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Washington DC 20009

Re: Docket EPA-HQ-OW-2018-0614-0001

We, the undersigned five non-profit organizations, are writing to comment on EPA's draft toxicity assessments for perfluorobutane sulfonic acid (PFBS) and hexafluoroproyplene oxide (or GenX chemicals). These are two chemicals in the massive family of synthetic per- and poly- fluorinated alkyl substances (PFAS), with over 5,000 PFAS CAS-name substances (US EPA 2018a). PFAS are characterized by incredible durability, which manifests as extreme persistence in the environment. The PFAS chemicals that have been studied show potent toxicity to internal organs, lipid metabolism, as well as the immune and endocrine systems.

Given the number of people exposed to these chemicals, their persistence in the environment, and the public concern about them, it is critical that this toxicity assessment provide the information necessary to guide regulators and communities in their efforts to protect themselves. In this letter, we outline areas where the EPA has taken steps in the right direction (e.g., the methodology in the systematic review of PFBS) as well as areas that need to be strengthened (e.g., adequately accounting for the uncertainty related to the limited availability of data for both chemicals). We recognize the importance of this assessment and that communities exposed to these chemicals are eager for the EPA to complete this assessment, but we strongly urge the EPA to update and strengthen this assessment by ensuring that it relies upon a more robust data set and/or adequately accounts for the insufficiencies.

Introduction.

PFBS and GenX are two of the hundreds of PFAS compounds in widespread use in the United States (Lerner 2018). PFBS is a component of aqueous film forming foam (AFFF) firefighting foams (Backe et al. 2013) and textile treatments (Danish Environmental Protection Agency 2015) and GenX chemicals are a processing technology used to form fluoropolymers. While exposures to GenX chemicals appear to be more limited to regions of the United States where fluorochemicals are manufactured and used, PFBS is much more widely detected in drinking water. People are often exposed to PFAS mixtures, via consumer products, contaminated drinking water, or accumulation in the food supply. Whether exposures are the result of fluorochemical production and use or the use of AFFF firefighting foams, EPA should assume that those communities with intense exposure to PFBS and GenX chemicals will generally have high exposure to legacy PFAS compounds as well.

We support the EPA Integrated Risk Information System (IRIS) program's state of the science, transparent systematic review criteria for PFBS. The IRIS program's systematic review framework received high praise in a thorough public and scientific review by the National Academies in 2014 and again in 2018. The IRIS systematic review framework should be adopted more widely by other divisions of EPA. In particular, it should supplant the broadly criticized and severely flawed systematic review being promoted by the EPA TSCA program. We also support EPA's choice of critical studies and endpoints for a quantitative assessment of health risks for both chemicals.

However, we are deeply concerned that these draft assessments do not include a sufficient margin of safety when considering the major gaps in our understanding of their individual and shared toxicological properties. EPA's quantitative assessment fails to adequately reflect the uncertainty about low dose toxicity of PFBS and GenX chemicals. The assessment proposed a surprisingly low uncertainty factor of 3 to account for the lack of thorough toxicity testing, yet the database for both chemicals is quite limited and neither have robust data for critical endpoints including developmental impacts to the immune and neurological systems.

Furthermore, we believe it is inappropriate for EPA to attempt to estimate the risks posed by these chemicals individually. The people most at risk of exposure to PFBS and GenX chemicals will generally also have greater than typical exposures to legacy PFAS chemicals. The available data suggests that both chemicals impact the same body systems as other, better-studied PFAS. EPA should use a database uncertainty factor of 10 to account for gaps in existing data and the high likelihood of additive effects with other legacy PFAS.

The current process of regulating toxic chemicals places scientists and government agencies at a disadvantage because public health protection is reliant on data-intensive risk assessments. PFAS chemicals are not included in most environmental statues. Therefore, information on production and releases to the environment is generally not disclosed. This is especially troubling for PFAS chemicals, as the fluorochemical industry has a history of failing to report information about PFAS exposures in workers and the general population, serious adverse effects in PFAS-exposed workers, and adverse effects in industry-performed laboratory studies.

The overall trend in PFAS chemistry is a shift from highly toxic and bioaccumulative classes of relatively data rich compounds to related chemicals with slightly more favorable environmental profiles yet little or no safety data. Because PFBS and GenX discharged into the environment cannot be efficiently removed from groundwater, soil and sediments, and because they are so persistent, the larger margin of safety will add greater assurance of protection in the event that future evidence proves a greater potency than EPA currently estimates.

Our comments address four major issues. Section 1 outlines the reasons that EPA's draft quantitative assessments for PFBS and GenX chemicals do not fully account for uncertainties regarding the potency of both chemicals. It also addresses the fact that individual potency is not the appropriate approach for gauging the safety of current exposures to these specific chemicals and determining whether on-going emissions should be curtailed. Section 2 addresses EPA's use of systematic review for PFBS and GenX chemicals. Section 3 provides detailed comments about EPA's quantitative assessment for GenX chemicals and Section 4 provides similar comments for PFBS.

1. EPA's draft quantitative assessments are not sufficiently protective given data gaps and the potential for additive effects.

Americans have chronic exposure to many different PFAS through multiple exposure pathways and the EPA approach to assessing toxicity is burdened by a lack of specific testing for each compound. Additionally, EPA's attempts to estimate the potency of PFBS and GenX chemicals are limited by significant data gaps and methodological limitations. We recommend that EPA employ additional uncertainty factors to account for the high potential for additive effects and limited data on these individual chemicals.

