UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF WATER

Brian D. Israel
Arnold & Porter Kaye Scholer LLP
601 Massachusetts Ave. NW
Washington, D.C. 20001

Dear Mr. Israel,

This letter is in response to the Request for Correction (RFC) received by the U.S. Environmental Protection Agency (EPA) from Arnold & Porter Kaye Scholer LLP (A&P) on March 18, 2022. The RFC request document, dated March 18, 2022, was assigned RFC 22001 for tracking purposes. In the RFC letter, A&P petitions EPA to withdraw and correct its October 25, 2021, *Final Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3) Also Known As "GenX chemicals."* EPA refers to this below as the "toxicity assessment for GenX chemicals" or the "toxicity assessment;" A&P refers to this assessment in their submission as the "HFPO-DA Assessment." A&P claims that the final toxicity assessment is not supported by the weight of scientific evidence and that the process EPA undertook to develop the toxicity assessment was procedurally flawed and significantly deviates from standard EPA toxicity assessment methods. The materials submitted by A&P present new analyses and express their views on how these products should have been used in the development of the assessment of GenX chemicals. After careful consideration, EPA has concluded that the underlying information and conclusions presented in the 2021 *Final Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3) Also Known As "GenX chemicals*" and its supporting materials are consistent with EPA's Information Quality Guidelines. Therefore, the RFC is denied.

The RFC process is intended to provide a mechanism to correct errors where the disseminated product does not meet information quality standards. The toxicity assessment for GenX chemicals followed current EPA human health assessment methods and guidance, and its conclusions are consistent with the current version of EPA's Scientific Integrity Policy.

The GenX chemicals toxicity assessment also followed the current, standard EPA toxicity assessment methods, and its conclusions are supported by the weight of scientific evidence. The 2021 toxicity assessment for GenX chemicals was subject to two rigorous independent peer reviews by scientists who were screened for conflicts of interest in 2018 and 2021. In addition, to diligently respond to public comments received, EPA requested the National Institute of Environmental Health Sciences National Toxicology Program (NIEHS-NTP) conduct a rigorous independent review of the liver histopathology slides from two key studies, including the critical study underpinning the toxicity value (reference dose,

RfD). EPA published detailed responses to comments from both peer reviews. The assessment was made available for public review and comment for 60 days, and EPA published detailed responses to those public comments.

Consistent with the EPA Information Quality Guidelines (USEPA 2002), the review steps EPA followed to develop the toxicity assessment for GenX chemicals provides an objective review of "best available" science at the time it was developed. The Information Quality Guidelines states that EPA will ensure, "to the extent practicable," that:

> "The substance of the information is accurate, reliable, and unbiased. This involves the use of (i) the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer- reviewed science and supporting studies… In applying these principles, "best available" usually refers to the availability at the time an assessment is made."

EPA Information Quality Guidelines recognize that scientific knowledge about chemical hazards and risk changes and may need to be updated over time. However, the RFC process is not a mechanism to commit EPA to undertake scientific updates of its risk assessment related products, such as human health toxicity assessments (e.g., GenX chemicals). EPA Information Quality Guidelines recognize explicitly that a decision to launch an updated assessment depends on important programmatic factors and resource availability (USEPA 2002). Given the finite resources of the EPA, assessment activities are based on the priority needs of EPA. EPA's human health toxicity assessment for GenX chemicals was initiated as a priority action in 2018 and announced by the agency in the Per- and Polyfluoroalkyl Substances (PFAS) Action Plan (USEPA, 2019), PFAS Action Plan: Program Update (USEPA, 2020), and again in the PFAS Strategic Roadmap (USEPA, 2021a).

The RFC process does not require that EPA make a specific change or even any change, but it does provide that EPA evaluate the information and determine whether information submitted in the RFC indicates the need for correction. The RFC process does not compel or require EPA to evaluate the potential impact of new scientific information presented in the RFC on an existing final toxicity value.

EPA is providing a technical review in its response to this RFC (Appendix A). However, the precise approach taken in this instance does not set a precedent for all future RFC responses.

EPA concludes that the scientific information described in this RFC would not alter the conclusions of the GenX chemicals toxicity assessment. EPA does not find that the A&P submission identified errors in the 2021 toxicity assessment or that the process used by EPA was flawed. The points raised by A&P have either been considered and addressed during the peer review process for the GenX chemicals toxicity assessment or would not meaningfully impact the assessment.

Your Right to Appeal

If you are dissatisfied with the response, you may submit a Request for Reconsideration (RFR) as described in EPA's Information Quality Guidelines. The EPA requests that any such RFR be submitted within 90 days of the date of the EPA's response. If you choose to submit an RFR, please send a written request to the EPA Information Quality Guidelines Processing Staff via mail

(Information Quality Guidelines Processing Staff, Mail Code 2821T, USEPA, 1200 Pennsylvania Avenue NW, Washington, D.C. 20460); or electronic mail (quality@epa.gov). If you submit an RFR, please reference the case number assigned to this original Request for Correction (22001). Additional information about how to submit an RFR is listed on the EPA Information Quality Guidelines website at https://www.epa.gov/sites/default/files/2020-02/documents/epa-info-quality-guidelines_pdf_version.pdf.

Sincerely,

BENITA BEST-WONG

Digitally signed by BENITA BEST-WONG
Date: 2022.06.14 21:01:24 -04'00'

Benita Best-Wong
Deputy Assistant Administrator

cc: Vaughn Noga, Chief Information Officer and Deputy Assistant Administrator for Environmental Information, Office of Mission Support

Katherine Chalfant, Director of Enterprise Quality Management Division, Office of Mission Support

Attachment

Appendix A: EPA Technical Review of Scientific Information Presented in RFC 22001

A. Background on the A&P Submission

In 2018, EPA initiated development of a toxicity assessment of HPFO dimer acid (HFPO-DA) and its ammonium salt, also known as "GenX chemicals." GenX is a trade name for a processing aid technology used to make high-performance fluoropolymers without the use of PFOA. GenX chemicals are the major chemicals associated with the GenX processing aid technology. GenX chemicals have been found in surface water, groundwater, drinking water, rainwater, and air emissions. EPA initiated development of the toxicity assessment for GenX chemicals to respond to growing concern about the potential human health impacts of these chemicals, particularly in drinking water and ambient water.

EPA followed its standard agency policies, procedures, guidelines, and guidance in developing the toxicity assessment for GenX chemicals to ensure the conclusions in the assessment were scientifically defensible and supported by the weight of the scientific evidence. EPA conducted a systematic review of the scientific literature, drafted the detailed and transparent assessment with input from states and other federal agencies, and conducted multiple reviews of the assessment by other EPA offices, independent expert peer reviewers, and the public. Much of the available data for health effects after GenX chemical exposure were from submissions to the agency made by DuPont under the Toxic Substances Control Act (TSCA) and were classified as confidential business information (CBI). EPA worked with Chemours to make these studies publicly available in order to use the best available science in the development of the toxicity assessment and to ensure transparency with the public about its scientific basis.

