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THROUGH: Nicholas A. Procopio, Ph.D., Director *NAP*

FROM: Gloria B. Post, Ph.D., D.A.B.T., Research Scientist *GBP*

DATE: May 24, 2023

SUBJECT: Interim Specific Ground Water Quality Criterion (ISGWQC) for hexafluoropropylene oxide dimer acid (HFPO-DA) and its ammonium salt (GenX)

On August 12, 2022, the Bureau of Ground Water Pollution Abatement, Division of Site Remediation & Waste Management, requested that the Division of Science and Research (DSR) develop an Interim Specific Ground Water Quality Standard (ISGWQS) for HFPO-DA and its ammonium salt (hereafter referred to as GenX). This memorandum provides the basis for the recommendation of an ISGWQC of 20 ng/L for GenX. The analytical Interim Practical Quantitation Level for GenX will be provided in a separate memorandum.

Establishment of Interim Specific Ground Water Quality Criteria (ISGWQC) by NJDEP

The New Jersey Ground Water Quality Standards (GWQS) regulations at N.J.A.C. 7:9C-1.7(c)(2) allow for the New Jersey Department of Environmental Protection (NJDEP) to establish an ISGWQC for a constituent not listed in the GWQS at N.J.A.C. 7:9C by providing notice and access to the supplemental information used in its derivation.

An ISGWQC is a health-based criterion intended to be protective for chronic (lifetime) exposure through drinking water, including for lifetime cancer risk at the one-in-one million (10^{-6}) risk level and for any adverse non-cancer effects resulting from chronic exposure. The human health risk assessment approaches used to develop the ISGWQCs generally follow USEPA risk assessment guidance and practices. The basis for the ISGWQC recommended herein was

reviewed by DSR human health toxicologists, Dr. Josephine Bonventre and Dr. Brian Pachkowski, and their comments have been incorporated.

NJDEP incorporated the ISGWQC into the GWQS to allow NJDEP and other parties to respond to environmental threats in a timely manner. The GWQS regulations state that, after establishing an ISGWQC, NJDEP shall replace it with a specific criterion as soon as reasonably possible by rule.

Background information

HFPO-DA (CAS Number 13252-13-6) and HFPO-DA ammonium salt (CAS Number 62037-80-3) are acid and salt forms of the same substance and are collectively referred to as GenX. They are six carbon perfluoroether carboxylates that are members of the per- and polyfluoroalkyl substances (PFAS) family. Both the acid and the salt forms dissociate to the anionic form in the environment, including in groundwater, and in the body.

HPFO-DA and HFPO-DA ammonium salt are the major components of the GenX processing aid technology developed by DuPont de Nemours, Inc. (DuPont) to replace the use of perfluorooctanoic acid (PFOA) as a processing aid in fluoropolymer production (USEPA, 2021). In 2015, the Chemours Company (Chemours) was created and separated from DuPont, and the GenX technology, including HFPO-DA and its ammonium salt, are now Chemours products (USEPA, 2021).

GenX has been released to the environment from industrial facilities where it is made or used (USEPA, 2021), including Chemours Chambers Works in Deepwater, New Jersey (information provided by NJDEP Site Remediation & Waste Management Program). GenX has been detected in environmental media near these facilities (USEPA, 2021), including in soil and ground water on and near the Chambers Works Site (NJDEP Site Remediation & Waste Management Program).

Development of an ISGWQC

Development of an ISGWQC involves the two primary components that are discussed below. They are: 1) toxicity evaluation, which includes determination of the weight of evidence for carcinogenicity and development of the toxicity factor (Reference Dose [RfD] or cancer slope factor), and 2) the selection of exposure assumptions, which include drinking water ingestion rate and Relative Source Contribution.

Toxicity evaluation

As discussed in a January 25, 2022 memorandum from DSR to the NJDEP Division of Air Quality (DAQ) (Attachment 1), DSR toxicologists extensively reviewed the scientific literature and risk assessment approaches relevant to toxicity evaluation of GenX in response to DAQ's November 2019 request for an inhalation Reference Concentration (RfC) for GenX[1]. When DSR was close to completing its draft document, the USEPA (2021) toxicity assessment of GenX was finalized. After a thorough review, DSR toxicologists agreed that the USEPA (2021) toxicity

[1] Although the November 2019 request from DAQ was for an inhalation RfC for GenX, DSR toxicologists reviewed the basis of the oral RfD, which (as detailed in Attachment 1) was used for route-to-route extrapolation to derive a screening RfC.

