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DATE: January 25, 2022

SUBJECT: **Recommendation for a Reference Concentration for GenX**

DSR Recommendation

This memorandum is written for the Division of Air Quality (DAQ) in response to their November 2019 request that the Division of Science and Research (DSR) develop an inhalation Reference Concentration (RfC) for GenX chemicals[a] (hereafter referred to as GenX).

In response to DAQ's request, DSR toxicologists thoroughly reviewed the health effects literature and risk assessment approaches relevant to the development of toxicity factors (e.g., Reference Dose [RfD], RfC) for GenX. Recently, the USEPA Office of Water finalized an oral RfD for GenX as 3 ng/kg/day (USEPA, 2021). This RfD is based on liver histological changes in female mice. USEPA (2021) stated that an inhalation RfC was not derived for GenX due to "data limitations".

[a] GenX chemicals refer to hexafluoropropylene oxide dimer acid (HFPO-DA) and HFPO-DA ammonium salt that are used as processing aids in the GenX technology developed by DuPont (now Chemours) to replace the use of PFOA as a processing aid in fluoropolymer production (USEPA, 2021).

DSR has reviewed the basis of the USEPA (2021) RfD of 3 ng/kg/day and concluded that it is scientifically justified and health protective. Therefore, DSR recommends that NJDEP use the USEPA RfD of 3 ng/kg/day for GenX.

DSR derived a Screening RfC of 0.01 µg/m^3 (10 ng/m^3) for the inhalation route of exposure based on oral-to-inhalation extrapolation using the USEPA RfD. The designation of the RfC as "Screening" indicates that it is more uncertain than other RfCs. DSR recommends the Screening RfC of 0.01 µg/m^3 (10 ng/m^3) to DAQ.

USEPA Toxicity Assessment and RfD for GenX

USEPA released a draft human health toxicity assessment, including a draft chronic RfD of 80 ng/kg/day, for GenX for public comment in 2018 (USEPA, 2018). The draft RfD of 80 ng/kg/day was based on liver effects, specifically hepatocyte necrosis in adult male mice in a reproductive and developmental toxicity study (DuPont-18405-1037, 2010). NJDEP provided comments on this draft (NJDEP, 2019a).

In October 2021, USEPA released the final GenX toxicity assessment, including a chronic RfD of 3 ng/kg/day, which is much more stringent than the draft USEPA (2018) RfD of 80 ng/kg/day. In the final assessment, USEPA (2021) used the Integrated Risk Information System (IRIS) systematic review process for evaluating study quality and considered new toxicology information that became available after the draft document was released in 2018. The new toxicology data included the results from a National Toxicology Program Pathology Working Group reevaluation of liver histopathology from the two key mouse studies using updated criteria for the evaluation of rodent liver histopathology (NTP, 2019), and publications on several new toxicology studies (USEPA, 2021). The updated USEPA assessment also underwent a second peer review, in addition to the earlier peer review of the 2018 draft, and the peer reviewers agreed with the decisions made by USEPA in the final document. USEPA Office of Water also requested review and input from numerous other USEPA programs and Regional Offices. In addition, revisions were made in response to some of the public comments on the 2018 draft, including several revisions suggested in the NJDEP (2019a) comments.

The change in the RfD to 3 ng/kg/day from the draft value of 80 ng/kg/day results from several differences between the draft (USEPA, 2018) and final (USEPA, 2021) risk assessments. Both the draft and final RfDs are based on histopathological changes in the liver in adult mice in the same study (mouse reproductive and developmental toxicity study; DuPont-18405-1037, 2010). However, the draft RfD was based on the incidence of hepatocyte necrosis from the original study report using earlier criteria for the evaluation of rodent liver histopathology, while the final RfD is based on the combined incidence of several histopathological changes from the NTP (2019) reevaluation using updated criteria for the evaluation of rodent liver histopathology. Also, the draft RfD was based on effects in males, while the final RfD is based on effects in females because the NTP (2019) reevaluation indicated that females are the more sensitive sex for the combined incidence of histopathological changes in the liver. Additionally, the uncertainty factor for study duration was increased from 3 to 10 in the final assessment, because females were exposed for a shorter period of time than males and because data indicate that the liver effects caused by GenX

can progress with longer exposure duration. The uncertainty factor for database completeness was also increased from 3 to 10 because recent studies suggest the potential for toxicity at lower doses than indicated in the previous studies.

