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The New Jersey Department of Environmental Protection (NJDEP) is pleased to provide the attached comments on the draft reports entitled *Draft Human Health Toxicity Assessments for Hexafluoropropylene Oxide Dimer Acid and its Ammonium Salt (GenX Chemicals)* and *Draft Human Health Toxicity Assessments for Perfluorobutane Sulfonic Acid (PFBS) and Related Compound Potassium Perfluorobutane Sulfonate*. The draft document was reviewed by NJDEP Division of Science and Research scientists who have extensive experience and expertise related to per- and polyfluoroalkyl substances (PFAS). NJDEP was one of the first state agencies in the nation to develop drinking water guidance for PFAS, including a chronic (lifetime) drinking water guidance value for PFOA of 40 ng/L in 2007. DSR scientists have also authored and co-authored several peer-reviewed papers on PFAS. These include a recent paper on key scientific issues in developing drinking water guidelines for PFAS, a paper on a PFOS Reference Dose based on immune toxicity, a highly cited review of PFOA as an emerging drinking water contaminant, an epidemiological study of associations of PFAS with hepatic effects in the general population, and three publications on occurrence, risk assessment, and sources of PFAS in drinking water.

Our comments address both general issues related to USEPA's assessment of PFAS as replacements for phased-out long-chain perfluoroalkyls acids (PFAAs) and specific points in the GenX and PFBS toxicity assessments. Our comments on the GenX assessment are more extensive than for PFBS, since NJDEP is more familiar with the scientific literature for GenX.

Thank you for the opportunity to comment on this important topic. If you have any questions or would like additional information, please contact Dr. Gloria Post of my staff at gloria.post@dep.nj.gov.

Sincerely,

Gary A. Buchanan, Ph.D.
Director

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Comments on USEPA Draft Human Health Toxicity Assessments for GenX and PFBS Submitted to Regulations.gov Docket ID: EPA-HQ-OW-2018-0614

NJDEP Division of Science and Research

January 22, 2019

General comments on USEPA's assessment of PFAS replacements for phased out long-chain perfluoroalkyl acids (PFAAs)

At the 2018 PFAS National Leadership Summit, USEPA stated that 900 PFAS entered the USEPA TSCA new chemical program between 2006 and 2018, and USEPA has reviewed 900 studies for only about 200 of these 900 new substances[1]. According to USEPA, only a small percentage of these 900 studies evaluated repeated dose toxicity, carcinogenicity, reproductive/developmental effects, or toxicokinetics (Morris, 2018) - the information needed to develop toxicity values such as Reference Doses. As stated elsewhere by USEPA, "The wide range in properties and limited available data on the majority of PFASs notices received [by USEPA] presents challenges in risk assessment process, requiring risk assessors to make use of limited analog information, professional judgement and often assumptions." (Henry, 2015). Taken together, these statements clearly indicate the need for more complete toxicity data and more thorough review of available information on PFAS replacements before they are approved by USEPA.

Just one specific example of the potential toxicity of replacement PFAS already approved by USEPA based on minimal toxicity data is the substance referred to as "Solvay's Product" (CAS #329238-24-6) by Wang et al. (2013). Solvay's product is a mixture of fluorinated polyether congeners with ≥7 carbons. It was approved by USEPA as a replacement for long-chain PFAAs in fluoropolymer production, and multiple congeners of the product have been tentatively identified in environmental media in New Jersey (USEPA, 2019).

