Human Health Toxicity Assessment for GenX Chemicals

In October 2021, EPA released the final human health toxicity assessment for hexafluoropropylene oxide (HFPO) dimer acid and its ammonium salt (referred to as "GenX chemicals") based on the Agency's review and analysis of the best available science on the health effects of these two chemicals (EPA, 2021a). The toxicity information and values included in the assessment can be useful to various EPA programs, other federal agencies, and state, tribal, and local communities facing GenX chemicals contamination issues. The GenX chemicals human health toxicity assessment can be used along with exposure information and other important considerations to allow policy makers to determine if, and when, it is appropriate to take action to reduce exposure to a chemical. For example, the oral toxicity values (reference doses or RfDs) included in this assessment can be used in various exposure scenarios to assess potential human health risk, such as when developing a drinking water health advisory.

Background

GenX chemicals are man-made, fluorinated organic chemicals that are part of the PFAS chemical class. PFAS have been manufactured and commercially used since the 1940s in the U.S. in many applications because of their unique physical properties such as resistance to high and low temperatures, resistance to degradation, and nonstick characteristics. HFPO dimer acid and its ammonium salt are the major chemicals produced from the GenX processing aid technology and have been used as replacements for PFOA since 2009. GenX chemicals may also be generated as a byproduct of fluoromonomer production. Because GenX chemicals can be used as a replacement for PFOA, they may be used in a similar fashion in the manufacture of the same or similar fluoropolymer end products. However, EPA does not have specific information from manufacturers on which commercial products rely on GenX chemicals as a processing aid. GenX chemicals have been found in surface water, groundwater, finished drinking water, rainwater, and air emissions.

What's in the Toxicity Assessment

EPA's toxicity assessment for GenX chemicals (EPA, 2021a) includes hazard identification and dose response assessment and results in the development of chronic and subchronic oral RfDs. An RfD is a toxicity value specifically for non-cancer effects associated with the oral (ingestion) route of exposure. An RfD is an estimate 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. For GenX chemicals, the subchronic RfD is based on the same hazard and dose-response information as the chronic RfD but is specifically derived for a shorter, less-than-lifetime duration of exposure. RfDs can be derived from a no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), or benchmark dose (through quantitative modeling) approach and applying uncertainty factors to account for data gaps. Further details about EPA human health risk assessment can be found online at: https://www.epa.gov/risk/conducting-human-health-risk-assessment.

EPA followed current EPA risk assessment guidance and recommendations[1] in identifying the health hazards and determining the points of departure (PODs) considered for the derivation of the RfDs for GenX chemicals. Consistent with the recommendations presented in EPA guidelines and current practice documents, EPA considered and applied uncertainty factors to the selected PODs to address, where applicable, intraspecies variability, interspecies variability, deficiencies in the database, extrapolating from LOAELs to NOAELs, and extrapolation of study data from a subchronic to a chronic exposure duration to develop the toxicity values.

The draft GenX chemicals toxicity assessment underwent agency review and two external independent expert peer reviews as well as public review and comment. EPA considered the reviewers' and public comments and revised the draft assessment accordingly to produce the final toxicity assessment document. External peer review comments and EPA's responses can be viewed online at: https://www.epa.gov/pfas/genx-chemicals-toxicity-assessments-documents. The public comments are available on Regulations.gov in the Docket ID No. EPA-HQ-OW-2018-0614.

Health Effects Summary

Most of the available data for HFPO dimer acid and its ammonium salt were submitted to EPA by DuPont/Chemours, the manufacturer of GenX chemicals, under the Toxic Substances Control Act (TSCA), as required pursuant to a consent order (EPA, 2009) or as required TSCA reporting requirements (15 U.S.C. § 2607.8(e)). Most of these submitted studies were conducted according to the Organisation for Economic Co-operation and Development (OECD) test guidelines, followed Good Laboratory Practices (GLP) and/or adhered to EPA health effects test guidelines for pesticides and toxic substances. Additionally, EPA conducted literature searches to identify the publicly available, peer-reviewed literature for HFPO dimer acid and its ammonium salt. All studies containing dose-response information submitted from DuPont/Chemours and the publicly available, peer-reviewed literature were evaluated for study quality using an approach consistent with the EPA Office of Research and Development (ORD) Handbook for developing IRIS assessments (EPA, 2020). Study quality was determined by two independent reviewers who assessed risk of bias and sensitivity for the following domains: reporting quality, risk of bias (selection or performance bias, confounding/variable control, and reporting or attrition bias), and study sensitivity (exposure methods sensitivity, and outcome measures and results display). A third reviewer made the final decision on the quality ratings based on primary ratings.

Oral animal (rat, mouse) toxicity studies for HFPO dimer acid and its ammonium salt were available for acute, short-term, subchronic, and chronic durations of exposure. These 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 available toxicity studies demonstrate that the liver is particularly sensitive to exposure to GenX chemicals. Currently, there are not enough data to determine the mode of action GenX chemicals are operating under to illicit these effects in animals.