A. Limited evidence exists to assure that EPA can accurately quantify toxicological risks for PFBS and GenX.

There are very few experimental studies in laboratory animals and no data on non-oral exposure routes for PFBS and GenX. There is currently no data to assess the impacts of PFBS and GenX effects to the mammary gland development and developmental immunotoxicity, which are the key indicators for longer-chain PFAS chemicals. The data EPA reviewed suggest that PFBS and GenX chemicals share many of the same toxicity endpoints as the legacy PFAS chemicals they replaced, including harm to the liver, thyroid, and kidney. People with PFBS and GenX exposure undoubtedly have exposures to legacy and other PFAS chemicals as evidenced by the studies in drinking water in the Cape Fear river which found most tap water had GenX, Nafion byproduct 2, PFMOAA, PFO2HxA and PFO4DA (NC State CHHE 2018). Yet EPA does not attempt to estimate or account for the potential for additive effects.

PFAS are characterized by large differences in toxicokinetics between different species. Better-studied PFAS chemicals show well documented differences in PFAS metabolism, with rats and mice metabolizing the chemicals more rapidly than humans. In the draft assessments for GenX chemicals and PFBS EPA uses allometric scaling to account for body size differences between laboratory animals and humans. However, these factors are not likely sufficient to account for the potential that people have greater sensitivity to PFAS effects.

There is very little published data on effects of PFBS and GenX chemicals in people. Human epidemiology is challenged by the fact that people have simultaneous exposures to dozens of PFAS chemicals, and by the number of study subjects and duration of follow up that would be needed to capture rare or subtle health effects. Furthermore, shorter-chain chemicals appear to accumulate in different organs and tissues. A rare autopsy study of 20 human cadavers conducted in Spain detected the highest concentration of PFBS in lung and kidney tissue (Perez et al. 2013), suggesting that risk managers should consider whether low detections in human blood and urine are appropriate assurance of rapid metabolism and lack of concern for shorter-chain PFAS chemicals.

As discussed in sections 3 and 4 below, EPA should explore the use of alternative methods to scale between animals and humans, and account for the fact that laboratory studies may not accurately reflect the risks of low dose exposure to PFBS and GenX chemicals in people, especially developing infants and children.

B. EPA should strengthen its toxicity assessments by using additional uncertainty factors to account for missing toxicity studies and the potential for additive effects.

Biomonitoring studies demonstrate that Americans have chronic exposure to multiple PFAS chemicals throughout their lifetimes. Therefore, it is impossible to be exposed to PFBS or GenX and no other PFAS chemicals. CDC's NHANES studies reveal that nearly every American has detectable concentrations of four PFAS chemicals in their bloodstream (PFOS, PFOA, PFHxS and PFNA) (Ye et al. 2018). At least eight other compounds are detected by NHANES studies: MeFOSAA, PFDA, PFUnDA, PFBS, FOSA, EtFOSAA and PFDoA, and PFHpA (CDC 2018). Most other PFAS chemicals are not routinely included in biomonitoring studies.

Toxicity assessment should account for simultaneous exposure to other PFAS chemicals that impact the same target organs. EPA does this for its reference dose (RfD) used to establish the present drinking water guideline for the sum of PFOS and PFOA:

> "Adverse effects observed following exposures to perfluorooctanoic acid (PFOA) and PFOS are the same or similar and include effects in humans on serum lipids, birth weight, and serum antibodies. Some of the animal studies show common effects on the liver, neonate development, and responses to immunological challenges. Both compounds were also associated with tumors in long-term animal studies. The RfDs for both PFOA and PFOS are based on similar developmental effects and are numerically identical; when these two chemicals co-occur at the same time and location in a drinking water source, a conservative and health-protective approach that EPA recommends would be to compare the sum of the concentrations ([PFOA] + [PFOS]) to the [Heath Advisory] (0.07 µg/L)" (EPA 2016).

The European Food Safety Authority also allows for the consideration of additive effects for chemicals that target the same health endpoint, even when mode of action is unknown (EFSA 2014), as does the National Academy of Sciences (National Research Council 2008, 2009). The Netherlands pioneered this approach for PFAS with a relative potency estimate for liver hypertrophy using experimental data for 11 perfluoroalkyl sulfonates and perfluoroalkyl carboxylates and read across assumptions for 7 additional PFAS (RIVM et al. 2018). While the potency of PFBS and GenX (FRD-902/-903) on liver hypertrophy were far lower than PFOS and PFOA, they should be considered to add to the burden of PFAS-related liver injury in the American population. EPA must promote similar assessments for other PFAS related health outcomes with potential for

additive toxicity, including kidney toxicity, lipid metabolism, birth outcomes, immunotoxicity and developmental effects.

EPA proposes a total uncertainty factor of 100 to 300 for every endpoint in the two draft assessments except chronic exposures to PFBS. In comparison, EPA used a combined uncertainty factor of 300 for PFOA, a chemical with hundreds more toxicological studies. Despite the relatively complete database for PFOS and PFOA, and the use of uncertainty factors to account for extrapolations from laboratory studies to human health, the available evidence suggests that EPA's practices of quantitative risk assessment were not fully protective of human health.