To NJDEP's knowledge, the only publicly available toxicity information for Solvay's product (CAS #329238-24-6) is for genotoxicity (EFSA, 2010). As is generally the case for PFAS, the product was negative for genotoxicity. However, repeated dose toxicity, reproductive/developmental effects, carcinogenicity and toxicokinetics (i.e. bioaccumulative potential) have not been studied. For comparison, Solvay's product consisting of congeners with ≥7 carbons is larger than GenX, a 6-carbon perfluorinated ether. As discussed in detail below, the data now available show that GenX causes toxicity at relatively low doses, and USEPA concluded that GenX is more potent than PFOA in mice, the most sensitive animal species for both compounds. Since toxicity and bioaccumulative potential of PFAS generally increase with longer carbon chain length, the data for GenX showing multiple non-carcinogenic and carcinogenic effects suggest that the longer chain-length polyether PFAS, such as the Solvay

[1] https://youtu.be/ayV8QqWJEr4, accessed January 8, 2019

product, may similarly cause toxicological effects of concern. Potentially relevant to this issue, fluorinated polyether compounds that are larger than GenX, but not GenX itself, have recently been detected at parts per billion levels in the blood serum of individuals with drinking water exposure to both GenX and the larger compounds (NC State University, undated; NC State University, 2018), indicating that these larger polyfluorinated polyether PFAS are bioaccumulative in humans. It is clear from the information above that it cannot be assumed that short-chain PFAS with non-PFAA structures, such as GenX, are "safe" replacements for phased out long-chain PFAAs. Obviously, these potential concerns are even greater for non-PFAA replacements of longer chain-length than GenX that were approved with minimal or no relevant data.

In addition to potential health effects, there are other important concerns about the PFAS that have been approved by USEPA as replacements for long-chain PFAAs. In contrast to the phased-out long-chain PFAAs which are detected by routinely available analytical methods, most replacement PFAS can only be detected by proprietary analytical methods or research laboratories (although GenX and a few others were recently added to Method 537.1 by USEPA). Additionally, like the phased-out long chain PFAAs, many replacement PFAS do not break down in the environment and will persist indefinitely, raising concerns for human health and ecological effects.

General comments on USEPA's assessment of GenX

In summary, the toxicological information for GenX presented by USEPA raises concern about its use as replacement for PFOA. In summary, the toxicological effects of GenX are similar to those of PFOA, and, as discussed in detail below, USEPA concluded that GenX is more potent than PFOA in mice, the species used as the basis for risk assessment for both compounds. It is noted that GenX was approved by USEPA as a PFOA replacement before key toxicology evaluations, including reproductive/developmental and chronic/carcinogenicity studies, were conducted. Subsequent to USEPA's approval, GenX was indeed found to cause reproductive, developmental, and carcinogenic effects. GenX has been released into the environment and has been found in environmental media in the U.S. and overseas, including:

- In private potable wells near an industrial source in NJ (NJDEP data).
- In the Delaware River between NJ and PA (Pan et al., 2018).
- In surface water and ground water sources, including private wells and surface water used as a public water system source, and finished public drinking water near an industrial source in NC (Strynar et al., 2015; Sun et al., 2016; NCDEQ, undated).
- In public and private drinking water wells, and in surface water, near an industrial source in Ohio and WV (Lindstrom et al., 2017; Hogue, 2018),
- In drinking water, surface water, and plants near an industrial source in the Netherlands (Gebbink et al., 2017; Brandsma et al., 2018)

- Ubiquitously in surface water locations sampled in China, the U.S., the United Kingdom, Sweden, Germany, the Netherlands, and Korea (Pan et al., 2018).

It is unfortunate that USEPA did not develop toxicity values for GenX until after this widespread contamination was discovered and became a public concern.

Differences in approaches used in GenX and PFBS assessments

While recognizing that the GenX and PFBS assessments were developed by different USEPA programs, it is noted that the approaches and information included in the two documents differ in several important ways.

For example, the GenX study evaluations were based on the approach described in the USEPA (2018) document "Application of Systematic Review in TSCA Risk Evaluations" while the PFBS study evaluations were based on Health Assessment Workplace Collaboration (HAWC) software. The evaluation criteria and scoring systems for these two approaches are not identical, and these differences could result in differing conclusions about the level of confidence in a study, potentially affecting the overall outcome of the toxicity evaluation. It is unclear whether USEPA considers one or the other of these approaches to be preferable, or if both are equally acceptable. It is suggested that USEPA provide the rationale for using these different approaches and whether a singular approach or multiple approaches will be used in future USEPA evaluations of PFAS.