In 2018, EPA initiated an independent letter peer review through a contractor who identified five scientific experts to conduct the review of the draft toxicity assessment for GenX chemicals and screened them for conflicts of interest. These peer reviewers agreed with EPA's selections of the critical effect and application of uncertainty factors and agreed with the derivation of RfDs. In November 2018, EPA published the draft toxicity assessment for GenX chemicals and EPA's response to external peer review for a 60-day public comment period that ended on January 22, 2019.

EPA received 36 sets of comments on the draft toxicity assessments from non-governmental organizations (NGOs), state health and environmental departments, industry, academia, private citizens, consultants, and water utilities. Three commenters (ToxStrategies, Inc. (submitted on behalf of Chemours), Green Toxicology LLC, and Dr. James Klaunig (submitted on behalf of Chemours) submitted comments focused on EPA's selection of the critical study and effect underlying the RfD, and specifically, the evaluation of liver pathology slides from studies conducted by DuPont submitted to EPA under the Toxic Substances Control Act (TSCA). Comments submitted by ToxStrategies, Inc. included a re-evaluation of the DuPont liver pathology slides by Dr. John Cullen, a veterinary pathologist retained by ToxStrategies, Inc. In his review, Dr. Cullen applied diagnostic criteria developed by experts from the International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) Organ Working Groups (Elmore et al., 2016). These criteria are used to distinguish between apoptosis and single-cell necrosis in standard hematoxylin and eosin- (H&E) stained tissue sections. Comments from Chemours and ToxStrategies, Inc. asserted that the observed liver lesions were apoptotic, and therefore, they concluded that this effect is likely attributable to the peroxisome proliferator-activated receptor-alpha (PPARα) signaling pathways, which are considered to be

relatively more active in rodents and may not be as relevant to humans. ToxStrategies, Inc. noted that based on the evidence for peroxisomal proliferation and PPARα involvement, liver hypertrophy would be considered non-adverse and should not be considered as the basis for risk assessment. Similar claims were made in a 2019 publication describing a reanalysis of the histopathology slides from the critical study (Thompson et al., 2019).

To respond to this comment, EPA engaged the NIEHS NTP who convened a Pathology Working Group (PWG) panel of seven expert scientists in liver histopathology that was coordinated by Dr. Elmore to provide independent, expert review of the liver tissues from the reproductive/developmental study (DuPont-18405-1037, 2010) and the 90-day mouse study (DuPont-18405-1307, 2010), two studies submitted to EPA under TCSA and reanalyzed by ToxStrategies, Inc as mentioned above. EPA had included the results and conclusions described in these DuPont studies in the toxicity assessment of GenX chemicals. This group of experts reached consensus conclusions on each liver pathology slide (process and recommendations are described in detail in EPA's response to public comments (USEPA, 2021c)) and provided their report (Elmore and Brix, 2019; also referred to as the "NIEHS-NTP report") to EPA in December 2019. As described in the response to public comment, the NIEHS-NTP report confirmed the conclusions presented in the studies submitted to EPA's Office of Pollution Prevention and Toxics (OPPT) by DuPont and in the draft toxicity assessment for GenX chemicals (EPA, 2018a) that the observed liver lesions, which include single-cell necrosis, are treatment-related adverse effects. EPA updated the final assessment to include a description of the NIEHS-NTP analysis and BMD modeling of these new dose response data. The reproductive/ developmental study (DuPont-18405-1037, 2010), which was identified as the critical study, identified liver effects in females (i.e., the constellation of lesions as defined by the NIEHS-NTP to include cytoplasmic alteration, hepatocellular single-cell and focal necrosis, and hepatocellular apoptosis) as the critical effect and used it as the basis for the calculation of the subchronic and chronic RfDs in the toxicity assessment for GenX chemicals.

Several commenters pointed out the deficiency of the GenX chemical database pertaining to human, immunotoxicity, and reproductive and developmental data. In order to base the final GenX chemicals toxicity assessment on the best available science, EPA conducted an updated literature search for relevant studies published through March 3, 2020. That search identified published toxicokinetic and toxicological findings after Gen X chemicals exposure including Blake et al. (2020) and Conley et al. (2019, 2021) that heightened EPA's concerns regarding the impact of GenX chemicals exposure on reproduction, development, and neurotoxicity. To address the information provided by the commenters and in the newly acquired studies, EPA increased the database uncertainty factor (UF_D) from 3 to 10 in the final assessment and increased the sub-chronic to chronic uncertainty factor (UF_S) from a 3 to 10 for the chronic RfD only. EPA also refined the endpoint classification consistent with the reevaluation of the pathology slides by NIEHS-NTP. The basis for these decisions is described in detail in the response to public comment (USEPA, 2021b).

EPA conducted a second independent letter peer review of the revised draft GenX toxicity assessment with seven expert scientists in April/May2021. This review focused on changes EPA made to the original draft toxicity assessment in response to public comment, considering the re-evaluation by the NIEHS-NTP and new information from a literature search. Charge questions focused on the refined endpoint in the critical study and changes to tow uncertainty factors. As described in EPA response to the second peer review (USEPA 2021c), the peer reviewers unanimously agreed with EPA's selection

of the critical study that included the refinement of the endpoint classification. They unanimously agreed with EPA's change to the UF_D. The majority (five of the six reviewers who responded) agreed with the change to the UF_S. The additional review by NIEHS-NTP and the second peer review were additional steps undertaken by EPA to enhance the scientific robustness of the toxicity assessment consistent with EPA's data quality and scientific integrity policies. All information used in the assessment is publicly available (the studies used to develop the assessment, the report from the NIEHS-NTP, the two peer review reports, EPA's responses to the peer review comments and EPA's response to public comments).

The RFC repeats many of the arguments made previously in public comments by these same commenters and raising the same science issues to which EPA has had peer reviewed (USEPA 2021c) and has previously responded to in public comments (USEPA 2021b).

The RFC states that Chemours is in the process of conducting new studies on the toxicity of GenX chemicals, but those data were not available to EPA when the toxicity assessment for GenX chemicals was finalized in October 2021, and they are not available today. EPA is not obligated to review unpublished works and scientific opinion pieces submitted under the RFC process.

The 2021 final toxicity assessment for GenX chemicals (USEPA 2021d) presents final toxicity values (i.e., RfDs), is wholly a science product, and is not a rulemaking. The toxicity values may subsequently be combined with exposure information (e.g., for drinking water, ambient water, soil) to help characterize potential public health risks from GenX chemicals and may be used in a non-regulatory Drinking Water Health Advisory or in rulemaking (e.g., under the Safe Drinking Water Act). A&P comments related to the Health Advisories that are under development are not addressed in this response to the RFC as they are not relevant to the publication of the final toxicity assessment for GenX chemicals. In the event that rulemaking is initiated for these GenX chemicals that uses this toxicity assessment, the rule will undergo additional public comment and other steps consistent with EPA rulemakings.