EPA translated its reference doses for PFOS and PFOA into a combined drinking water guideline of 70 parts per trillion. However, several human studies for PFOS and PFOA find sensitive effects in populations at this level. The Scientific Advisory Committee advising the state of Michigan reviewed select epidemiology endpoints from the C8 Science Panel study and determined that several epidemiology studies reported increased risks of ulcerative colitis and several cancers at concentrations in the range of EPA's water guideline (Michigan PFAS Science Advisory Panel 2018). The Committee recommended that Michigan take epidemiology studies into account when setting drinking water exposure values, and set advisory limits for novel PFAS chemicals based on similar chemical structures and toxicity.

Human epidemiology suggests effects to the immune systems at serum levels that are relatively common in the American population. Philippe Grandjean calculated the benchmark dose level for vaccine antibody responses in PFOA and PFOS to be approximately 1 ug/L serum, which would correspond to a drinking water limit of less than 1 ng/L (Grandjean 2018).

In this light, we are concerned that EPA's quantitative toxicity assessments for PFBS and GenX chemicals are premature. Importantly, toxicology studies using even lower doses and examining effects on sensitive endpoints such as the immune system and mammary gland have not yet been conducted for PFBS and GenX chemicals. Several major research efforts are underway that will provide more information about these chemicals, as well as ways to assess groups of PFAS chemicals for similar effects. EPA should commit to updating these toxicity assessments and incorporating new studies on additive or synergistic effects including any data published before the draft documents are finalized. For example, major *in vitro* screening efforts are underway at EPA and the National Toxicology Program (NTP) that could help determine shared toxicological properties of PFBS and GenX chemicals in-vitro. Also, several new abstracts to be presented at the Society of Toxicology meeting in March 2019, indicate forthcoming in-

vivo data for GenX (Blake and Fenton 2019; Cope et al. 2019). Once finalized EPA should also commit to reevaluating these assessments to reflect the best available information on health risks.

C. Quantitative assessments for individual PFAS chemicals are not the appropriate approach for determining risk management or human exposure guidelines.

EPA claims this toxicity assessment will be useful to guide national, state and tribal decisions about exposure. Yet the Cape Fear Water Public Utility Authority correctly points out that for many water drinkers in North Carolina, this assessment also arrived decades too late (Cape Fear Public Utility Authority 2018). Chemours discharged untold quantities of GenX chemicals and other mystery fluorocarbons directly into the water source of more than 200,000 people for nearly four decades before state and federal agencies were alerted to the emissions, and performed any examination of associated health risks.

EPA's quantitative toxicity assessments will inevitably be used as a tool to gauge the safety of ongoing PFAS emissions. But the Norwegian Environmental Agency has taken a different approach to assessing these very persistent compounds, concluding that, "Given the irreversibility of environmental contamination a threshold concerning the level of risk caused by the continued manufacture, use and emissions of PFBS in the long term cannot be derived with any certainty" (ECHA 2018). Deviating from a risk-based approach, Norway nominated PFBS for special classification as a Substance of Very High Concern under Europe's REACH legislation, and is taking precautionary action to restrict further emissions.

2. EPA successfully implemented systematic review for the draft assessment of PFBS.

We appreciate the EPA IRIS program's use of transparent systematic review practices that has been reviewed and praised by the National Academies in 2014 and again in 2018, (in contrast to the flawed and highly criticized approach used by the Toxics Substances Control Act (TSCA) program), particularly in the draft PFBS toxicity assessment. Systematic review has long been used to inform evidence-based choices about health interventions in clinical settings. Though the application of a valid systematic review to questions in environmental health is still relatively new by comparison, the IRIS program at EPA has been steadily implementing systematic review practices since receiving feedback in 2011 from the National Academies of

Sciences, Engineering, and Medicine suggesting the need for programmatic reform (National Academies of Sciences 2018).

We were pleased to see the adoption and implementation of rigorous systematic review methodology in line with current best practice recommendations by the Office of Research and Development (ORD), specifically in the draft PFBS assessment. In particular, we support the use of the study confidence rating, which is in line with best practices for assessing risk of bias and closely aligns to the methods used by the NTP's Office of Health Assessment and Translation (OHAT) (OHAT 2015). Importantly, the PECO (populations, exposures, comparators and outcomes) statement clearly outlines the criteria for inclusion and exclusion of studies in the assessment. We also support the transparent GRADE-like methods used for evidence integration in the draft PFBS assessment.

Finally, we appreciate the display of extracted PFBS data in HAWC, which made it very easy to evaluate the statements made in the draft PFBS assessment. To this end, we also appreciate that EPA made public the industry studies that have not been peer reviewed, but comprise the bulk of the literature that the draft assessments are based on. Without access to these reports, it would not have been possible to fully evaluate these EPA draft assessments. Moving forward, we encourage EPA to make the data for GenX chemicals available in HAWC when finalizing the assessment.

We assume that the draft assessment on GenX chemicals was completed using EPA review methods that were in place before the complete adoption of systematic review best practices. Given that the GenX assessment was not conducted following best practices in systematic review, we encourage EPA to reformat and reevaluate the data, if necessary, so that the GenX assessment, like the PFBS assessment, adheres to best practice guidelines for systematic review. It is confusing to the public that these two assessments were released by EPA at the same time but were conducted using different methods.