In addition to the difference in approaches, the PFBS document discusses the level of confidence in the Reference Doses while the level of confidence in the Reference Doses is not presented in the GenX document.

General comments on Draft GenX Toxicity Assessment

As reviewed in the draft document, GenX causes toxicological effects similar to those caused by PFOA, including toxicity to the liver, kidney, blood, and immune system, as well as reproductive and developmental effects, and tumors. Furthermore, recent studies of GenX not considered in the draft USEPA assessment report additional toxicological effects including postnatal mortality and delayed mammary gland development, the latter of which is known to be a sensitive developmental endpoint for PFOA (Conley et al., 2019; Cope et al., 2019).

Of particular note, the LOAEL identified by USEPA for GenX (0.5 g/kg/day) is lower than for PFOA (1 mg/kg/day; USEPA, 2016); both LOAELs are from mouse studies. Because of its more rapid excretion, the same administered dose results in a much lower internal dose for GenX than for PFOA. Therefore, the lower LOAEL for GenX indicates that, at least in mice, it is substantially more potent than PFOA on an internal dose basis.

Additionally, GenX increased the incidence of hepatic, pancreatic, and possibly testicular tumors in chronic rat studies; PFOA also caused these same three tumor types in chronic rat studies (Biegel et al., 2001; Butenhoff et al., 2012). Although not mentioned in the draft USEPA document, it is notable and concerning that PFOA increased only benign tumors (adenomas) while GenX increased both malignant (carcinomas) and benign tumors of the liver and pancreas (Caverly Rae et al., 2015; DuPont-18405-1238, 2013).

The USEPA chronic Reference Dose for GenX (80 ng/kg/day) is only four-fold higher than for PFOA (20 ng/kg/day; USEPA, 2016). However, these Reference Doses are not directly comparable because the PFOA Reference Dose considers the much longer half-life in humans versus mice, while the GenX Reference Dose is based on the default approach for interspecies extrapolation (a Dosimetric Adjustment Factor [DAF] based on body weight$^{3/4}$; USEPA, 2011) and does not fully take into account species differences in half-life. As discussed in more detail below, although the human half-life of GenX is not available, it is likely that it is much longer than in mice. If the human versus mouse half-life ratio for GenX is similar to the ratio for other PFAS, a chronic Reference Dose that considers the relative half-lives of the two compounds (i.e., GenX and PFOA) would be lower for GenX than for PFOA (based on the LOAELs identified by USEPA).

Specific comments on draft GenX evaluation

p. 13. First full paragraph.
It is unclear why the increases in serum albumin and albumin/globulin (A/G) ratio observed in rats and mice support the hypothesis that GenX binds to albumin, as stated here. To our knowledge, serum albumin levels are not affected by binding of xenobiotics to albumin. Additionally, it is stated later in the document (p. 29) that the increased A/G ratio is most likely due to decreased production of globulin, and that "the observed changes in albumin and A/G ratio…are considered early markers of potential immunotoxic effects" (p. 51).

p. 14. Section 2.3.4 – Metabolism, 2nd line.
Hepatocytes were incubated with 5 **micromolar** (not 5 "micrometers") of HFPO dimer acid ammonium salt.

p. 14. Section 2.3.5. – Metabolism-Urine, 3rd line.
The dose in the cited study (DuPont-18405-1017 RV1, 2011) was 30 mg/kg, not 10 mg/kg.

p. 20-21. Conceptual Model and Diagram.
The conceptual model and diagram should indicate that the information on organ systems affected comes from animal studies and that human epidemiological data is lacking for GenX. Additionally, the diagram should include fields for toxicokinetic information in humans and

laboratory animals (i.e. how external exposures translate into internal exposures), and it should indicate that toxicokinetic data for GenX in humans are not available.

p. 22-23. Section 3.2 – Overall Scientific Objectives.
The relationship between external exposure and internal dose (i.e. toxicokinetics) should be considered in developing a Point of Departure (POD) and should be included here. If relevant data are not available, this should be discussed as an important uncertainty.