B. Technical Consideration of the 2022 A&P RFC 22001

Under EPA's Information Quality Guidelines, the RFC process does not require that EPA evaluate the potential impact of new scientific information on a previously published Toxicity Assessment. EPA is providing a technical analysis as part of its consideration of the March 2022 RFC. In this response, the EPA is addressing the following assertions raised in the A&P RFC 22001:

Assertion 1	The rodent liver effects underpinning the assessment are peroxisome proliferator-activated receptor alpha ("PPAR-alpha") effects that are not relevant to humans. EPA did not cite an important 2020 peer-reviewed study by Dr. Grace A. Chappell et al. that supports this conclusion and references in the assessment to non-PPAR-alpha modes of action are not supported by scientific data.
Assertion 2	The assessment by the National Toxicology Program did not follow evaluation criteria set forth in the peer-reviewed scientific literature and erroneously concluded that effects observed are adverse in humans.

Assertion 3	The assessment uses inappropriate and significantly inflated uncertainty factors that are inconsistent with EPA's own guidance and practice in other toxicity assessments.
Assertion 4	EPA has not taken into account available epidemiological evidence showing no increased risk of cancers or liver disease attributable to exposure to GenX chemicals.
Assertion 5	EPA's process in developing the assessment was flawed. A significant change from the draft toxicity assessment necessitated additional public comment. EPA failed to provide a publicly available Administrative Record, failed to undertake a proper literature review, and failed to submit the assessment for review by EPA's Science Advisory Board.

Assertion 1: The rodent liver effects underpinning the assessment are solely attributed to peroxisome proliferator-activated receptor alpha ("PPAR-alpha") effects that are not relevant to humans. EPA did not cite an important 2020 peer-reviewed study by Dr. Grace A. Chappell et al. that supports this conclusion and references in the assessment to non-PPAR-alpha modes of action are not supported by scientific data.

EPA Response: Animal toxicity studies following oral exposure to GenX chemicals have found health effects on the liver, the kidney, the immune system, and developmental effects, as well as cancer. The liver appears to be particularly sensitive after oral exposure to GenX chemicals. EPA conducted a systematic review of the literature in 2017 and 2018 to develop the draft toxicity assessment. Additional updates to the literature search were completed in February 2019, October 2019, and March 3, 2020 using the same search strategy. The scientific literature supporting the toxicity assessment shows that PPARα is one of the multiple modes of action (MOAs) and led to the effects (constellation of liver lesions) described by the NIEHS-NTP in their report (Elmore and Brix, 2019).

In the first independent external peer review, EPA asked questions about the role of PPARα and links to adversity:

> *The draft assessment for GenX chemicals identifies liver effects as a potential human hazard. EPA evaluated the available evidence for liver effects, including the potential role of PPARα, using Hall et al. (2012) criteria for adversity.*
> *a. Please comment on whether the available data have been clearly and appropriately synthesized for these toxicological effects.*
> *b. Please comment on whether the weight of evidence for hazard identification has been clearly described and scientifically justified.*
> *c. Please comment on whether the conclusions regarding adversity are scientifically supported and clearly described.*

As described in the response to comments from the first peer review (USEPA, 2018b), peer reviewers on the first peer review panel agreed that EPA's conclusions regarding adverse effects on the liver were scientifically supported and clearly described. They agreed with EPA that the MOA of GenX chemicals is largely unknown and that given the paucity of data, could not conclude that PPARα is the sole cause for observed liver effects, such as liver weight and single-cell necrosis. EPA does not agree with Chemours assertion that PPARα is the sole MOA, and EPA does not agree with Chemours assertion that

PPARα is not relevant to humans. This is not an error in the EPA toxicity assessment for GenX chemicals.

EPA met with representatives from Chemours and ToxStrategies, Inc. on January 27, 2022, at the request of Chemours, to discuss science issues related to EPA's final toxicity assessment for GenX chemicals. First, in that meeting, EPA addressed the question of why the Chappell et al., 2020 study was not included in the EPA assessment. As indicated in the final toxicity assessment (USEPA 2021d), EPA updated the literature for GenX chemicals in a search that covered published literature as of March 3, 2020. The Chappell et al. (2020) publication was first published online March 6, 2020, and the journal containing this article was published April 1, 2020. Both the online publication and the journal publication postdate the last literature update.

Second, in the January 27, 2022 meeting, EPA also explained that in the second peer review of the assessment (conducted April/May 2021), EPA asked the seven peer reviewers to identify recent literature not cited in the toxicity assessment in a charge question:

> *"Are you aware of any recent literature pertinent to the derivation of subchronic and chronic RfDs for GenX chemicals that is not identified in this document? If so, please provide citations along with a justification for why the studies might quantitatively impact the calculation of the RfDs."*

In their peer review comments, none of the seven peer reviewers included the Chappell et al. (2020) publication as a reference that EPA should consider.

Third, although EPA is not required to review scientific information that was not available at the time of the final assessment, EPA has reviewed the Chappell publication and determined that the results of the study do not change EPA's conclusions in the toxicity assessment for GenX chemicals (see Sec. 6) that there is evidence that these GenX chemicals have multiple MOAs**,** including PPARα, underlying the observed liver effects. Chappell et al. (2020) describes a gene expression analysis focused on the PPARα MOA after 90-day exposure to GenX chemicals in mice. The study found transcriptomic support for the PPARα MOA but did not explore other MOAs. The independent external peer reviewers agreed that there are multiple MOAs that may have led to the effects observed. It is important to note that the Chappell et al. (2020) study reports liver histopathological incidence data in a manner that is not consistent with the criteria for necrosis incidence identification that the NIEHS-NTP used in their re-analysis of the pathology slides. The NIEHS-NTP was comprised of seven pathologists who unanimously identified both apoptotic and necrotic cells in the 90-day subchronic mouse. In contrast, the Chappell et al. (2020) study was based on an assessment performed by one pathologist who identified only apoptotic cells and subsequently used caspase-3 staining to confirm the finding of apoptosis. However, the positive caspase-3 staining does not eliminate the possibility that necrotic cells were also present as it only provides evidence that apoptotic cells were present. Moreover, the observation of apoptotic cells is an expected result, as the NIEHS-NTP report (Elmore and Brix, 2019) also reported apoptotic cells in the high dose groups of the DuPont studies. Similarly, Chappell et al. (2020) only observes "occasional apoptotic bodies" (grade 3) in the high dose group of the 90-day mouse study (DuPont-18405-1307, 2010). Therefore, the Chappell publication supports data already summarized in the toxicity assessment for GenX chemicals.

