 UF_A-3 UF_L-1 UF_S-1 UF_D-3 Total UF-100	**0.04 mg/kg-day**
Draft Candidate Subchronic RfD (kidney effects)	Two-generation reproductive study; Lieder et al. (2009b)	Kidney histopathology – papillary epithelial tubular/ductal hyperplasia in adult female rats	$BMDL_{10}$ = 11.5 mg/kg-day	UF_H-10 UF_A-3 UF_L-1 UF_S-1 UF_D-3 Total UF-100	**0.1 mg/kg-day**
Draft Candidate Chronic RfD (thyroid effects)	Gestational exposure study (GD1-20); Feng et al. (2017)	Decreased serum total T4 in newborn (PND1) mice	$BMDL_{20}$ = 4.2 mg/kg-day	UF_H-10 UF_A-3 UF_L-1 UF_S-1 UF_D-10 Total UF-300	**0.01 mg/kg-day**
Draft Candidate Chronic RfD (kidney effects)	Two-generation reproductive study; Lieder et al. (2009b)	Kidney histopathology – papillary epithelial tubular/ductal hyperplasia in adult female rats	$BMDL_{10}$ = 11.5 mg/kg-day	UF_H-10 UF_A-3 UF_L-1 UF_S-10 UF_D-3 Total UF-1000	**0.01 mg/kg-day**

** Allometric scaling adjustment according to EPA guidance using default body weight ¾ scaling*

Chronic Toxicity Comparison

EPA previously published final health effects support documents for two other PFAS: PFOA and PFOS. Based on these EPA assessments, the draft chronic RfD for GenX chemicals is within one order of magnitude (4x) higher than the chronic RfDs for PFOA and PFOS (Table 3). The draft chronic RfDs for PFBS are approximately three orders of magnitude (~1000x) higher than the chronic RfDs for these other PFAS (Table 3). Therefore, based on currently available animal toxicity data, it appears that GenX chemicals are slightly less toxic and PFBS is much less toxic than PFOA and PFOS.

Table 3. Comparison of Chronic Toxicity for PFAS With EPA Health Effects Assessments

Chemical [Citation]	**EPA Chronic RfD [mg/kg-day]**	**Critical Effect (Study)**
GenX Chemicals [EPA 2018a (*PUBLIC REVIEW DRAFT*)]	0.00008	Single cell necrosis in the liver (DuPont 18405-1037, 2010)
PFBS [EPA 2018b (*PUBLIC REVIEW DRAFT*)] – Candidate RfD for thyroid effects	0.01	Decreased serum T4 in newborn mice (Feng et al., 2017)
PFBS [EPA 2018b (*PUBLIC REVIEW DRAFT*)] – Candidate RfD for kidney effects	0.01	Increased incidence of kidney papillary epithelial tubular/ductal hyperplasia in the rats (Lieder et al., 2009b)
PFOA [EPA 2016a (FINAL)]	0.00002	Skeletal effects and accelerated puberty in males (Lau et al., 2006)
PFOS [EPA 2016b (FINAL)]	0.00002	Decreased pup weight in rats (Luebker et al., 2005)

Applications for Risk Assessment and Risk Management

Following publication of final health effects assessments, these RfDs will provide information on health effects and may be used to inform health-based national standards, clean-up levels at local sites, and non-regulatory advisory levels. RfDs can be applied in a variety of exposure scenarios to characterize potential risk from chemical exposure and develop health protective levels for chemicals in water, soil, and other media. For example, RfDs can be combined with exposure information to develop regulatory standards (e.g., Maximum Contaminant Levels) or non-regulatory guideline values (e.g., health advisories) for drinking water under the Safe Drinking Water Act (SDWA), and human health water quality criteria for permitting discharges into ambient waters under the Clean Water Act (CWA). RfDs are also used in risk assessments under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), also known as Superfund; under the CWA for pollutants in biosolids; and under the Resource Conservation and Recovery Act (RCRA) to develop cleanup levels for contaminated soil and groundwater. The levels developed for these risk management tools may vary due to the type of exposure being evaluated. As such, the RfD is not meant to be the standard itself, but the starting point for risk managers to develop those standards.

Once final, the EPA will work with our state, tribal, and local partners to provide technical assistance as they begin considering the final values in relevant exposure scenarios. It is the risk management part of the risk assessment/risk management paradigm where the supporting science, as well as statutory and legal considerations, risk management options, public health considerations, cost/benefit considerations, economic factors, social factors, and other considerations are weighed.

How to Learn More and Provide Comments

To view the draft toxicity assessments and other related information on GenX chemicals and PFBS, visit www.epa.gov/pfas.

Submit your comments, identified by Docket ID No. EPA-HQ-OW-2018-0614, to the public docket at: http://www.regulations.gov. Follow the online instructions for submitting comments. Once submitted, comments cannot be edited or withdrawn. For additional submission methods, the full EPA public comment policy, information about confidential business information or multimedia submissions, and general guidance on making effective comments, please visit http://www2.epa.gov/dockets/commenting-epa-dockets.

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