p. 23. Bullets at top of page.
The explanations of subchronic and chronic durations need to be clarified. The durations for humans (up to 10% of a lifetime; greater than 10% of a lifetime) are not distinguished from the durations for laboratory animals (30 days to 90 days; 90 days to 2 years). It should be stated that subchronic duration of 30 to 90 days is up to about 10% of the lifespan of the laboratory animals and is intended to reflect human exposure of up to about 10% of the human lifespan. Similarly, exposure to animals of 90 days to 2 years is intended to reflect chronic/lifetime human exposure.

p. 23. First full paragraph, last line – carcinogenicity descriptor.
The phrase "…suggestive evidence of tumor formation…" should be revised to "*Suggestive Evidence of Carcinogenic Potential* in humans" as stated on p. 47. There is no doubt that GenX caused tumors in animals, but these tumor data have been interpreted as providing "suggestive evidence" for human carcinogenicity. Additionally, the description of the carcinogenic potential of GenX should be included in the Executive Summary, as in the PFBS document.

p. 23. Second full paragraph, evaluation of liver effects in the context of the Hall criteria. These comments also apply to discussions of this topic later in the document (pages 43 and 51).
NJDEP agrees with USEPA that the hepatic effects caused by GenX should be considered adverse. However, the rationale provided by USEPA should be clarified. USEPA states that increased liver weight or hepatocellular hypertrophy, in the absence of other liver toxicity, may result from PPAR-alpha activation which may be more relevant to rodents than humans. However, as discussed by NJDEP, the New Jersey Drinking Water Quality Institute (DWQI) and others elsewhere (DWQI, 2015; DWQI, 2017; DWQI, 2018; NJDEP, 2018; Post et al., 2017), multiple lines of evidence demonstrate that increased liver weight and hepatocellular hypertrophy caused by other PFAS (e.g. PFOA, PFNA, PFOS) are partially or primarily independent of PPAR-alpha. Additionally, USEPA states that when increased liver weight/hepatocellular hypertrophy are accompanied by necrosis, inflammation, or fibrosis, the increased liver weight and hepatocellular hypertrophy are considered adverse and relevant to humans. However, the rationale provided for this conclusion needs clarification, because it is not stated whether these more severe hepatic effects are considered to be potentially related to PPAR-alpha or not.

Importantly, as noted by Health Canada (2016), NJDEP (2018), and Michigan PFAS Science Advisory Panel (2018), when considering increased liver weight and hepatocellular hypertrophy in the development of a chronic Reference Dose, duration-of-exposure issues must be considered. Hall et al. (2012) emphasize that the *expected* duration of exposure must be considered in determining the adversity of hepatic effects such as increased liver weight and hepatocellular hypertrophy. Specifically, they state that:

> *"[Increased liver weight and hepatocellular hypertrophy] may be reversible if the anticipated duration of exposure is short, while progression to more severe hepatic effects may occur from longer exposures to the same dose. However, prolonged exposure to a xenobiotic at levels that have previously been shown to be adaptive may eventually result in liver cell injury due to a failure of adaptive mechanisms. In this case, the combination of dose level and duration of exposure to the xenobiotic under the terms and conditions of the new experiment would now be considered adverse."*

It should be noted that the primary focus of Hall et al. (2012) is hepatic effects observed in pre-clinical toxicity studies for drug development. In this scenario, drugs are normally administered for a limited period of time (i.e. less than chronic exposure). Hepatic effects which may result from exposure to the drug may be adaptive, particularly if they are reversible following cessation of exposure. In contrast, chronic Reference Doses are intended to protect for a lifetime of exposure. Therefore, reversibility upon cessation of exposure is not relevant, the potential for progression of initial effects to more severe effects must be considered. As such, potential reversibility when shorter-than-chronic exposure ends is not a reason to discount the adversity of increased liver weight and hepatocellular hypertrophy in chronic Reference Dose development, since these lesions may progress with longer exposure.