On July 4, 2019, Chemours applied to the European Chemicals Agency (ECHA) seeking annulment of

ECHA's decision to list these GenX chemicals[1] as substances of very high concern under REACH (ED/71/2019). Chemours challenged ECHA's assessment of developmental toxicity, repeated dose toxicity, toxicokinetics and bioaccumulation, carcinogenicity and, reproductive toxicity. On February 23, 2022, the General Court rejected Chemours application ([2022] EUECJ T-636/19, EU:T:2022:86, ECLI:EU:T:2022:86) and upheld ECHA's decision thereby retaining the designation of GenX chemicals as substances of very high concern. The court held that Chemours did not put forth any arguments calling onto question the credibility of the findings and held that these were not errors in ECHA's assessment. Assertions made by Chemours regarding the ECHA assessment are repeated in this RFC, and addressed in the General Court's decision (point 53):

> *"The applicant asserts that ECHA's conclusion on repeated dose toxicity – that the main target organs of FRD-902 in rodents included the liver, the kidneys, the haematological system and the immune system – is relevant only to rodents and not to humans. According to the applicant, HFPO-DA may induce the peroxisome proliferator-activated receptor alpha ('PPARα'), which is specific to rodents. At the hearing, the applicant stated that it did not dispute that PPARα exists in humans, but rather claimed that ECHA had neither evaluated nor established the relevance of the effects observed for humans."*

The court determined that Chemours did not put forth any arguments calling into question the credibility of the findings and held that this was not an error in ECHA's assessment (point 56)*:*

> *"... it is apparent from the support document that ECHA took into account the fact that HFPO-DA could induce PPARα and described the function of that receptor and other receptors in the body. ECHA also stated in that document that there was a scientific debate, in particular as regards the induction of liver cancer in humans and the fact that there was less information on the differences between species as regards PPARα-related effects in other organs and during development. According to that document, ECHA also took into account information indicating that HFPO-DA could reinforce other modes of action relevant for humans. In addition, ECHA found in the support document that certain liver effects could be rodent-specific phenomena, but that those effects should be considered relevant to human health if they are accompanied by certain other effects. Liver necrosis indicates that another mode of action could be in place. Subsequently, ECHA found, inter alia, that the effects observed were repeatedly accompanied by necrosis."*

The final EPA toxicity assessment (USEPA 2021d) concluded there are not yet enough data to conclude that PPARα activation is the sole mechanism underlying the liver effects associated with exposure to GenX chemicals and pointed to studies that indicate other MOAs are plausible.

> "*The available data indicate that multiple MOAs could be involved in the liver effects observed after GenX chemicals exposure. The available studies provide support for a role for PPARα, cytotoxicity, mitochondrial dysfunction, and PPARγ. The potential MOA(s) for the observed reproductive and developmental effects (e.g., changes in GWG and placental lesions) are unknown. Additionally, no data support identification of a potential carcinogenic MOA for tumors in the pancreas and testes as being related to any of the proposed MOAs for the tumor development in either organ."*

[1] These chemicals are registered with ECHA as 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propionic acid, its salts and its acyl halides (and their isomers and combinations of isomers) ('HFPO-DA').

Five of the six authors of exhibits in the RFC submitted by A&P submitted public comments on these same topics, and EPA responded to those points in 2021. EPA received comments on the evaluation of liver pathology slides submitted to the agency by DuPont from Dr. James Klaunig, on behalf of Chemours; ToxStrategies, Inc., on behalf of Chemours; the American Chemistry Council; and Green Toxicology LLC. These comments are repeated in this RFC; EPA's response to their comments, can be found on pp.12-14 of the Response to Public Comment (USEPA 2021b) and summarized in this response to the RFC.

In Exhibit 1, Tox Strategies emphasizes conclusions consistent with the PPARα MOA and discounts or does not comment on conclusions consistent with other MOAs. For example, while some of the molecular indicators of the PPARα MOA (e.g., beta-oxidation, apoptosis) presented in Table 1 (reproduced from Chappell et al, 2020) were particularly strong in the high dose groups (> 0.5 mg/kg/day), liver necrosis, an endpoint consistent with a non-PPARα MOA, is observed in both the mid- (0.5 mg/kg/day) and high-dose groups. In Figure 4 (reproduced from Thompson et al., 2019), the graph does not show a statistically significant increase at 0.1 nmol/min/mg protein and at 3 nmol/min/mg protein there is a statistically significant increase. At the January 27, 2022 meeting with Chemours and ToxStrategies, Inc. EPA asked about this observation, and they responded that they agreed with the observation that this indicates a steep slope in response at the higher doses, but they interpreted these data as supporting the PPAR-α MOA as the sole MOA. Additionally, it is important to note that the data that Chemours displayed on perturbation of cell growth and survival (key event 3 of a PPARα MOA (Table 2) are limited to changes in liver weight. While EPA summarized these data in the GenX chemical toxicity assessment, the available histopathological data regarding changes in cell growth were included in the summary of MOA. The EPA document concluded that there was "evidence of perturbations to cell proliferation and apoptosis in the liver following short-term and subchronic exposure to HFPO dimer acid ammonium salt, particularly in the high-dose groups" and that "increases in mitoses/mitotic figures and apoptosis are consistently restricted to the high-dose group in all available mouse studies; however, necrosis is observed in both the mid- and high-dose groups," which suggests that cytotoxicity is also a possible MOA.

Chemours states that necrosis did not increase with dose and therefore the cytotoxicity MOA is not supportable for GenX chemicals. However, there is clear evidence of a dose response for combined necrosis in the reproductive/developmental study (DuPont-18405-1037, 2010; see table 11 of EPA's final toxicity assessment). In addition to the increased necrosis with GenX chemical exposure, the cytotoxicity MOA is also supported by the data indicating that GenX chemicals are not DNA reactive and that they are associated with increases in apoptosis (as supported by the ToxStrategies, Inc. submissions) and serum liver enzymes (see section 6 of EPA's final toxicity assessment for additional detail).

The studies cited by Chemours do not provide new evidence that MOAs other than PPARα are not plausible. This conclusion is not an error and is consistent with ECHA conclusions.

EPA does not agree with Chemours claims that the effects resulting from PPARα are not relevant to humans (Exhibit 1). A recent article by Conley et. al. (2021) rebuts this claim.

> *The gene expression data reported here and in our previous study (Conley et al. 2019) provides evidence for PPAR alpha (α) activation in the maternal, fetal, and neonatal livers. The relevance of rodent hepatocarcinoma induced via a PPARα mechanism of action has been described as an adverse effect that is not relevant to humans due to signaling pathway differences between*

rodents and humans (Corton et al., 2014, 2018). However, PPARα is universally recognized as the "master regulator of lipid metabolism" and also plays a key role in carbohydrate metabolism in all vertebrate classes (Kersten et al., 1999; Kersten, 2014). PPARs are a well-known pharmacological target for the treatment of multiple diseases in humans, including the PPARα-activating fibrates and the PPAR gamma (γ)-activating thiazolidinediones; however, the development of some of these was halted because of adverse side effects such as increased cardiovascular risk, carcinogenicity, liver toxicity, and renal injury in clinical trials (Hong et al. 2018). Further, the dual PPARα/PPARγ-activating glitazar class of drugs have been studied for several years and thus far all candidate drugs have failed either Phase II or III clinical trials due to adverse toxicities (Fievet et al., 2006; Waites et al., 2007). Clearly, modulation of both PPARα and/or PPARγ by exogenous agents, such as PFAS, are relevant to human health and the spectrum of adverse effects in laboratory animal studies are consistent with the physiological mechanisms that are targeted by pharmacologic agents/therapies.