evaluation was scientifically justified and recommended that NJDEP accept the USEPA (2021) conclusions. Specific details are discussed below:

Weight of evidence for carcinogenicity

NJDEP agrees with the USEPA (2021) conclusion that GenX should be described as having *Suggestive Evidence of Carcinogenic Potential* under the USEPA (2005) *Guidelines for Carcinogen Risk Assessment.* The carcinogenicity of GenX has been evaluated only in a single chronic rat study (DuPont, 2013; Caverly Rae et al., 2015) in which there was a statistically significant increase of both hepatocellular adenomas and hepatocellular carcinomas in high dose (500 mg/kg/day) females, as well as a statistically significant increase in the combined incidence of pancreatic acinar cells adenomas and carcinomas in high dose (50 mg/kg/day) males. Also in high dose males, the incidence of testicular interstitial (Leydig) cell adenomas was above the historical control range, and the incidence of testicular interstitial cell hyperplasia, potentially a precursor to interstitial cell adenomas, was increased. Although the increases in testicular tumors and hyperplasia were not statistically significant, Caverly Rae et al. (2015) concluded that "a relationship to treatment for these findings…cannot be ruled out"

The USEPA (2005) guidelines also specify that a non-threshold mode of action is assumed unless a threshold mode of action has been conclusively demonstrated. Since the mode of action of the tumors caused by GenX is unknown (USEPA, 2021), the non-threshold assumption is applicable to GenX.

DSR agrees with the USEPA (2021) conclusion that the tumor data for GenX do not support development of a cancer slope factor that could be used by NJDEP as the basis for criterion development, since tumor incidence was increased only at the highest dose in both males and females. As such, the ISGWQC is based on an RfD (i.e., non-cancer effects). In addition, the GenX dose resulting in one-in-one million (1×10^{-6}) risk was estimated for comparison purposes based on linear extrapolation from the high dose tumor data, as discussed below.

Selection of RfD

As discussed in the January 25, 2022 memorandum from DSR to DAQ (Attachment 1), DSR reviewed the basis of the USEPA (2021) RfD of 3 ng/kg/day and concluded that it is scientifically justified and health protective. DSR therefore recommended that NJDEP use the USEPA (2021) RfD of 3 ng/kg/day for GenX.

As explained in USEPA (2021), the RfD is based on histopathological changes in the livers of parental female mice exposed before mating, during gestation, and during lactation, for a total of 53-64 days, in a reproductive/developmental study (DuPont18405-1037, 2010). USEPA (2021) performed Benchmark Dose (BMD) modeling of the dose-response data for hepatic histopathological changes and identified the point of departure (POD) as a $BMDL_{10}$ (lower confidence level of the BMD for a 10% change) of 0.09 mg/kg/day.

The $BMDL_{10}$ of 0.09 mg/kg/day was converted to a Human Equivalent Dose POD (POD_{HED}) of 0.01 mg/kg/day (10,000 ng/kg/day) with a dosimetric adjustment factor (DAF) of 0.14 (based on animal-to- human body weight scaling) as follows:

Dose to animals (ng/kg/day) x DAF (unitless) = HED (ng/kg/day)

0.09 mg/kg/day x 0.14 = 0.01 mg/kg/day

A total uncertainty factor (UF) of 3000 (10 for intraspecies variability, 3 for interspecies extrapolation, 10 for subchronic-to-chronic exposure duration, and 10 for database uncertainties [for potentially more sensitive effects]) was applied to the POD_{HED} of 0.01 mg/kg/day to derive the chronic RfD of 3×10^{-6} mg/kg/day (3 ng/kg/day), as follows:

POD (mg/kg/day) / UF = RfD (mg/kg/day)

0.01 mg/kg/day / 3000 = 3×10^{-6} mg/kg/day (3 ng/kg/day)

It is noted that the critical study for the RfD was of subchronic duration (total exposure of 53-64 days) and that USEPA (2021) also derived a subchronic RfD of 30 ng/kg/day. The subchronic RfD of 30 ng/kg/day was derived by applying a total UF of 300 (10 for intraspecies variability, 3 for interspecies extrapolation, and 10 for database uncertainties; no duration adjustment needed) to the same POD_{HED} of 0.01 mg/kg/day that was used for the chronic RfD of 3 ng/kg/day.