p. 26. Step 3. Use of body weight$^{3/4}$ scaling for animal-to-human toxicokinetic extrapolation (conversion of Point of Departure [POD] to Human Equivalent Dose [HED]).
The default approach recommended in the USEPA (2011) guidance cited by USEPA is body weight$^{3/4}$ scaling to account for toxicokinetic (and some toxicodynamic) differences in HED development, with application of an uncertainty factor of 3 to account for other interspecies differences. When chemical-specific data are available, USEPA (2011) recommends that other approaches (e.g. toxicokinetic modeling, or "intermediate approaches" based on "what is known about species differences, and the toxicokinetic and toxicodynamics of the chemical") be used to "derive an appropriate cross-species adjustment (e.g., a data-supported scaling function or a different UF or combination of the two)".

Although the human half-life of GenX is not available, it is likely that it is much longer than in mice. This conclusion is based on the relative human and mouse half-lives for other PFAS (long- and short-chain) for which data are available (Michigan PFAS Science Advisory Panel, 2018 - Table 2, updated from Lau, 2015). As such, the GenX risk assessment developed by The

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Netherlands National Institute for Public Health and the Environment (RIVM, 2016) considered the potentially much longer half-life in humans than in rodents with an interspecies toxicokinetic factor of 66, which is 10-fold greater than the factor of 6-7 based on the DAF of 0.14-0.15. If the human versus mouse half-life ratio for GenX is similar to the ratio for other PFAS, a chronic Reference Dose that considers the relative half-lives would be lower for GenX than for PFOA (based on the LOAELs identified by USEPA).

p. 27. First full paragraph, last line.
It is not clear what is meant by "the tumor data failed to demonstrate a direct response to dose." Statistically significant increases in pancreatic tumors in males and liver tumors in females were observed at the highest doses, but not lower doses. The highest doses were 50-fold and 10-fold greater than the next lowest doses in males and females, respectively.

p. 36. Last two paragraphs.
As above, it is notable and should be mentioned that GenX increased the incidence of hepatic carcinomas, as well as adenomas in female rats and the incidence of combined pancreatic acinar cells adenomas and carcinomas in male rats, while PFOA increased only the incidence of benign hepatic and pancreatic tumors in rats (Biegel et al., 2001).

p. 37. First full paragraph.
Although the incidence of testicular interstitial cell adenomas was not statistically significant compared to controls, the authors of the study conclude that "a relationship to treatment for these findings in the 50 mg/kg [i.e. high dose] group cannot be ruled out" (Caverly Rae et al., 2015). This conclusion should be noted in the USEPA document.

p. 37-40.
As noted by USEPA in the discussion of database uncertainties (p. 56), there are several major data gaps in the reproductive and developmental data. See comments about database uncertainties (p. 56) below.

p. 43. First full paragraph.
Hepatic steatosis is mentioned here as an indicator that is consistent with PPAR-alpha agonism, although this is not necessarily the case. A recent paper by USEPA scientists, Das et al. (2017), concludes that PFAAs induce hepatic steatosis, while strong PPAR-alpha activators such as WY-14643 do not, and that some PFAAs cause hepatic steatosis in PPAR-alpha-null mice.

p. 43. Section 5.1 – Hepatic.
See the above comments on the application of the Hall et al. (2012) criteria for the development of a chronic Reference Dose.

Additionally, the intended meaning of the following sentences is unclear: "Hepatocellular hypertrophy and an increased liver-to-BW ratio are common findings in rodents, but are considered nonadverse and less relevant to humans when there is evidence for PPARα activation. The increased relative liver weight and hepatocellular hypertrophy are only considered adverse when they are accompanied by effects such as necrosis, fibrosis, inflammation, steatosis, and significantly increased serum levels for enzymes indicative of liver tissue damage (Hall et al., 2012)." These statements raise the following questions about the consistency of USEPA's approach to liver toxicity: Are hepatocellular hypertrophy and increased liver-to-BW ratio, in the absence of other effects, always considered non-adverse and less relevant to humans by USEPA, or only when there is evidence for PPAR-alpha activation? Does USEPA consider the other more severe effects mentioned (necrosis, etc.) to be indicative of a non-PPAR-alpha mode of action that is more relevant to humans?