It has also been argued that humans are considerably less responsive to PPARα-active chemical exposures because human hepatocytes were reported to display ~ 10-fold lower PPARα-DNA binding activity than mouse hepatocytes (Palmer et al. 1998). In contrast, more recent laboratory studies have reported that PPARα is well expressed in human liver slices (Janssen et al. 2015) and that gene expression levels of PPARα in primary human and mouse hepatocytes are similar (Rakhshandehroo et al. 2009). Prototypical PPARα regulated genes such as Angptl4, Cpt1a, Pdk4, which were highly upregulated in maternal, fetal, and neonatal livers here, were robustly upregulated in human liver slices following exposure to the PPARα-specific agonist Wy14643 (Janssen et al. 2015). Human and mouse primary hepatocytes both displayed upregulation of Cpt1a, Hmgcs2, Fabp1, and Acsl1 following fenofibrate exposure, similar to the HFPO-DA exposures here. These studies also reported divergent sets of genes between mouse and human, however it is important that the overall pathway of lipid metabolism as regulated by PPARα is highly conserved between rodents and humans. Although the PPAR pathways are conserved in all mammalian species and share a common molecular initiating event (i.e., PPAR binding and activation), differences in some of the downstream genomic key events in PPAR-relevant AOPs lead to different profiles of adverse effects among rodents and humans when the pathways are activated.

Further, the record from the findings of the Court of Justice of the European Communities indicates that Chemours claim that effects were only relevant to rodents was rejected in a ruling on February 23, 2022, ([2022] EUECJ T-636/19, EU:T:2022:86, ECLI:EU:T:2022:86). The court held that Chemours did not put forth any arguments calling into question the credibility of the findings and held that these were not errors in ECHA's assessment. Also, the record notes that "*At the hearing, the applicant [Chemours] stated that it did not dispute that PPARα exists in humans*".

Some of the assertions made by Chemours on the ECHA assessment regarding the relevance of the PPARα MOA to humans are repeated in this RFC, (point 53)

"The applicant asserts that ECHA's conclusion on repeated dose toxicity – that the main target organs of FRD-902 in rodents included the liver, the kidneys, the haematological system and the immune system – is relevant only to rodents and not to humans. According to the applicant, HFPO-DA may induce the peroxisome proliferator-activated receptor alpha ('PPARα'), which is specific to rodents. At the hearing, the applicant stated that it did not dispute that PPARα exists in humans, but rather claimed that ECHA had neither evaluated nor established the relevance of the effects observed for humans."

EPA conclusions that the adverse liver effects observed induced by exposure to GenX chemicals are relevant to humans, including those resulting from PPARα, are not an error. EPA recognizes, as did ECHA, that there is ongoing scientific debate on this topic.

Assertion 2: The assessment by the National Toxicology Program did not follow evaluation criteria set forth in the peer-reviewed scientific literature and erroneously concluded that effects observed are adverse in humans.

EPA Response: Chemours asserts that the NIEHS-NTP did not follow evaluation criteria by Elmore et al. (2016) set forth in the peer-reviewed scientific literature when they re-evaluated the liver pathology. Not only did EPA arrange for an independent external re-evaluation of the liver histopathology slides that took into account the Elmore criteria, coordinated by Dr. Elmore herself, but additionally EPA arranged a second external independent peer review to ensure that the science underlying the toxicity assessment was robust.

EPA requested that the NIEHS-NTP in Research Triangle Park, NC, convene a Pathology Working Group (PWG) to provide independent, expert re-evaluation of slides from the two critical studies: the reproductive/developmental study (DuPont-18405-1037, 2010) and the 90-day mouse study (DuPont-18405-1307, 2010). The re-evaluation was initiated in response to public comments on the draft toxicity assessment for GenX chemicals by many of the same people who contributed to this RFC. The process the NIEHS-NTP PWG used to reevaluate slides is described in detail in EPA's Response to Public Comment document (USEPA, 2021b):

> *"As part of this PWG, one pathologist reviewed all the slides from the two studies that DuPont submitted to EPA and classified liver cell death according to the INHAND Organ Working Group's diagnostic criteria (Elmore et al., 2016). Other liver effects were classified according to the INHAND document containing standardized terminology of the liver (Thoolen et al., 2010). The PWG coordinator then confirmed the classifications and selected example slides representative of the observed liver effects for review by the other six members of the group (a total of seven pathologists reviewed the slides). The selected slides included three examples each of normal liver, hepatocellular apoptosis, hepatocellular single-cell necrosis, and hepatocellular cytoplasmic alteration; two examples each of focal necrosis, pigment, increased mitoses, mixed-cell infiltrates, and cytoplasmic vacuolation; and one example of oval cell hyperplasia. There was a majority agreement on all reviewed lesions. The PWG consensus opinion for each slide, including any additional diagnoses made by the PWG panel, was recorded and presented in the final PWG report (appendix D in EPA, 2021a).*"

The coordinator of the PWG was Dr. Susan Elmore, the same pathologist who was the lead author of the publication outlining the criteria, outlined in Elmore et al. (2016). As stated in EPA's Response to Public Comment (USEPA 2021b), the PWG's classification of liver lesions included, but was not limited to apoptosis, single-cell necrosis, cytoplasmic alteration, and focal necrosis. The PWG confirmed single-cell necrosis and focal necrosis in the mid- and high-dose groups of both studies. NIEHS-NTP pathologists used the INHAND criteria outlined in Elmore et al. (2016) to separate single-cell necrosis from apoptosis. EPA updated the final toxicity assessment to include a description of the NIEHS-NTP analysis (Elmore and Brix, 2019) and BMD modeling of these new dose response data.

The reproductive/developmental study (DuPont-18405-1037, 2010), which was identified as the critical study, identified liver effects in females (i.e., the constellation of lesions as defined by the NIEHS-NTP to include cytoplasmic alteration, hepatocellular single-cell and focal necrosis, and hepatocellular apoptosis) as the critical effect and EPA used these results as the basis for the calculation of the subchronic and chronic RfDs.

EPA went to extraordinary effort to take into account public comment and assure that the best available science was used to develop the final toxicity assessment for GenX chemicals. Public comments, which are similar to the assertions in this Request for Correction, are addressed in the response to public comments (USEPA 2021b) and have been publicly available since October 2021, along with the NIEHS-NTP report (Elmore and Brix, 2019). EPA is confident that the Elmore criteria were appropriately applied by the independent expert pathologists that made up the NIEHS-NTP because all seven pathologists on the NTP PWG, including Dr. Susan Elmore, the lead author of the Elmore criteria, unanimously agreed on the classifications of single cell necrosis, focal necrosis and apoptosis in the reanalysis of the slides (and later referred to as a constellation of lesions). The NIEHS-NTP report is also included as an appendix in the GenX chemicals' toxicity assessment (USEPA, 2021d).