DSR Evaluation of GenX Toxicity and the USEPA RfD

DSR toxicologists had performed a detailed and extensive review of the scientific literature on the health effects of GenX. This review included 87 human health-related studies (62 experimental animal studies, 20 *in vitro* mechanistic studies, and 5 human biomonitoring studies), as well as review articles and risk assessments developed by other groups. DSR was close to completing a draft document and recommendation for an RfD and RfC, when the USEPA (2021) assessment and RfD were finalized. It was decided to forego completion of the DSR document in light of the EPA final assessment of GenX.

Based on a thorough review by DSR toxicologists, DSR agrees that the USEPA approach is scientifically justified and that the USEPA RfD of 3 ng/kg/day is health protective. The USEPA (2021) assessment and the draft DSR assessment of GenX have the same general basis. Both USEPA and DSR concluded that liver toxicity is the most sensitive and well-established adverse effect of GenX, and that the liver toxicity caused by GenX in rodents is relevant to humans. Out of several possible rat and mouse studies, USEPA and DSR both chose the mouse reproductive and developmental study (DuPont-18405-1037, 2010) as the key study and identified liver toxicity from this study as the critical effect. The RfD that DSR toxicologists were considering when the USEPA RfD was finalized is very close to the EPA RfD (less than a factor of 2 difference), and it is not less stringent than the USEPA RfD.

Based on the information discussed above, DSR recommends that NJDEP use the USEPA RfD of 3 ng/kg/day for derivation of an inhalation RfC for GenX.

Development of Screening Inhalation RfC

As had been done for PFOA and PFOS (NJDEP, 2019b), DSR thoroughly reviewed the relevant literature and toxicology studies to evaluate the appropriateness of oral-to-inhalation extrapolation for GenX. As stated in USEPA (2021), no data for GenX are available to characterize the absorption rate through the lungs for systemic distribution, and only one rat acute inhalation toxicity study of HFPO-DA ammonium salt is available, in which systemic toxicity was not evaluated (DuPont-17751-723, 2009). There is limited chemical-specific information to support oral-to-inhalation extrapolation for GenX. However, some properties of GenX are similar to other PFAS (e.g., PFOA and PFOS), for which inhalation toxicokinetic and toxicity data that support oral-to-inhalation extrapolation are available. Like PFOA and PFOS, GenX: 1) has a low vapor pressure and is not expected to volatilize; 2) is not highly bioaccumulative in the liver and fat; 3) is not metabolized in the liver; and 4) all or almost all excretion is in the urine.

Therefore, DSR concludes that a Screening RfC can be developed for GenX using the default oral-to-inhalation extrapolation methodology recommended by USEPA (2009). As shown in the

Appendix, an inhalation Screening RfC of 0.01 µg/m^3 (10 ng/m^3) was derived using the USEPA RfD of 3 ng/kg/day with assumed average adult body weight of 70 kg and inhalation rate of 20 m^3/day. It is noted that a chronic inhalation exposure limit for GenX was developed by the Netherlands National Institute for Public Health and the Environment using a similar approach (RIVM, 2016).

Based on the discussion above, DSR recommends that DAQ uses this Screening RfC of 0.01 µg/m^3 (10 ng/m^3) for GenX.

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Appendix

Development of a Screening Inhalation RfC from the USEPA Oral RfD Using Default Oral-to-Inhalation Extrapolation Methodology

While it is preferred that an inhalation RfC be developed based on inhalation toxicity data when such data are available, route-to-route extrapolation from the oral RfD to the inhalation RfC is recommended when inhalation data to develop a RfC are not available (USEPA, 1994).

Chemical-specific data, including physicochemical properties (e.g., volatility, speciation), portal-of-entry effects, absorption rates, and first-pass metabolism by different routes of exposure need to be considered for a chemical-specific route-to-route extrapolation.

