North Carolina Department of Environmental Quality
and
North Carolina Department of Health and Human Services

Secretaries' Science Advisory Board
Review of the North Carolina Drinking Water Provisional Health Goal for GenX

August 29, 2018

DRAFT

Section 1 – The Secretaries' Science Advisory Board

The Secretaries for the North Carolina Departments of Environmental Quality (DEQ) and of Health and Human Services (DHHS) established their Science Advisory Board (SAB) in July 2017. It is founded on recognition that clean air, water and land are critical to quality of life, to protect health and to promote a vibrant economy for all North Carolinians. The Board comprises experts in toxicology, epidemiology, environmental science, environmental engineering, medicine and other disciplines and their expertise will help guide the two agencies in carrying out their responsibilities to protect the safety and health of the citizens. The Board provides advice on the adverse effects of environmental contaminants, monitoring and measuring exposure to environmental contaminants, and on their control.

The Board performs or recommends reviews and evaluations of contaminants released to the environment; acts as consultants on DEQ's determinations to regulate releases of contaminants; assists both agencies in identifying contaminants of emerging concern and helps determine whether the contaminants should be studied further; assists the Secretaries in providing expertise to evaluate the human and environmental impacts of exposure to hazardous contaminants; and provides input to DHHS as the agency establishes health goals for emerging contaminants.

Specifically, the charter of the NC DEQ and NC DHHS Secretaries' Science Advisory Board (SAB) describes the duties of the board as:

> *(a) To perform or recommend reviews and/or evaluations of matters concerning the release of contaminants to the environment that are placed on the Board agenda by DEQ or DHHS.*
>
> *(b) To advise the EMC* [Environmental Management Commission] *on information concerning the regulation and evaluation of releases of contaminants that come to the attention of the Board.*
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> *(c) To review the effects of chemicals that are proposed to be regulated by DEQ as contaminants and to recommend the necessity and/or urgency for controlling the releases of such chemicals that are found to cause deleterious environmental and human health effects with priority given to the study of contaminants for which control has been deferred pending further study.*
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> *(d) To act as consultants regarding the DEQ's determinations to regulate releases of contaminants and in determining factors for establishing acceptable levels for contaminants and for remediation levels for contaminants in other media.*

(e) To recommend concentrations of contaminants in a "range of risks" to DEQ and EMC for regulation that will minimize adverse health responses in the exposed citizenry and to advise the EMC of the scientific basis for these recommendations.

Section 2 – The Board's Charge for GenX

The Departments asked the Board to review information on GenX[1], including a review of the DHHS provisional drinking water health goal and of available scientific information about health and environmental concerns and their control, and to provide recommendations to DEQ on the starting point for developing regulatory standards.

During the January 29, 2018 SAB meeting DEQ and DHHS were asked for clarification on the type of deliverables the Board was requested to provide to the agencies. DEQ requested the Board provide recommendations on a reference dose which would be used to establish water quality standards for GenX. DHHS requested the Board review and provide recommendations on the derivation and calculation of the health goal for GenX, including the point of departure (POD), the calculation parameters, the uncertainty factors, and the options to use benchmark dose (BMD) modeling in lieu of a NOAEL (No Observed Adverse Effect Level) approach, and to provide feedback on any future modifications to these values and calculations that may be considered as additional GenX-related health studies are published.

Section 3 – GenX in North Carolina

GenX, $C_6HF_{11}O_3$, is a clear, colorless liquid with high water solubility (100,000 – 300,000 mg/L), apparent low organic carbon partitioning capacity (estimated K_{ow} 1.3 – 2.0)[2], that under normal environmental conditions exists as an anionic acid (2.8 *p*Ka acid dissociation constant)[3] (Hoke et al., 2016). Biodegradability test data (Mitsubishi Chemical Medience Corporation, 2009; Kaplan, 2010) indicate GenX is not easily biodegradable and therefore expected to be relatively persistent in the environment. With its high water solubility at environmentally-relevant pH, GenX will move readily in water (i.e., surface water, groundwater, rainwater). The fate of GenX in terms of ultimate sites of deposition in the environment is uncertain. Potential transport

[1] GenX is correctly the name of the manufacturing process, but is commonly used, and is used here, to refer to a key chemical in the process: 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-propanoic acid (CASN 13252-13-6)

[2] K_{ow} is the octanol-water partitioning coefficient, the ratio of the equilibrium concentration of a dissolved chemical in a two-phase system of n-octanol and water. n-Octanol serves as a surrogate to biota lipids and K_{ow} values are used as an indicator of a chemicals tendency to bioaccumulate, or to be taken-up by organisms from the environment.

[3] The pKa predicts that GenX will be in acid form (as a negative ion, or an anion) at pH levels at or above a pH of 2.8.

mechanisms of GenX and other PFAS released into the environment from industrial sources are illustrated in Figure 1.