The draft assessment on GenX chemicals would benefit from increased transparency regarding the inclusion and exclusion criteria that were used during the study screening process, as this information is not explicitly stated in Section 3.3.2 (though it was available in Appendix A, it was not referred to in the text). While not completely adhering to all recommended best practices, EPA did provide in Appendix B of the draft assessment on GenX chemicals, a data quality evaluation that is similar in content to the study confidence rating used in the draft PFBS assessment. It is important to note that we do not support derivation of a numerical value for this type of evaluation, as that is not in line with current best practices for systematic review methodology. The US

Institute of Medicine recommended standards for conducting high-quality systematic reviews that specifically warn against scoring systems, and particularly against ones relying on reporting:

> "Quality scoring systems have not been validated. Studies assessed as excellent quality using one scoring method may be subsequently assessed as lower quality using another scoring method (Moher et al. 1996). Moreover, with an emphasis on risk of bias, the Systematic Review more appropriately assesses the quality of study design and conduct rather than the quality of reporting." (Institute of Medicine 2011).

In summary, experts warn against the scoring system. The current state of the science for evaluating clinical and environmental health research is to describe or document each component of the assessment tool separately, without trying to calculate an overall numeric score.

We also note that one portion of the literature search for GenX chemicals, that for HFPO dimer acid, was completed in July 2017 and has not been updated. Given how rapidly research on PFAS is being published, EPA should have, at the very least, updated the search for HFPO dimer acid when the search for HFPO dimer ammonium salt was conducted in January/February 2018. Moving forward, the EPA should ensure that all literature searches are conducted within six months of final publication, and that the cut-off date is reported in the assessments, as these represents best practices in systematic review.

One additional important aspect about GenX chemicals is that future health assessments should consider the solvent used for preparation and storage of the chemicals, as it has recently been brought to light that GenX chemicals degrade in DMSO. Though not an issue for the studies included in this analysis, the choice of solvent and stability of the chemicals is an important study aspect that should be considered in future reviews of GenX chemicals and possibly other PFAS.

GenX chemicals and PFBS are of high concern to citizens across the US. It is of great importance that EPA is responsive to emerging environmental health concerns in a timely manner. However, a major tenet of systematic review is increased transparency, and best practice guidelines in systematic review methodology require the publication of a review protocol in order to improve transparency. The need for public comment and a finalized protocol in EPA assessments was also recently highlighted by The National Academies (National Academies of Sciences 2018). For example, in addition to not fully adhering to systematic review best practices in the draft assessment on GenX

chemicals, we note that “GenX chemicals” has been too narrowly defined by the literature search terms used, which we will discuss in more detail below. This is important feedback for EPA that could have possibly been provided at the outset of the review, had a protocol been made available before the assessment was conducted. Importantly, we note that the US EPA IRIS program recently (12/19/18) listed five additional PFAS as upcoming program products (EPA 2018b) and we strongly encourage EPA to make protocols for these assessments publicly available for comment before conducting the reviews.

3. Specific comments on the draft assessment for GenX Chemicals.

A. **GenX mixture, transformation products and byproducts**.

The EPA should be considering the whole mixture involved in the GenX process and associated byproducts when assessing the toxicity of GenX chemicals. Considering what is now known about GenX chemicals, the history of GenX suggests that accounting for byproducts and transformation products of processes involving chemicals being assessed is particularly important. GenX chemicals -- including as byproducts of other manufacturing processes and as a replacement for PFOA -- were discharged into the Cape Fear River by Chemours for several decades before the public became aware of GenX (NC DEQ 2017a).

GenX is a technology that enables the use of fluoropolymers without the use of PFOA. Although HFPO dimer acid and its ammonium salt are the main chemicals involved in this fluoropolymer manufacturing process, there are likely other PFAS chemicals that are part of the GenX process. A community exposed to HFPO dimer acid and its ammonium salt from GenX processing will likely be concurrently exposed to other PFAS chemicals involved in the process and the resulting byproducts and transformation products as well.

For example, a non-targeted analysis of Chemours wastewater discharge into the Cape Fear River in North Carolina showed, in addition to HFPO dimer acid, at least three additional PFAS (PFMOAA, PFO2HxA, PFO3OA) and two polyfluoroalkyl ether sulfonic acid byproducts (Nafion 1 and Nafion 2) (US EPA 2017). Similar to GenX chemicals, the estimated concentrations of PFMOAA, PFO2HxA, PFO3OA dropped significantly after Chemours stopped discharging GenX chemicals. Thus, it is believed that these three PFAS were part of the same wastewater discharge that included GenX chemicals (NC DEQ 2017b). In addition to high concentrations of the legacy PFAS, PFOA and PFOS, these and other GenX related chemicals are now being detected in exposed citizens. The GenX Exposure Study, set in the Lower Cape Fear River Basin, recently reported to study participants that there were four new PFAS found in participants’ blood (Nafion

2, PFO4DA, PFO5DoDA and Hydro-EVE) (NC State Center for Human Health and the Environment 2018; Smart 2018).

B. Toxicological profile similar to PFOA and other PFAS.

The EPA found studies that link the GenX chemicals, HFPO dimer acid and its ammonium salt, to adverse effects on the liver, kidney, immune system and development, as well as cancer. These adverse health effects have also been associated with other PFAS, including PFOA. As described above, this highlights the need to account for simultaneous exposure to other PFAS chemicals that impact the same target organs.