Consideration of application of additional uncertainty factor for potential carcinogenicity

It is the general policy of NJDEP, the New Jersey Drinking Water Quality Institute (DWQI), and USEPA Office of Water to apply an additional uncertainty factor of 10 to an RfD for a non-cancer endpoint to account for potential cancer risk of "suggestive carcinogens" (formerly called Group C carcinogens under USEPA [1986] guidance), such as GenX, when a cancer slope factor is not available or is considered uninformative (DWQI, 2009).

DSR agrees with the USEPA (2021) conclusion that the tumor data for GenX do not support a cancer slope factor, since the incidence of tumors was increased only at the highest dose in the chronic rat study (DuPont, 2013; Caverly Rae et al., 2015).

For comparison purposes only, DSR estimated the GenX dose corresponding the one-in-one million cancer risk (1×10^{-6}) specified in the Ground Water Quality Standards Regulations from the pancreatic tumor data from the chronic rat study (DuPont, 2013; Caverly Rae et al., 2015) by linear extrapolation from the high dose tumor incidence. Specifically, the combined incidence of pancreatic acinar adenomas and carcinomas in males of 7.1% (7.1×10^{-2}) at a dose of 50 mg/kg/day was used to develop this estimate.

Cancer risk estimates were not developed based on the increased incidence of hepatic adenomas (5.7%) and carcinomas (15.7%) in females at 500 mg/kg/day because the high dose of 50 mg/kg/day in males is 10-fold lower than the high dose of 500 mg/kg/day in females. Therefore, it is apparent that the estimated dose for a 1×10^{-6} cancer risk will be much lower for the pancreatic tumors in males than for the liver tumors in females.

The dose of 700 ng/kg/day that was estimated to result in a 1×10^{-6} cancer risk, based on an assumption of a linear relationship between dose and tumor incidence (i.e., approximation of the

cancer slope factor by dividing the dose [50 mg/kg/day] by the incidence [0.071]) was calculated from the pancreatic tumor data in males as follows:

$(1 \times 10^{-6} / 7.1 \times 10^{-2}) \times 50$ mg/kg/day = 0.0007 mg/kg/day (700 ng/kg/day)

The dose of 700 ng/kg/day was converted to the HED using the DAF of 0.32 for adult male rats in the chronic study[2] as follows:

Dose to animals (ng/kg/day) x DAF (unitless) = HED (ng/kg/day)

700 ng/kg/day x 0.32 = 224 ng/kg/day

As discussed above, an uncertainty factor of 10 for potentially more sensitive carcinogenic effects is considered in development of RfDs for chemicals, such as GenX, that are classified as having *Suggestive Evidence of Carcinogenic Potential* (USEPA, 2005).

Since the estimated human risk-dose of 224 ng/kg/day corresponding to a 1×10^{-6} cancer risk is higher than the RfD of 3 ng/kg/day for on non-carcinogenic effects, this RfD is protective for potential carcinogenicity at the 1×10^{-6} risk level. Therefore, there is no need to adjust the RfD downward by applying an uncertainty factor for potential carcinogenicity, and this uncertainty factor was not applied to the RfD of 3 ng/kg/day.

Number of significant figures in RfD

Proposed amendments to the Ground Water Quality Standards, N.J.A.C. 7:9C are currently undergoing legal review, and the Division of Water Monitoring and Standards (DWMS) anticipates that the rule will be proposed in Fall 2022. The proposed rule will include amendments to the provisions for significant figures in criteria development, and the approach described in the proposed rule was used to determine the RfD to be used for development of the ISGWQC. The relevant section of the current draft of the rule proposal is copied below; DWMS does not expect revisions to this section in the final version of the rule proposal:

> The Department is proposing to include a policy regarding significant figures at N.J.A.C. 7:9B-1.5(c)11. This policy will be applicable to water quality criteria presented at N.J.A.C. 7:9B-1.14(f). The proposed policy indicates that criteria are expressed in two significant figures when all factors (e.g., toxicity factor, exposure assumptions) of the criteria equation are available in two or more significant figures; otherwise, the final criteria will be rounded to one significant figure. This approach is consistent with that used by the United States Environmental Protection Agency (USEPA) for their 2015 update to the Human Health Criteria. Specifically, factors including body weight, drinking water intake and relative source contribution (for non-carcinogens) are generally reported as 2 significant figures. However, for some substances, toxicity factors (i.e., cancer slope factor for carcinogens, Reference Dose for non-carcinogens) are available as 1 significant figure. In such cases, the Department ascertained whether a 2 significant figure toxicity factor could be derived for that substance (e.g., by determining whether the derivation of a 1 significant figure Reference Dose was based on a point of departure