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

Reference Doses

Subchronic and chronic RfDs were derived for liver effects associated with GenX chemicals. An oral reproductive/developmental toxicity mouse study (DuPont-18405-1037, 2010) and its pathologic demonstration of liver effects, specifically the constellation of lesions including cytoplasmic alteration, hepatocellular single-cell and focal necrosis, and hepatocellular apoptosis in females were selected as the critical study and effect, respectively, for deriving the subchronic and chronic RfDs for HFPO dimer acid and its ammonium salt. The RfD based on this group of effects occurred at the lowest dose among the available dose-response studies and therefore provides the most health-protective RfD among the modeled endpoints based on the available data. The selection of the constellation of lesions is supported by the National Toxicology Program (NTP) Pathology Working Group's (PWG) conclusion that the dose response and constellation of lesions (i.e., cytoplasmic alteration, apoptosis, single-cell necrosis, and focal necrosis) rather than one lesion by itself, represents adversity within the confines of the study.

Several of the other studies provide support for the selection of the DuPont-18405-1037 (2010) study as the critical analysis and the constellation of liver lesions as the critical effect on which to base the subchronic and chronic RfDs. The liver is the primary target organ for toxicity from oral exposure to HFPO dimer acid and its ammonium salt. Liver effects are observed in both male and female mice and rats at varying durations of exposure and doses of GenX chemicals. Specifically, changes in liver enzyme levels, histopathological lesions, and tumors are observed in both male and female mice and rats at varying durations of exposures (15 days to 2 years) and doses of these GenX chemicals (0.5–1,000 mg/kg/day).

Benchmark dose modeling was used to empirically model the dose-response relationship in the range of observed data (EPA, 2012). EPA endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic (PBTK) modeling (EPA, 2011). In the absence of a PBTK model for GenX chemicals, the use of chemical-specific information to derive a data-informed derivation of human equivalent oral exposures is the next preferred approach. Though some human half-life information exists for GenX chemicals, it is limited and has not been subject to peer review. EPA concluded that data for GenX chemicals are not adequate to support derivation of a data-informed dosimetric adjustment and employed the default procedure of body weight scaling to the ¾ power (i.e., $BW^{3/4}$) to derive human equivalent oral exposures from animal studies. The resulting point of departure (POD) human equivalent dose (HED) for liver effects is 0.01 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 for duration extrapolation because the POD comes from a subchronic study (UF_S), and 10 for database deficiencies (UF_D), to yield a **subchronic RfD of 0.00003 mg/kg-day** (Table 1). In the derivation of the chronic RfD, in addition to the uncertainty factors above, the UF_S was increased to 10 to further account for the lack of chronic duration studies, to yield a **chronic RfD of 0.000003 mg/kg-day** (Table 1).

Table 1. Final GenX Chemicals Reference Doses (RfDs)

Reference Dose	Critical Effect and Principal Study	POD (HED)* (mg/kg-day)	Total UF	RfD (mg/kg-day)
Subchronic RfD	Liver constellation of lesions in parental female mice (DuPont-18405-1037, 2010)	$BMDL_{10}$ = 0.01	300	$\mathbf{3 \times 10^{-5}}$
Chronic RfD	Liver constellation of lesions in parental female mice (DuPont-18405-1037, 2010)	$BMDL_{10}$ = 0.01	3000	$\mathbf{3 \times 10^{-6}}$

** The Human Equivalent POD (POD [HED]) was calculated from the POD using the body weight to the ¾ scaling as per EPA guidance (EPA, 2011).*

Applications for Risk Assessment and Risk Management

The GenX chemicals toxicity assessment provides qualitative and quantitative toxicity information that can be used along with exposure information and other important considerations to assess potential health risks to determine if, and when, it is appropriate to take action to address this chemical. This assessment is available for use across multiple EPA program and regional offices, other federal agencies, states, tribes, external stakeholders, and other entities, as needed. The RfDs and associated hazard evidence in the toxicity assessment provides information on health effects after exposure to GenX chemicals and can be combined with specific exposure information 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 help characterize potential risk from chemical exposure.

RfDs can be used to develop health protective levels based on oral exposure for chemicals in drinking water, ambient water, soil, and other media through further analyses. For example, RfDs can be combined with exposure information in risk assessments, and subsequent risk management activities can lead to the development of regulatory standards (e.g., Maximum Contaminant Levels) or non-regulatory 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 other laws: the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), also known as Superfund; the CWA to assess the potential risk of pollutants in biosolids; and the Resource Conservation and Recovery Act (RCRA) to develop cleanup levels for contaminated soil and groundwater. The levels developed for these risk management applications may vary due to the type of exposure being evaluated. As such, the RfD is not a standard itself, but a fundamental piece of the risk assessment along with other information considered by risk managers to develop those standards/levels.

Where to Find More Information

To view the toxicity assessment, EPA's response to public and peer review comments, and other related information on GenX chemicals, go to: https://www.epa.gov/pfas/genx-chemicals-toxicity-assessments-documents.

To view the *PFAS Strategic Roadmap: EPA's Commitments to Action 2021-2024*, go to: https://www.epa.gov/pfas/pfas-strategic-roadmap-epas-commitments-action-2021-2024.

References

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