The "constellation of lesions" terminology originated from the NIEHS-NTP, who used that term to describe the group of lesions that together constitute adverse liver observations following exposure to GenX chemicals. It is not accurate to state, as A&P assert, that the NIEHS-NTP was not clear that the lesions should be combined. The NIEHS-NTP concluded that the dose response and constellation of lesions (i.e., cytoplasmic alteration (including hepatocellular hypertrophy), single-cell necrosis, focal necrosis, and apoptosis), rather than each lesion individually, represent adversity in these studies (Elmore and Brix, 2019).

In addition to the expertise of the NIEHS-NTP, EPA is also relying on a second independent peer review of the toxicity assessment conducted by seven independent external peer reviewers. The second group of peer reviewers were asked the following charge question about the study and toxicological endpoints identified by the NIEHS-NTP (constellation of lesions):

> *"In this updated assessment, candidate subchronic and chronic RfDs were calculated for GenX chemicals based on the NTP review of the same liver pathology slides from the oral reproductive/developmental toxicity study in mice (DuPont-18405-1037, 2010). Candidate RfDs were developed based on liver effects identified by the NTP as a constellation of lesions (cytoplasmic alteration, hepatocellular single cell and focal necrosis, and hepatocellular apoptosis) in parental males and females. The candidate RfDs derived from the oral reproductive/developmental toxicity mouse study (DuPont-18405-1037, 2010) and liver effects in females (constellation of lesions including cytoplasmic alteration, hepatocellular single-cell and focal necrosis, and hepatocellular apoptosis) were selected as the subchronic and chronic RfDs for HFPO-DA The RfDs based on this grouping of effects are the most health-protective of the modeled endpoints.*
>
> *a. Is the selection of the oral reproductive/developmental toxicity study in mice (DuPont-18405-1037, 2010) for the derivation of the subchronic and chronic RfDs for HFPO-DA scientifically justified and clearly described?*
>
> *i. If so, please explain your reasoning.*
>
> *ii. If you disagree with the selected critical study and effect, please provide your rationale and identify an alternative key study to support the derivation of the subchronic and chronic RfDs and provide the scientific support for the alternative choice.*

As described in the Response to the Second Peer Review comments (USEPA 2021c) the seven peer reviewers agreed with the selection of critical study and the constellation of lesions endpoint. Several reviewers characterize EPA's assessment as thoroughly described and well justified. Two reviewers refer to the NIEHS-NTP's application of the INHAND criteria. No errors were identified in the NIEHS-NTP analysis.

Assertion 3: The assessment uses inappropriate and significantly inflated uncertainty factors that are inconsistent with EPA's own guidance and practice in other toxicity assessments.

EPA Response: EPA correctly characterized the available toxicity data for these GenX chemicals as 'limited' as key studies are not available. The toxicity database for GenX chemicals is relatively small (12 dose response studies in comparison to the almost 400 new dose response studies published since 2016 for PFOA and PFOS (USEPA 2021e and USEPA 2021f). As summarized in EPA's Response to Public Comments (USEPA 2021b), public commenters pointed out the deficiency of the GenX chemicals database pertaining to human, immunotoxicity, and reproductive and developmental data. Recently published toxicokinetic and toxicological findings after GenX chemicals exposure [Blake et al. (2020) and Conley et al. (2019, 2021)] heighten concerns regarding the impact of exposure to GenX chemicals on reproduction, development, and neurotoxicity.

Consistent with EPA guidance, the agency increased two uncertainty factors (the UF_D and UF_S), which represented a change between the draft and final toxicity assessment. EPA made these changes as a result of public comments an updated literature search (through March 3, 2020), and a new analysis conducted by NTP-NIEHS (Elmore and Brix, 2019). EPA followed its risk assessment recommendations and guidance to select the appropriate uncertainty factors to apply when deriving an RfD (EPA, 2002).

EPA's justification for selecting the UF_D is clearly and transparently described and documented in great detail in EPA's Response to Public Comments document (EPA, 2021b; pp. 21-24):

> *"As stated above, a number of commenters pointed out the deficiency of the GenX chemical database pertaining to human, immunotoxicity, and reproductive and developmental data. Recently published toxicokinetic and toxicological findings after Gen X chemicals exposure of Blake et al. (2020) and Conley et al. (2019, 2021) heighten concerns regarding the impact of GenX chemicals exposure on reproduction, development, and neurotoxicity. To address the information provided by the commenters and in recently published studies, EPA has increased the UF_D from 3 to 10 in the final assessment. These points that justify the selection of a UF_D of 10 are summarized in brief in this response (above) as well as in section 7.3 of the assessment (EPA, 2021a)."*

EPA bases its decisions on the specific types of toxicity information that are lacking from the database **of the specific chemical** at the time of the assessment. The EPA Toxicity assessment for GenX chemicals was based on data available through March 3, 2020, and included studies submitted to EPA by DuPont through the PMN and through a consent order. These data were assessed in the final toxicity assessment and uncertainties remain. As the science on health effects for GenX chemicals evolves, EPA may in the future, depending on priorities, determine to update the assessment. However, speculation on how a chemical's database may change in the future based on new studies that are planned cannot be

considered in determining a chemical's database uncertainty factor.

EPA's justification for selecting the UF_S for the chronic RfD is clearly and transparently described and documented in great detail in EPA's Response to Public Comments document (EPA, 2021b; pp. 26-27):

> *"The UF_S is applied to account for use of a critical study with less than chronic studies in the derivation of chronic reference values. Its application addresses the possibility that, with additional exposure duration, adverse effects might be observed at lower doses. Therefore, application of a UF_S is appropriate and consistent with EPA guidance (EPA, 2002)."*

EPA ensured that the selections of uncertainty factors were consistent with EPA's standard toxicity assessment methods, objective, reasonable, and supported by the weight of scientific evidence by conducting a second independent expert peer review. All seven independent expert peer reviewers concurred on EPA's selected uncertainty factor to account for uncertainty of the database. The majority (5 of 6 peer reviewers that responded) agreed with EPA's selected uncertainty factor to account for the extrapolation from a subchronic to a chronic study. Their comments and the agency's responses are publicly available. This was not an error in the assessment.

Assertion 4: EPA has not taken into account available epidemiological evidence showing no increased risk of cancers or liver disease attributable to exposure to GenX chemicals.

EPA Response: No epidemiological studies have been published that include measures of exposure to GenX chemicals and health outcomes after exposure. Chemours confirmed this fact in a meeting with EPA on January 27, 2022. In that meeting, EPA asked Chemours and their representatives if they were aware of any existing published epidemiological studies on HPFO dimer acid. Chemours and their consultants replied that they were not aware of epidemiology studies for GenX chemicals. Chemours assertion that EPA has not taken into account epidemiological data is therefore puzzling.