In particular, a comparison of the toxicological properties of GenX chemicals and PFOA is especially relevant, as the GenX process is a replacement for PFOA in the production of fluoropolymers, thus communities exposed to GenX will likely have legacy contamination with PFOA. GenX chemicals are cleared from animal models faster than PFOA, however, GenX chemicals and PFOA are associated with similar health effects at roughly comparable external dose levels. Given that a similar external dose would result in lower internal concentrations of GenX chemicals, it is possible that the toxicity of GenX chemicals on certain targets could be *greater than PFOA*. For example, in rats, exposure to GenX chemicals can lead to adenomas and carcinomas in the pancreas and liver (Dupont Chem 2010b), but only adenomas in the pancreas and liver from PFOA exposure (Biegel et al. 2001). This suggests that GenX chemicals may have similar, if not greater, carcinogenic potential than PFOA.

The chemical and toxicological similarities between GenX chemicals and other PFAS should also be used in the assessment of GenX toxicity. For example, in addition to liver effects, immune and hematological effects were observed at low doses. However, the EPA failed to adequately incorporate these effects, stating on page 51 of the assessment that there is “some uncertainty regarding the biological significance of both the hematological and immune endpoints,” and that currently “little or no data on the potential for GenX chemicals to impact aspects of immune function beyond the immunosuppression (e.g., allergic responses and autoimmunity) exist.” Though immunotoxicity data is limited for GenX chemicals, immunotoxicity is a common effect of PFAS. Adverse effects on immune system function, in addition to changes in early markers of immunotoxic effects, have also been associated with more well-studied PFAS. The chemical and toxicological similarities between GenX chemicals and other PFAS reduce the uncertainty regarding biological significance of immune endpoints for GenX chemicals. Especially considering the evidence of these effects for the class of PFAS, the EPA should not assume that there is no harm or effects when there are data gaps.

C. Critical review and analysis of data.

We support the EPA's critical review and analysis of industry-sponsored studies, which is especially important given the tendency for industry-sponsored studies to be biased in favor of the regulatory approval of their products (Mie et al. 2018).

For example, on page 39 the EPA states that delays in genital development may be related to observed effects on body weight during the pre-weaning period but does not discount the possibility of this effect being related to GenX chemical exposure. This conclusion is in contrast to the authors' dismissal of the genital developmental delay as only a consequence of body weight, and not a direct effect of GenX chemical administration. Another example is EPA's conclusion that the occurrence of combined pancreatic acinar adenomas and carcinomas is related to GenX chemical exposure, despite the authors' conclusion that the evidence is equivocal.

However, there are some instances where further clarification of study data should be provided. For example, EPA reports no reproductive effects associated with exposure to GenX chemicals, but there was a mention of 11 mating pairs not able to successfully produce litters in DuPont-18405-1037 (Dupont Chem 2010a). No further discussion on this was provided. As there were 100 pairs in the study, this indicates 11% were unable to successfully mate. The significance of this effect cannot be assessed without reporting of how these pairs are distributed among the exposure groups.

D. Critical study selection.

We support EPA's selection of the subchronic reproductive/developmental toxicity study in mice (DuPont-18405-1037) (Dupont Chem 2010a) over the chronic toxicity study in rats (DuPont-18405-1238) (Dupont Chem 2010b). Although chronic studies are the preferred duration of study for generating a lifetime RfD, the only chronic study available for GenX chemicals was performed in rats. Rats are less sensitive than mice to the effects of GenX chemicals, which is reflected in the significantly lower NOAEL for liver toxicity in the subchronic study in mice compared to the chronic study in rats.

E. Derivation of human equivalent oral exposures.

The EPA uses the Body Weight$^{3/4}$ allometric scaling approach to calculate a human equivalent dose from an animal-based point of departure. The Body Weight$^{3/4}$ allometric scaling approach is based on body surface area and basal metabolic rate in adults. While the liver effects in the critical study for GenX occurred in adult mice, developmental effects also occur at low doses, and infants and children may be a more vulnerable population. The EPA states that this approach is not suitable for estimating an equivalent dose in infants and children. Therefore, it is unclear how the human

equivalent dose based on liver effects in adults would compare to the human equivalent dose based on developmental effects in infants and children. This uncertainty should be acknowledged, and the EPA should explore alternative approaches to extrapolating from animal to human doses that are relevant to infants and children to better address this uncertainty.

Furthermore, this approach does not account for differences in toxicokinetics between animals and humans, which for PFAS are often vastly different. Even within animal models, data suggest a potentially complex toxicokinetic profile for HFPO dimer acid when dosing occurs over multiple days (Rushing et al. 2017). When male mice received doses of 1, 10 and 100 mg/kg/day for 28 days, their serum levels did not reach a steady state. This indicates possible changes in toxicokinetics after repeated dosing.

Depending on the specific PFAS, human clearance time can be an order of magnitude, or more, higher than in animal models. Therefore, the Netherland's National Institute for Public Health and the Environment (RIVM) determined that although the elimination rates for GenX are faster than PFOA in animal models, without data in humans, it is not possible to make assumptions on the toxicokinetics of GenX chemicals in humans (RIVM et al. 2016).

Due to the uncertainty from lack of human toxicokinetic data on GenX chemicals, RIVM calculated and applied an additional uncertainty factor to account for the potential kinetic difference between animals and humans (RIVM et al. 2016). RIVM postulated that the vast differences in clearance rates between animals and humans may be due to species differences between organic anion transporters (OATs). Differences in OATs could result in stronger reabsorption of anions, like the anion forms of PFOA and HFPO dimer acid, from the lumen of the kidney back into the blood in humans (Yang et al. 2010).