[2] The DAF of 0.32 was calculated using the mean body weight (BW) for male rats of 0.843 kg from the chronic (2-year) study (DuPont, 2013; Caverly Rae, 2015) and the default NJDEP human body weight of 80.0 kg (see *Drinking Water Ingestion* section, below) as follows: $DAF = (BWanimal^{1/4} / BWhuman^{1/4})$.

reported as 2 significant figures and then applying the original uncertainty factors to derive a 2 significant figure Reference Dose). Uncertainty factors, relative source contribution factors, cancer risk levels, and conversion factors do not inform the final number of significant figures in the criteria, which is consistent with the USEPA approach in 2015.

The RfD of 3 ng/kg/day for GenX provided by USEPA (2021) has one significant figure. Following the process described in the section from the rule proposal above, DSR determined that a two significant figure RfD could not be determined for GenX because the POD of 0.09 mg/kg/day used to derive the RfD has only one significant figure (USEPA, 2021; Table 13 - $BMDL_{10}$ for parental female mice from DuPont18405-1037, 2010). Therefore, the USEPA (2021) RfD of 3 ng/kg/day was not adjusted by DSR.

Exposure Assumptions

Drinking water ingestion

The default drinking water ingestion factors used for New Jersey water criteria based on chronic exposure (ISGWQC, GWQC, Health-based Maximum Contaminant Levels [MCLs]) are an adult body weight of 80.0 kg and an adult drinking water intake of 2.4 L/day, which are equivalent to a drinking water intake of 0.030 L/kg/day. As explained in DWQI (2021), these are the default factors currently recommended by USEPA (2015). Use of these default adult exposure factors is appropriate for derivation of the ISGWQC for GenX because the RfD is based on a systemic effect (liver toxicity) in adult animals and chronic (lifetime) exposure.

Relative Source Contribution factor

A Relative Source Contribution (RSC) factor accounts for non-drinking water exposure sources (e.g., food, soil, air, consumer products) and is used by the NJDEP, the New Jersey DWQI, USEPA, and other states in the development of health-based drinking water, ground water and surface water concentrations based on non-carcinogenic effects (i.e., when RfDs are used as the toxicity factor). The RSC is intended to prevent total exposure from all sources from exceeding the RfD (Post, 2021; USEPA, 2000).

When sufficient chemical-specific information on non-drinking water exposures is not available, a default RSC of 0.2 (20%) is used (i.e., 20% of the RfD is allocated to drinking water and 80% is allocated to other sources). When sufficient chemical-specific exposure data are available, a less stringent chemical-specific RSC may be derived, with floor and ceiling RSC values of 20% and 80%, respectively (USEPA, 2000). DSR agrees with USEPA (2022) that there are insufficient data to develop a chemical-specific RSC for GenX. The default value of 0.2 was therefore used in the ISGWQC.

Derivation of ISGWQC

The ISGWQC for GenX is derived as follows:

$$\frac{3\ \text{ng/kg/day} \times 80.0\ \text{kg} \times 0.2}{2.4\ \text{L/day}} = 20\ \text{ng/L}\ (0.02\ \mu\text{g/L})$$

Where:

3 ng/kg/day = RfD
80.0 kg = assumed adult body weight
0.2 = RSC from drinking water
2.4 L/day = assumed adult drinking water intake

ISGWQC Recommendation

The recommended ISGWQC for GenX is 20 ng/L (0.02 µg/L). This ISGWQC is intended to be protective for chronic (lifetime) exposure to GenX (HFPO-DA and its ammonium salt) in drinking water.

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ATTACHMENT 1:

NJDEP Division of Science and Research Memorandum:
Recommendation for a Reference Concentration for GenX
January 25, 2022.

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THROUGH: Gary A. Buchanan, Ph.D., Director GB
Division of Science and Research

FROM: Gloria Post, Ph.D., D.A.B.T., Research Scientist GP
Mingzhu Fang, Ph.D., D.A.B.T., Research Scientist MF

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[3] (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".

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.

[3] 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 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 $\mu g/m^3$ (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):

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

Where:

- Average body weight is 70 kg[4]
- 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[5] is not highly bioaccumulative in 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).

[4] 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.

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

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)[6] 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)

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

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