The 124-page Exhibit 5 (prepared by Exponent, Inc) presents an observational analysis comparing cancer and liver disease rates in North Carolina to rates in other states. Exhibit 5 does not present the results of a new epidemiological study that included GenX chemicals exposure measures, health outcome measures, or an assessment of association between exposure and health outcome. It consists of a secondary analysis of disease rate information that was collected from various sources. It has not been peer reviewed and does not provide new, high quality scientific information that can be used to assess the impact of exposure to concentrations of GenX chemicals on human health. The conclusions in Exhibit 5 make spurious claims regarding the safety of GenX chemicals without the support of results from a rigorous scientific study. EPA found that sound epidemiological evidence adds important information to understand the public health impacts from PFAS and has used such data in the recent updates of toxicity assessments for PFOA and PFOS (USEPA 2021e and USEPA 2021f). Comparable data are not yet available for GenX chemicals.

It is also interesting that that Exhibit 5 focused on two health outcomes: cancer and liver disease. EPA did not conclude in the toxicity assessment that GenX chemicals are a known human carcinogen; we concluded that there is suggestive evidence of carcinogenic potential from oral exposure to GenX (USEPA, 2021d, p. 81). In fact, the lack of oral data on cancer is identified as a database deficiency, and EPA also noted in the toxicity assessment the lack of data available to evaluate cancer risk via dermal,

and inhalation exposure. Thus, the analysis correlating increased risk of cancer in populations "exposed" or "unexposed" to GenX chemicals is also puzzling.

Thus, there are no errors identified that require correction.

Assertion 5: EPA's process in developing the assessment was flawed. A significant change from the draft toxicity assessment necessitated additional public comment. EPA failed to provide a publicly available Administrative Record, failed to undertake a proper literature review, and failed to submit the assessment for review by EPA's Science Advisory Board.

EPA Response: EPA followed agency policies, procedures, and guidance in developing the toxicity assessment for GenX chemicals. There is an extensive administrative record available for the toxicity assessment for GenX chemicals that is publicly available (FRL-9986-79-OW). Development of the toxicity assessment included EPA guidance and policies and **several additional nonmandatory steps (in bold below)** to ensure the scientific rigor, objectivity, input from experts and the public, and transparency of the assessment process:

- Conducted a review of scientific literature using EPA's systematic review methods
- **Declassified data on GenX chemicals submitted under TSCA so these data could be considered for use in the toxicity assessment**
- **Transparent sharing of scientific studies; All studies are publicly available on the Health and Environmental Research Online database (HERO) (https://hero.epa.gov/hero/index.cfm/project/page/project_id/2627)**
- Conducted internal review of draft by EPA program offices
- Conducted external review of draft by federal agencies and key state stakeholders
- Conducted an independent expert peer review
- Released the assessment for public comment for 60 days
- **Coordinated a reevaluation of liver histopathology slides by independent science experts at the NIEHS-NTP in order to address specific public comments**
- **Conducted a second external independent peer review of the revised toxicity assessment**
- Published the final toxicity assessment and all associated documents:
    - the final toxicity assessment,
    - response to comments from the first independent external peer review,
    - response to comments from the second independent external peer review, and
    - response to public comments.

Contrary to A&P claims, EPA performed the systematic review for the GenX chemicals database in accordance with EPA's state-of-the-art ORD systematic review practices to identify the best available science as the basis for the final toxicity assessment for GenX chemicals. The process is described in detail in the Response to Public Comment (USEPA, 2021b):

> *"Specifically, relevancy screenings were conducted on all the studies submitted from DuPont/Chemours and the publicly available, peer-reviewed literature resulting from the literature searches. These studies were subjected to title and abstract screening to determine relevancy according to the population, exposure, comparator, and outcome (PECO) criteria statement/inclusion and exclusion criteria outlined in Table A-6 in appendix A of the assessment*

(EPA, 2021a). The title and abstract of each study were independently screened by two screeners using Distiller SR. The studies that met the PECO criteria were tagged as having relevant human data, animal data in a mammalian model, or a PBPK model. A study was included as relevant if it was unclear from the title and abstract whether it met the inclusion or exclusion criteria. Studies that did not meet the inclusion criteria but provide supporting information were categorized as supplemental, relative to the type of supporting information they provided. When two screeners did not agree if a study should be included, excluded, or tagged as supplemental, a third reviewer made the final decision. The title and abstract screening resulted in 12 studies tagged as relevant (i.e., containing dose-response information). The relevancy of these studies was confirmed by a full-text review. The 12 studies providing dose-response information were then evaluated for study quality using an approach consistent with the draft ORD Handbook for developing IRIS assessments."

EPA strongly supports peer review to ensure the quality of EPA's science. In conducting peer review of the GenX chemicals' Toxicity assessment. EPA followed the agency's Peer Review Handbook (USEPA, 2009).

EPA conducted not one but two separate independent external peer reviews; the first peer review included five expert reviewers and the second peer review included seven experts all of whom were screened for conflicts of interest. This extensive second peer review of the Toxicity Assessment for GenX chemicals went well beyond the peer review requirements described in agency guidance, which does not require a second peer review. In addition, to address questions about liver endpoint classification methods raised in public comments, EPA coordinated with the NIEHS-NTP, who assembled an independent panel of seven expert pathologists to conduct the re-evaluation. One of the scientists was the lead author of the classification method recommended by public commentors to re-evaluate the pathology slides. EPA's engagement of the NIEHS-NTP in an independent review of the primary data illustrates EPA's commitment to rigor and responsiveness to public and peer review comments; the additional independent review went beyond the peer review requirements for EPA toxicity assessments.

EPA did make a change to the toxicity assessment based on the consideration of public comments, consistent with EPA process for developing toxicity assessments. As described above, some public comments disagreed with the classification of the draft critical effect and asserted that EPA should have applied additional criteria (Elmore et al., 2016). EPA responded to this comment by requesting an independent, expert re-analysis of the pathology slides from two key studies. The NIEHS-NTP PWG's re-evaluation Elmore and Brix, 2019) confirmed the original study conclusions by DuPont scientists who authored the studies and recommended a change in the classification of adverse liver histopathology effects based on the Elmore et al. (2016) criteria classification. Using the new classification of a constellation of liver lesions, NIEHS-NTP PWG identified the females as the more sensitive group in the study, which expanded our understanding of the original results. EPA made the original study publicly available and added the NIEHS-NTP PWG report to the public docket. EPA determined that the NIEH-NTP study results, which confirmed the original study conclusions described in the public review draft, did not warrant another round of public comment. EPA followed established processes; the assertion that we failed to follow established processes is incorrect.

Chemours asserts that SAB review is required for toxicity assessment and that because EPA did not have SAB review of the toxicity assessment for GenX chemicals EPA failed to follow established procedures. EPA's Peer Review Handbook provides the agency multiple options for conducting

independent external peer review, including the contractor-led peer reviews used for the GenX chemicals toxicity assessment. There is no requirement for EPA to have toxicity assessments reviewed by the Science Advisory Board. The extensive additional peer review steps that EPA engaged in for the GenX chemicals toxicity assessment are an example of EPA's commitment to ensure the scientific basis of the GenX chemicals toxicity assessment is robust and transparent and went well beyond guidance in EPA's Peer Review Handbook and demonstrate EPA's strong commitment to peer review to assess the quality of the science.