It is possible that the shorter half-live of GenX in animal models is due to little to no reabsorption by OATs in these species. However, RIVM reasoned that it could not be assumed this would be the same for humans, due to the genetic differences of the OATs between animal models and humans (Yang et al. 2010). RIVM states, "contrary to other perfluorinated compounds, no data are available for FRD-902 [GenX chemical] to confirm whether the fast elimination and absence of accumulation as seen in several animal species also applies to humans. In view of the above, an additional toxicokinetic assessment factor is applied to take into account the uncertainty in the human elimination rate of FRD-902."

This additional toxicokinetic factor used by RIVM is based on the difference in half-lives between cynomolgus monkeys and humans for PFOA. A half-life ratio was calculated using a half-life of 1378 days in humans (Olsen et al. 2007) and of 20.9 days in male cynomolgus monkeys (Butenhoff et al. 2004) resulting in an additional toxicokinetic factor of 66 (1378 / 20.9). This additional uncertainty factor to account for the potential kinetic difference between animals and humans is an example of an alternative approach to extrapolating animal doses to human doses for PFAS that do not yet have human toxicokinetic data.

F. Database uncertainty.

As mentioned in our overarching comments, there are significant database limitations for HFPO dimer acid and its ammonium salt. These include:

- Lack of toxicity data from inhalation and dermal exposure routes.

  Both the HFPO dimer acid and its salt can be transported through air (DuPont CCAS 2009). Inhalation could be a significant exposure route, especially in areas where GenX processing occurs. In 2017 the North Carolina Division of Air Quality estimated that despite some cutback in emissions, the Chemours Fayetteville Works plant emitted approximately 2,700 pounds of GenX chemicals per year (NC DEQ 2018a) and GenX chemicals have been found in rainwater up to 7 miles from the Chemours Fayetteville Works plant (NC DEQ 2018b). Minimal dermal absorption of the HFPO dimer acid ammonium salt has also been demonstrated (DuPont 2008), however, there is a lack of information on the dermal absorption potential or toxicity of the HFPO dimer acid.

- Limited data on developmental toxicity and immunotoxicity.

  Developmental toxicity and immunotoxicity are common health effects associated with PFAS exposure, both of which can occur at extremely low levels of exposure (ATSDR 2018). Two developmental toxicity studies, only one of which was in mice, and a single study that specifically assesses immune effects is a serious database limitation. One critical data gap is the lack of a full 2-generation toxicity study evaluating exposures during early organogenesis. Additionally, there are many developmental and immune effects that have yet to be assessed, including reproductive system development (i.e. mammary gland development and function), neurodevelopment, autoimmunity, infectious disease resistance, and immune hypersensitivity (i.e. asthma and allergies).

- No human data.

Human data has significantly improved our understanding of the toxicological profile of many PFAS (ATSDR, 2018). Human data is especially important considering the difference in elimination rates for PFAS between animal models and humans. A lack of human data to complement and compare to animal toxicological data is a critical data gap.

- No chronic studies in mice.

  The single chronic study was performed in rats, which are less sensitive than mice to GenX chemicals. An additional limitation of this study is that there were higher than normal early deaths across all study groups (DuPont-18405-1238, 2013) (Dupont Chem 2010b).

- Limited peer-reviewed, independently funded studies for HFPO dimer acid and its ammonium salt.

  Of the studies that assess health effects of GenX, only three were peer-reviewed. Of these three, one was independently funded (Rushing et al. 2017), one was funded by DuPont (Caverly Rae et al. 2015), and one was independently funded but excluded from the assessment (Wang et al. 2017).

- New toxicity data on GenX chemicals

  New toxicity data on GenX chemicals is expected to be available soon, as there are several studies abstracts submitted for presentation at the upcoming Society of Toxicology meeting in March, 2019. In one study of gestationally exposed mice, puberty delays were evident in female pups exposed to PFOA or 10 mg/kg GenX. Mammary gland development was also stunted in all dose groups of GenX and PFOA, with mammary glands from exposed mice displaying limited branching, lack of ductal growth, and fewer terminal end buds (Cope et al. 2019).

  In another study, gestational exposure to HFPO-DA caused significant dose-responsive increases in maternal liver weight (≥62.5 mg/kg), reduced maternal serum thyroid hormone and altered lipid profiles (≥30 mg/kg), and highly upregulated gene expression related to PPAR signaling pathways in maternal and fetal livers (≥1 mg/kg) 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) was also noted (Conley et al. 2019).

A factor of 3 is insufficient to cover this level of uncertainty in the database. In contrast, the Agency for Toxic Substance and Disease Registry (ATSDR) used a database uncertainty factor of 10 for PFNA and PFHxS due to lack of, or limited testing of developmental and immunological effects, which ATSDR identified as two of the most sensitive PFAS endpoints (ATSDR 2018).

G. Overall uncertainty not addressed.

The total uncertainty factor used by North Carolina's Department of Environmental Quality was 1000. The total uncertainty factor used by the RIVM was 1088. Both North Carolina and RIVM concluded that the current overall uncertainty in assessing the toxicity of HFPO dimer acid and its ammonium salt is at least ten times greater than what the EPA is acknowledging through its application of a total uncertainty factor of 100.

