Executive Summary

The U.S. Environmental Protection Agency (EPA) is issuing draft subchronic and chronic oral toxicity values (i.e., reference doses, or RfDs) for 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoic acid (Chemical Abstracts Service Registry Number (CASRN) 13252-13-6)—or hexafluoropropylene oxide (HFPO) dimer acid—and 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoate (CASRN 62037-80-3)—or HFPO dimer acid ammonium salt for public comment. These chemicals are also known as "GenX chemicals" because they are the two major chemicals associated with GenX processing aid technology. The toxicity assessment for GenX chemicals is a scientific and technical report that includes toxicity values associated with potential noncancer health effects following oral exposure (in this case, oral reference doses (RfDs). This assessment evaluates human health hazards. The toxicity assessment and the values contained within is not a risk assessment as it does not include an exposure assessment nor an overall risk characterization. Further, the toxicity assessment does not address the legal, political, social, economic, or technical considerations involved in risk management. When final, the GenX chemicals toxicity assessment can be used by EPA, states, tribes, and local communities, along with specific exposure and other relevant information, to determine, under the appropriate regulations and statutes, if, and when, it is necessary to take action to address potential risk associated with human exposures to GenX chemicals.

These GenX chemicals are fluorinated organic chemicals that are part of a larger group of chemicals referred to as "per- and polyfluoroalkyl substances." In 2006, the PA initiated a stewardship program with the goal of eliminating chemical emissions of perfluorooctanoic acid (PFOA) and related chemicals by 2015. GenX chemicals are replacements for PFOA. Specifically, GenX is a trade name for a processing aid technology that enables the creation of fluoropolymers without the use of PFOA. Fluoropolymers are used in many applications, including the manufacture of nonstick coatings for cookware, water repellent garments, and other specialty agrochemical and pharmaceutical applications.

For HFPO dimer acid and its ammonium salt, oral animal toxicity studies of acute, short-term, subchronic, and chronic duration are available in rats and mice. Limited information identifying health effects from inhalation or dermal exposures to GenX chemicals in animals is available. Repeated-dose toxicity data are available for oral exposure, but not for the other exposure routes (inhalation and dermal exposures). Thus, this assessment applies only to the oral route of exposure. One oral reproductive and developmental toxicity study in mice and one prenatal developmental toxicity study in rats are available. These studies report 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). Overall, the available toxicity studies demonstrate that the liver is particularly sensitive to HFPO dimer acid- and HFPO dimer acid ammonium salt-induced toxicity.

The EPA followed the general guidelines for risk assessment set forth by the National Research Council (1983) and the EPA's *Framework for Human Health Risk Assessment to Inform Decision Making* (2014a) in determining the point of departure (POD) for the derivation of the RfDs for these chemicals. Consistent with the recommendations presented in the EPA's *A Review of the Reference Dose and Reference Concentration Processes* (USEPA 2002), the

Agency applied uncertainty factors (UF) to address intraspecies variability, interspecies variability, and extrapolation from a subchronic to a chronic exposure duration.

The critical study chosen for determining the subchronic and chronic RfDs for HFPO dimer acid and/or its ammonium salt is the oral reproductive/developmental toxicity study in mice with a no-observed-adverse-effect level of 0.1 milligrams per kilogram per day (mg/kg/day) based on liver effects (single-cell necrosis in males) (DuPont-18405-1037, 2010). Using the 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, the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (2011b) 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 uncertainty factor). The resulting POD human equivalent dose is 0.023 mg/kg/day. UF applied include a 10 for intraspecies variability, 3 for interspecies differences, and 3 for database deficiencies, including immune effects and additional developmental studies, to yield a subchronic RfD of 0.0002 mg/kg/day. In addition to those above, a UF of 3 was also applied for extrapolation from a subchronic to a chronic duration in the derivation of the chronic RfD of 0.00008 mg/kg/day.