Finally, in October 2021, A&P submitted a Freedom of Information Act (FOIA) requesting EPA release EPA's Administrative Record associated with its GenX chemicals toxicity assessment. EPA corresponded with A&P several times and had a teleconference on March 31, 2022, to better understand the request and prioritize record review. To date, EPA has released a total of 5,079 pages in response to this FOIA request (1,178 pages released on April 12, 2022; 2,368 pages on May 6, 2022; and 1,533 pages released on June 2, 2022). EPA continues to review and release responsive records. EPA is following the established process for responding to FOIA requests.

References

- [2022] EUECJ T-636/19, EU:T:2022:86, ECLI:EU:T:2022:86, 23 February 2022, BAILII >> Databases >> Court of Justice of the European Communities (including Court of First Instance Decisions) >> Chemours Netherlands v ECHA (REACH - substances of very high concern - error of assessment - Judgment) URL: *http://www.bailii.org/eu/cases/EUECJ/2022/T63619.html*

- Chappel, G.A., Chad M. Thompson, Jeffrey C. Wolf, John M. Cullen, and Laurie C. Haws, 2020, Assessment of the Mode of Action Underlying the Effects of GenX in Mouse Liver and Implications for Assessing Human Health Risks, Toxicologic Pathology, V 48(3), 494-508

- ECHA, 2019, Member State Committee Support Document For Identification Of 2,3,3,3-Tetrafluoro-2-(Heptafluoropropoxy)Propionic Acid, Its Salts And Its Acyl Halides (Covering Any Of Their Individual Isomers And Combinations Thereof), https://echa.europa.eu/documents/10162/53fa6a5b-e95f-3128-ea9d-fa27f43b18bc#page54

- Elmore, S.A., D. Dixon, J.R. Hailey, T. Harada, R.A. Herbert, R.R. Maronpo, T. Nolte, J.E. Rehg, S. Rittinghausen, T.J. Rosol, H. Satoh, J.D. Vidal, C.L. Willard-Mack, and D.M. Creasy. 2016. Recommendations from the INHAND apoptosis/necrosis working group. *Toxicology Pathology* 44(2):173-88. doi:10.1177/0192623315625859.

- Elmore, S.A., and A. Brix. 2019. Pathology Peer Review of Liver Findings—H-28548: Subchronic Toxicity 90 Day Gavage Study in Mice (DuPont-18405-1307) and an Oral (Gavage) Reproduction/ Developmental Toxicity Screening Study of H-28548 in Mice (WIL-189225; DuPont-18405-1037). Final report of the National Toxicology Program Pathology Working Group. Appendix D In *Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3)*, EPA 822R-21-010. U.S. Environmental Protection Agency, Office of Water, Health and Ecological Criteria Division, Washington, D.C.

- Justin M. Conley, Christy S. Lambright, Nicola Evans, James McCord, Mark J. Strynar, Donna Hill, Elizabeth Medlock-Kakaley, Vickie S. Wilson, L. Earl Gray Jr, 2021, *Hexafluoropropylene oxide-dimer acid (HFPO-DA or GenX) alters maternal and fetal glucose and lipid metabolism and produces neonatal mortality, low birthweight, and hepatomegaly in the Sprague-Dawley rat,* Environment International, Volume 146, January 2021, 106204

- Thompson, C.M., S.E. Fitch, C. Ring, W. Rish, J.M. Cullen, and L.C. Haws. 2019. Development of an oral reference dose for the perfluorinated compound GenX. Journal of Applied Toxicology 39(9):126–1282. doi:10.1002/jat.3812

- USEPA, 2002, Guidelines for ensuring and maximizing the quality, objectivity, utility, and integrity of information disseminated by the Environmental Protection Agency, EPA/260R-02-008, https://www.epa.gov/sites/production/files/2017-03/documents/epa-info-quality-guidelines.pdf

- USEPA, 2009, Peer Review Handbook, 3rd edition, EPA 100/b-06/002

- USEPA, 2012, USEPA's 2012 Scientific Integrity Policy: https://www.epa.gov/sites/default/files/2014-02/documents/scientific_integrity_policy_2012.pdf

- US EPA, 2018a. Draft Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037- 80-3) Also Known as "GenX Chemicals." Office of Water (4304T) Health and Ecological Criteria Division Washington, D.C. Document #EPA-823-P-18-01. Available online at: https://www.epa.gov/sites/default/files/2018-11/documents/genx_public_comment_draft_toxicity_assessment_nov2018-508.pdf

- US EPA, 2018b. Response to Peer Review Comments on the Draft Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037- 80-3). Office of Water (4304T) Health and Ecological Criteria Division Washington, D.C. Document #823-R-18-003, Available online at: https://www.epa.gov/sites/default/files/2018-11/documents/genx_epa_response_to_peer_review_comments_nov2018-508.pdf

- USEPA, 2019. EPA's Per- and Polyfluoroalkyl Substances (PFAS) Action Plan. EPA/823/R-18/004. EPA. Accessed July 2020. https://www.epa.gov/sites/production/files/2019-02/documents/pfas_action_plan_021319_508compliant_1.pdf.

- USEPA, 2020, PFAS Action Plan: Program Update, EPA publication number: 100K20002; https://www.epa.gov/sites/default/files/2020-01/documents/pfas_action_plan_feb2020.pdf

- USEPA, 2021a, PFAS Strategic Roadmap: EPA's Commitment to Action 2021-2024, https://www.epa.gov/system/files/documents/2021-10/pfas-roadmap_final-508.pdf

- USEPA, 2021b. EPA Response to Public Comments on Draft Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3). Office of Water (4304T) Health and Ecological Criteria Division Washington, D.C. Document # 822R-21-008. Available online at: https://www.epa.gov/system/files/documents/2021-10/final-genx-assessment-resp-to-public-comments_508.pdf

- USEPA, 2021c. Response to Additional Focused External Peer Review of Draft Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and its Ammonium Salt (GenX chemicals). Office of Water (4304T) Health and Ecological Criteria Division Washington, D.C. Document #822R-21-009. Available online at: https://www.epa.gov/system/files/documents/2021-10/epa_2nd-response-to-peer-review_genx_508.pdf

- USEPA, 2021d. Final Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3). Office of

Water (4304T) Health and Ecological Criteria Division Washington, D.C. Document #822R-21-010. Available online at: https://www.epa.gov/system/files/documents/2021-10/genx-chemicals-toxicity-assessment_tech-edited_oct-21-508.pdf

- USEPA, 2021e, EXTERNAL PEER REVIEW DRAFT- Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctane Sulfonic Acid (PFOS) (CASRN 1763-23-1) in Drinking Water, EPA Document No.822D21002, https://sab.epa.gov/ords/sab/f?p=100:18:16490947993:::RP,18:P18_ID:2601#doc

- USEPA, 2021f, EXTERNAL PEER REVIEW DRAFT- Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) (CASRN 335-67-1) in Drinking Water, EPA Document No.822D21001, https://sab.epa.gov/ords/sab/f?p=100:18:16490947993:::RP,18:P18_ID:2601#doc