4. Specific comments on the draft assessment of PFBS.

A. Evidence synthesis conclusions

Overall we support EPA's evidence synthesis conclusions (Section 4). One notable exception is the conclusion reached in Section 4.2.2.1 that "the viability index in F1 pups and the lactation index in F1 and F2 pups showed statistically significant changes at various doses but were not dose-dependent (Lieder et al., 2009b)." It is true that these effects do not show a linear dose response, but the possibility and implications of nonmonotonic dose responses should not be ignored. Importantly, in the study by Lieder et al., 2009b, at 30 mg/kg/day PFBS there were fewer live pups born per litter and the viability index was reduced indicating fewer animals survived to postnatal day 4. This is a significant finding that should not be ignored, and we strongly encourage EPA to consider reevaluating this endpoint. Further, the effects on the lactation index, particularly in the F1 are concerning, especially since Lieder et al. 2009b seemingly do not discuss the death of pups after postnatal day 1 and why there were litters with no surviving pups. One possibility is that there were impacts on the mammary gland or the ability of the P generation to nurse the F1. To our knowledge, the mammary glands of exposed animals were not examined and other aspects of mammary gland function were not measured, so this possibility cannot be further explored in the available study. Of note, however, is that the mammary gland appears to be one of the most sensitive tissue identified to date for PFOA. White et al., (2007) reported significant delays in mammary gland development in P generation mice exposed to PFOA during gestation, and this possibility should be further explored for PFBS and other PFAS (White et al. 2007).

B. Evidence integration and hazard characterization.

We support EPA's evidence integration and hazard characterization (Section 5) conclusions with the exception of the conclusion reached in Section 5.7 for immune effects. Other PFAS are known immunotoxicants. PFOA and PFOS were recently determined by OHAT to be *presumed* immune hazards to humans (NTP 2016). We strongly encourage EPA to review the human immune effect studies as the information presented throughout the draft assessment seems inconsistent and at times contradictory. This is perhaps, in part, to some of the studies not being listed in HAWC (discussed further below). For example, page 46 states "Immune effects were observed in two human studies, including associations with asthma (Dong et al., 2013a) and atopic dermatitis (Chen et al., 2018). Because of the lack of additional evidence and some concerns about risk of bias, the evidence in human studies is equivocal." However, both Dong et al., 2013a and Chen et al., 2018 received good or adequate ratings for each component of the study confidence rating and were judged overall to be medium confidence studies, so it is not clear from this statement where concerns about risk of bias originated (Chen et al. 2018; Dong et al. 2013). The information in Table 7 further confuses the matter by listing three studies as medium confidence for asthma, some of which are not discussed in the narrative in Section 5.7, and there is discussion of additional human immune studies in Section 4.7.1 that are subsequently not discussed in Section 5.7 (e.g. (Qin et al. 2016)).

C. Critical study selection.

We support EPA's decision to derive POD_{HED} for thyroid, developmental, and kidney effects. EPA clearly and transparently presented how these bench mark responses (BMR) were derived. We specifically appreciate that EPA described the derivation of the biological level of concern for the benchmark dose modeling. Further, we agree with the discussion regarding hypothyroxinemia and offer our support for identifying decreases in total T3, total T4 and free T4 as health outcomes of great importance for neurodevelopment and cognition. EPA has expertly made the case for the selection of Feng et al. 2017 as the principle study for the derivation of the candidate subchronic RfD based on thyroid effects, and specifically on the choice of total T4 as the critical effect. Not only was this study rated as high confidence, but the design and conduct allowed for many related biological endpoints to be assessed.

D. Derivation of human equivalent oral exposures.

As was the case in the draft assessment of GenX chemicals, the EPA used the Body $Weight^{3/4}$ allometric scaling approach to calculate a human equivalent oral dose from an animal-based point of departure. The Body $Weight^{3/4}$ allometric scaling approach is based on body surface area and basal metabolic rate in adults. Importantly, EPA stated

in the draft assessment for GenX chemicals that the Body Weight$^{3/4}$ approach is not suitable for estimating an equivalent dose in infants and children (US EPA 2018c). EPA derived RfD based on kidney effects in adult rats and thyroid effects in newborn mice. Given the lack of toxicokinetic information available in humans, rats, and mice, especially at different life points, it is unclear how appropriate the default Body Weight$^{3/4}$ scaling approach is for estimating human equivalent doses. This uncertainty should be acknowledged, and the EPA should explore alternative approaches to extrapolating from animal to human doses that are relevant to infants and children to better address this uncertainty.

E. Confidence in the database versus uncertainty factors for database deficiencies.

After calculating reference doses, EPA presents confidence descriptors for the candidate RfDs (e.g. Tables 12, 13). In this display, and in the executive summary, there are statements made about the confidence in the database. EPA failed, however, in the draft assessment for PFBS to describe this step in the process. Thus, while there is adequate documentation of how study confidence was determined, and how evidence was integrated to reach a hazard characterization, there was no information about how the confidence in the body of evidence (i.e. the database) was evaluated. This is important because the relationship between the confidence in the database (i.e. the confidence in the body of available evidence) seems to be confused with choosing an uncertainty value for database deficiencies. It would seem that these are two separate issues (as elaborated below), but whether or not that was the intent of EPA cannot be judged without additional explanation about how the confidence in the database was determined.