p. 47. Section 5.6 – Cancer.
As above, it should be mentioned that in rat studies, GenX increased the incidence of both benign and malignant liver tumors, and the combined incidence of benign and malignant pancreatic tumors, while PFOA increased the incidence only of benign tumors of these same organs.

p. 51. Third full paragraph (about liver effects).
As above, duration of exposure must be considered when applying the Hall criteria to studies of less-than-chronic duration for the purpose of chronic Reference Dose development. Also, as above, USEPA's rationale for evaluation of liver effects is not clearly presented. Are liver weight and hypertrophy, in the absence of the other effects mentioned, discounted for risk assessment because they are considered by USEPA not to be relevant to humans because they can occur via PPAR-alpha activation, or because they are not considered to be adverse? It is well documented that PPAR-alpha activation is not required for the increased liver weight caused by PFOA, PFNA, and PFOS (reviewed in DWQI, 2015; DWQI, 2017; DWQI, 2018; NJDEP, 2018; Post et al., 2017). Are the other effects mentioned known to not occur through a PPAR-alpha mode of action?

p. 52. First full paragraph.
NJDEP agrees with the rationale presented by USEPA for selecting the mouse reproductive/developmental study instead of the longer 90-day subchronic study for BMD modeling. NJDEP agrees that the higher LOAEL in the longer 90-day study may result from the smaller number of animals per dose group.

p. 52. Final paragraph.
NJDEP also agrees with the rationale presented by USEPA for selecting the shorter duration mouse study instead of the chronic (2-year) rat study as the critical study. NJDEP agrees that

this choice is appropriate because, as stated by USEPA, mice appear to be more sensitive than rats to GenX toxicity.

However, the following statement appears to be inaccurate: "Conversely, male and female rats exhibited no subchronic hepatocellular necrosis in the 90-day study (DuPont-17751-1026, 2009), yet hepatocellular necrosis is observed in the chronic study at **much higher doses** [bold added] (DuPont-18405-1238, 2013)." In the 90-day study, hepatic necrosis was not reported in male rats at up to 100 mg/kg/day or in female rats at up to 1000 mg/kg/day. In the 2-year study, statistically significant increases in hepatic necrosis occurred in males at 50 mg/kg/day and in females at 500 mg/kg/day; a non-significant dose-related increase occurred in females at 50 mg/kg/day. Therefore, the LOAELs for hepatic necrosis in the chronic study (50 mg/kg/day in males; 500 mg/kg/day in females) were lower, not much higher, than the NOAELs for this effect in the subchronic study (100 mg/kg/day in males; 1000 mg/kg/day in females).

p. 53. Section 6.3 – Dosimetric Adjustment of the Experimental Animal-Based POD to POD_{HED}.
See comments regarding p. 26 above. As above, it is unclear whether the DAF of 0.14 - 0.15, equivalent to a factor of 6-7, is sufficient to account for the higher internal dose in humans compared to mice from the same administered dose.