When limited chemical-specific data are available for oral-to-inhalation extrapolation, as a default approach, the inhalation RfC can be extrapolated from the oral RfD using the following formula (USEPA, 2009):

$$\text{RfC } (\mu g/m^3) = \text{RfD } (\mu g/kg/day) \times [(\text{body weight, kg}) \div (\text{inhalation rate per day, } m^3/day)]$$

Where:

- Average body weight is 70 kg[b]
- Inhalation rate is 20 m^3/day

NJDEP developed inhalation RfCs from oral RfDs for PFOA and PFOS using this default route-to-route extrapolation approach (NJDEP, 2019). This approach has also been used by the Michigan Department of Environmental Quality (MDEQ, 2018a; MDEQ, 2018b) and the Minnesota Department of Health (MDH, 2021a; MDH, 2021b) for PFOA and PFOS, and a similar approach was used by the Netherlands National Institute for Public Health and the Environment (RIVM, 2016) for GenX. As discussed by MDEQ (2018a, 2018b) and NJDEP (2019), this default approach is applicable when portal of entry effects (i.e., respiratory tract effects) are not expected, first pass effects (i.e., metabolism in the liver and/or gastrointestinal tract after oral administration, prior to reaching systemic circulation) do not occur, and systemic absorption occurs in the lungs. This approach was considered appropriate for PFOA and PFOS, because no respiratory tract effects are expected in the range of the RfC, they are not metabolized in the liver, and they are known to be absorbed through the lungs (DWQI, 2017; DWQI, 2018).

These considerations also apply to inhalation exposure to GenX (i.e., HFPO-DA and HFPO-DA ammonium salt) for similar reasons, including 1) HFPO-DA and its ammonium salt have low vapor pressures and are not expected to volatilize; 2) HFPO-DA[c] is not highly bioaccumulative in

[b] While the USEPA Office of Water and Superfund programs have updated the default adult body weight assumption to 80 kg and increased the default drinking water ingestion rate accordingly, USEPA has not updated its exposure assumptions for body weight and daily inhalation rate for the development of inhalation toxicity factors.

[c] The ammonium salt of HFPO-DA converts to HFPO-DA when it enters the body.

the liver and fat; 3) HFPO-DA is not metabolized in the liver; and 4) all or almost all excretion is in the urine (USEPA, 2021).

However, no toxicokinetic data are available for GenX to characterize its systemic bioavailability through the lung, and only one acute inhalation toxicity study is available (DuPont-17751-723, 2009). In this acute inhalation study in rats, mortality was not observed in male or female rats following a 4-hour exposure to the ammonium salt of HFPO-DA at concentrations up to 5200 mg/m^3. This study did not evaluate toxicokinetics or systemic toxicity, and it only examined histopathology in the respiratory system. Portal of entry effects (discharge from the nose, eyes, and/or mouth; red staining of faces or heads) were observed, but there were no histopathological changes in the upper or lower respiratory tract. The high dose, when converted to the equivalent oral dose, is substantially below the doses that are lethal to 50% of animals (LD50s) and the lowest acute lethal dose from the oral acute studies in rats (DuPont-22932, 2007; DuPont-25438 RV1, 2008). Because the dose ranges in the acute inhalation study and the acute oral studies are not comparable, it cannot be determined whether the HFPO-DA ammonium salt is more or less acutely toxic by inhalation than orally. Additionally, as stated above, there are no data on whether GenX chemicals cause systemic effects via inhalation.

Given the fact that GenX is a short chain PFAS and has similar physicochemical and physiochemical properties as PFOA and PFOS (ITRC, 2020), GenX can be reasonably expected to be absorbed through the lung. While there are more uncertainties about oral-to-inhalation extrapolation of GenX than for PFOA and PFOS, the information on these two related PFAS provides support for use of such an extrapolation for GenX. Because of the higher uncertainty associated with the oral-to-inhalation extrapolation for GenX, DSR recommends the development of a Screening RfC for GenX. Such a Screening RfC is analogous to the Screening Provisional Peer-Reviewed Toxicity Values (PPRTVs)[d] developed by USEPA.

The Screening RfC for inhalation exposure is developed for GenX by an extrapolation from the oral RfD of 3 ng/kg/day (0.003 µg/kg/day) with the same default methodology that was used to develop the PFOA and PFOS RfCs, as follows:

RfC (µg/m^3) = RfD (µg/kg/day) x [(body weight, kg) ÷ (inhalation rate per day, m^3/day)]

= 0.003 µg/kg/day x [70 kg ÷ 20 m^3/day]

= 0.01 µg/m^3 (10 ng/m^3)

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[d] See more details at https://www.epa.gov/pprtv/basic-information-about-provisional-peer-reviewed-toxicity-values-pprtvs#basicinfo.

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