Regarding the derivation of RfDs for kidney effects, it is unclear in Tables 13 and 18, why a lack of neurodevelopmental effects is viewed as a limitation in evaluating the confidence in the database for deriving subchronic and chronic RfDs for kidney effects. At no prior point in the document does EPA indicate that neurodevelopmental changes are an expected downstream event following the observed kidney effects. In fact, this stands in contrast to the evidence integration judgement (Table 7) that lists the following factors as increasing support for a hazard:

> “1) the two high-confidence studies with the longest exposure durations reported consistent effects on kidney histopathology in male and female rats (females were more sensitive), and 2) the histopathological effects related to inflammation were largely dose-dependent and of a concerning magnitude, although primarily at high doses (300 or 600 mg/kg-d), and the following as factors that decrease support for a hazard: 1) there was inconsistency in kidney weight changes across

> studies, and 2) findings are from a single laboratory and species, with the following note included: the general lack of effects on other pathology endpoints in the shorter term studies was not considered to decrease support for hazard, as this was not interpreted as inconsistent."

Thus, this rationale for decreased confidence in the database of studies investigating effects on the kidney appears arbitrary, and we strongly encourage EPA to reevaluate this decision. On the other hand, it is logical to judge the confidence in the database for thyroid effects as medium, given the lack of studies evaluating the functional implications related to altered T4.

For the RfDs based on kidney effects, the lack of studies on neurodevelopmental effects is more appropriately addressed in the uncertainty factor for database deficiencies. Unlike the judgment of the confidence in the body of evidence (i.e. confidence in the database), which should evaluate the studies related to the identified hazard, the uncertainty factor for database limitations should address the database of PFBS studies more globally and indicate if the most sensitive adverse effects have or have not been evaluated for PFBS. We agree with EPA that studies evaluating endpoints that are extremely sensitive to disruption by other PFAS (including mammary gland development and immunotoxicity) have not yet been conducted for PFBS, and this is clearly a database deficiency.

To be clear, we suggest that the uncertainty factor for database deficiencies should be 10 for each of the draft RfDs. This value for database deficiencies should be applied to all RfDs calculated in this draft assessment because at this time there are no immunotoxicology studies or evaluations of mammary gland development for PFBS, both of which are endpoints that are sensitive to disruption by other PFAS. To this point, effects for a variety of endpoints are seen at doses of PFOA that are one to two orders of magnitude lower than the lowest doses used in the available PFBS studies. Furthermore, there are currently only a limited number of independently funded studies of PFBS available. Of the 15 available animal publications, only the 20-day developmental study by Feng et al. 2017, and the as of yet un-peer reviewed 28-day study from NTP are independently funded. In addition, a LOAEL-to-NOAEL uncertainty factor of at least 3 should be applied for the RfDs based on thyroid hormone because the critical effect was in newborn mice and it is unclear how appropriate the default Body Weight$^{3/4}$ scaling approach is for estimating human equivalent doses in infants. Also, EPA inconsistently applied the subchronic to chronic uncertainty factor of 10 when deriving the chronic RfDs, and the reasoning for this is unclear.

F. Other comments on the structure and display of presented information.

Overall, the PFBS draft assessment was presented in such a way that was easy to follow. We strongly encourage EPA to continue pursuing the display of extracted data in HAWC for future assessments (including the final assessment of GenX chemicals). The use of HAWC to display the data greatly improved the readability and usefulness of the draft assessment by displaying data from multiple studies examining similar endpoints on a common plot. The presentation of data in HAWC also facilitates making data readily available that otherwise might not be easily accessible to the public. There were, however some questions and inconsistencies that were noted and are indicated below:

- It was unclear why some of the epidemiological publications were not listed in HAWC. On page 22 of the assessment it states that were seven epidemiological studies presented in 10 publications, and an additional seven studies that were excluded based on study evaluation (Table 4). This indicates that there should be 17 epidemiological publications in HAWC, yet there are only 13, including six of the seven excluded publications.
- Likewise, it is unclear why some of the animal publications are not listed in HAWC. On page 22 of the assessment it states that there were 10 studies presented in 15 papers. All 15 papers are listed on page 25 of the assessment, yet only 12 are listed in HAWC.
- It is unclear why some of the answers to the study confidence rating questions in HAWC appear in italics and others do not.
- In some of the data pivots in HAWC (e.g. that for PFBS T3 (effect size, animal) the legend indicates a red square for significance, but in fact the plot uses a red circle.
- There were data entry errors in the Feng study. There were errors in the line for “animal husbandry” for the P0 Females, specifically the temperature and humidity. Further, in the F1 data some of the uterine effects (e.g. uterine diameter and others) have “ovary” listed as the organ.
- The funding line should be updated for two animal studies: 3M should be listed as funding source, not just in the extraction comments for Bijland, 2011, 1578502 and Bayer should be listed as the funding source for Bomhard, 1996, 3859928
- It is unclear what “adequate-deficient” means in the rationale for the study confidence rating question for outcome ascertainment in Dong et al. 2013 pertaining to asthma severity score.

In conclusion, we urge the agency to strengthen its final assessments and have outlined dozens of ways in which the current drafts discount the significant uncertainties about the individual chemicals’ effects on human health. EPA should commit to updating its assessments when new data is available to reduce uncertainties in low dose health

effects for these chemicals. It must take urgent action to control direct releases of PFBS and GenX chemicals into the environment.

Sincerely,

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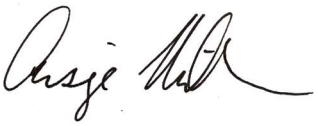

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