p. 55-56. Subchronic-to-chronic duration uncertainty factor.
It is stated (p. 56): "The NOAELs for the [mouse] oral reproductive/developmental toxicity study and the [rat] chronic study are within one order of magnitude of each other, suggesting consistency in dose-response relationships between these studies. The combined chronic toxicity/oncogenicity study was conducted, however, in rats that appear to be less sensitive than mice. For these reasons, a UF of 3 was used to account for extrapolation from subchronic to chronic exposure duration for the chronic RfD." The rationale for using a duration of exposure UF of 3 instead of the default value of 10 in the chronic RfD is unclear. The RfD is based on hepatic single-cell necrosis in male mice exposed for 84-85 days (DuPont-18405-1037, 2010). The NOAEL for hepatic single-cell necrosis was 0.1 mg/kg/day and the LOAEL was 0.5 mg/kg/day in males. In the chronic rat study, the doses were widely spaced (0, 0.1, 1, and 50 mg/kg/day in males; 0, 1, 50, 500 mg/kg/day in females), and the highest doses (M-50 mg/kg/day; F – 500 mg/kg/day) were identified as LOAELs. The LOAEL in males for the chronic rat study (50 mg/kg/day) is therefore 100-fold higher than the LOAEL in males exposed for 84-85 days (0.5 mg/kg/day) in DuPont-18405-1037, 2010. Furthermore, the actual level at which no effects occur may be substantially higher than the lowest dose level (1 mg/kg/day) in the chronic study, particularly in males for which there is a 50-fold difference between the LOAEL and the NOAEL. Accordingly, the no effect levels in the mouse subchronic and rat chronic studies are not within one order of magnitude of each other. As stated in the peer-reviewed publication of the chronic rat study (Caverly Rae et al., 2015): "The no-observed-adverse-effect-level in this study lies between 1 and 50 mg/kg for males and between 50 and 500

mg/kg for females." Finally, comparison of the rat subchronic (DuPont-17751-1026, 2009) and chronic studies (Caverly Rae et al, 2015; DuPont-18405-1238, 2013) (see comments about p. 52 above) indicate that hepatic necrosis occurred after chronic exposure at doses below the subchronic NOAEL for this effect. Based on the above, it is suggested that a subchronic to chronic UF of 10 be considered by USEPA.

p. 56. Database uncertainties.
NJDEP agrees with USEPA regarding database deficiencies for developmental and immune effects, lack of a chronic mouse study, and need for more information on hematological effects as well as human epidemiological information in general. It is noted that the reproductive/developmental study in mice did not assess fetal malformations or skeletal development, although PFOA is known to cause fetal malformations and delayed skeletal development in mice (USEPA, 2016). Conversely, the prenatal and developmental study in rats did not assess postnatal mortality, while an abstract to be presented at the upcoming 2019 Society of Toxicology meeting (Conway et al, 2019) reports that maternal doses of 10-250 mg/kg/d GenX on GD8-PND3 "resulted in significant, dose-responsive neonatal mortality at ≥62.5 mg/kg/d and reduced body weight of surviving pups at all doses (≥10 mg/kg/d)."

Additional important data gaps are not mentioned by USEPA. There are no data for GenX on neurobehavioral effects, including from developmental exposure, and such effects have been reported for other PFAS (Cui et al., 2009; Fuentes et al., 2007; Johannson et al., 2008; Long et al., 2013; Onishenko et al., 2011; Sato et al., 2009; Sobolewski et al., 2014; Viberg et al., 2013). Additionally, the lack of information on the human half-life of GenX is a major data gap, since human half-life data are needed for the appropriate animal-to-human extrapolation for PFAS.

<u>Comments on draft PFBS evaluation</u>

p. 9-10. Conceptual Model and Diagram.
The conceptual model and diagram should include fields for toxicokinetic information in humans and laboratory animals (i.e. how external exposures translate into internal exposures).

p. 56-57. Use of body weight$^{3/4}$ scaling for animal-to-human toxicokinetic extrapolation (conversion of Point of Departure [POD] to Human Equivalent Dose [HED]).
While recognizing that there are uncertainties about the PFBS half-life data for humans and rodents, the default approach based on body weight$^{3/4}$ scaling clearly does not adequately account for the much higher internal dose in humans compared to rats or mice from the same administered dose. NJDEP supports the approach used by the Minnesota Department of Health (2017). This approach uses a chemical-specific toxicokinetic adjustment based on the ratio of half-lives in humans versus animals. The human half-life of PFBS was reported as 26 days (Olsen et al., 2009), while the half-life in rats and mice is only a few hours (studies reviewed in USEPA draft document). Thus, the human half-life is at least 100-fold longer than the rodent

half-lives. However, the DAFs based on body weight$^{3/4}$ scaling are equivalent to a factor for toxicokinetic differences of only about 4 for rats and 7 for mice.

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