GenX is an artificial chemical and does not occur naturally. It is produced commercially for use in manufacturing non-stick coatings and may be an unintended by-product of other processes that produce related compounds. The Chemours (formerly DuPont) facility in Fayetteville NC has manufactured GenX since 2010 (Sun et al., 2016) as a replacement for PFOA and PFOS[4], two chemicals which have been associated with health effects in animals including developmental, reproductive, immunological, and cancer adverse health outcomes (EPA 2016a, EPA 2016b) and are part of the same broad family of chemicals known as per- and polyfluoroalkyl substances (PFAS). GenX has also been produced as a by-product of the facility's vinyl ether manufacturing process for more than three decades. GenX, and previously PFOA, have been released from the DuPont/Chemours plant in Fayetteville to air and to surface water. Public concern about GenX and related compounds escalated in June 2017 following reports that GenX had been detected in the Cape Fear River (Sun et al., 2016), which is the primary source of drinking water to the city of Wilmington and some other communities in North Carolina. GenX and other PFAS were also found in finished municipal drinking waters sourced from the Cape Fear River downstream of the Chemours/DuPont plant. GenX has also been found in the environment close to the Chemours/DuPont plant in Fayetteville. There are presently no federal nor state standards for GenX for water, soil, air or food.

Section 4 – The Board's GenX Review Process

The Board addressed GenX at its meetings on October 23, 2017; December 4, 2017; January 29, 2018; March 19, 2018; April 30, 2018; and June 18, 2018. It invited and received comments from concerned entities during public comment portions of those meetings and between meetings, and thanks the persons and entities that contributed comments. Board members reviewed extensive documentation provided by the Departments and accompanying written submissions and sought insights from related activities in the Netherlands, where GenX has been found in the environment around a Chemours facility (Netherlands 2016). The Board recommended additional analyses by the Departments and received the results. The Board recognizes the participation of staff of the Department of Agriculture and Consumer Services in its discussions. A summary of the meetings, documents and work are provided below and related documents are available on the SAB website at https://deq.nc.gov/news/hot-topics/genx-investigation/secretaries-science-advisory-board.

October 23, 2017 – During this meeting, the Department of Environmental Quality and the Department of Health and Human Services identified priority areas about which they requested

[4] The chemical name for PFOA is perfluorooctanoic acid (CASN 335-67-1). The chemical name for PFOS is perfluorooctane-sulfonate (CASN 1763-23-1).

input from the Board. Issues relevant to PFAS and GenX were identified as among those priorities.

The family of per- and poly-fluoroalkyl substances (PFAS) contains many compounds, including more than 3000 manufactured chemical structures (Wang Z, et al., 2017). Some older or "legacy" PFAS compounds (those PFAS produced historically and commonly represented by larger PFAS compounds), e.g. PFOA and PFOS, have substantial health data and regulatory standards. However, the PFAS family also contains many emerging compounds about which there are few or no health or ecological effects data, and for which there are no regulatory standards. Many of these emerging PFAS compounds have been found as environmental contaminants in North Carolina. GenX is one of the emerging PFAS compounds for which there are no current environmental regulatory standards for water, soil, air or food. However, there are health data regarding GenX that were judged sufficient by DHHS to calculate a "reference dose" (RfD)[5] and provisional health goal (PHG) for drinking water. The state agencies requested the Board examine and provide input on the current reference dose and provisional drinking water health goal for GenX. The Division of Air Quality (DAQ) also identified researching the inhalation risks and potential acceptable ambient levels for GenX and other emerging compounds as their current priorities.

DHHS stated that health data for other emerging PFAS compounds identified in NC were insufficient to calculate a health goal. The Board was asked to consider how or if the presence of the additional compounds may influence the calculation of a GenX provisional health goal for drinking water. The Board was requested to consider a standardized approach for addressing other emerging PFAS with limited health data and establishing provisional health goals for drinking water among its recommendations.

December 4, 2017 – An interim DEQ report and discussion on the GenX investigation and actions taken by DEQ was given. It included the regulatory programs and framework, history of GenX and PFAS production at Chemours-Fayetteville Works site, surface water monitoring results, additional emerging compounds, enforcement actions, groundwater monitoring results, information on air emissions from the Chemours-Fayetteville Works facility, and DEQ's planned next steps under emerging compounds

DHHS provided documentation describing their role in drinking water recommendations. DHHS gives guidance on public health by conducting health risk assessments, communicating those

[5] Reference dose (RfD) is a risk assessment term employed by the U.S. EPA to articulate non-cancer, non-mutagenic health-risk effects associated with systemic toxicity study data. The EPA states "In the case of systemic toxicity, however, organic homeostatic, compensating, and adaptive mechanisms exist that must be overcome before a toxic endpoint is manifested." The EPA defines a reference dose as: "The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." Source: https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments

risks and giving guidance on the levels of exposure to certain contaminants. When issuing guidance on drinking water, DHHS follows established methodology and rules and uses established reference standards when available. In the event, such as with GenX, when no existing health goal or standard is available, DHHS calculates a provisional health goal for drinking water based on health data available at that time and following methodology endorsed by the U.S. Environmental Protection Agency (EPA). DHHS monitors and may update a provisional health goal for drinking water based on new information provided by laboratory animal studies, epidemiologic studies, or other sources. The DHHS health goal is not legally enforceable.

DHHS also provided information on available GenX health studies relevant to calculating a provisional health goal for drinking water and provided documentation on how the provisional health goal for drinking water for GenX was calculated including the NOAEL used as the point of departure, uncertainty factors, and a relative source contribution.

The Board noted that the methodology used by DHHS to develop the GenX drinking water provisional health goal followed commonly accepted human health risk assessment practices.

January 29, 2018 - Four representatives from the Netherlands, where there is also a Chemours facility using GenX in their production operations, joined the SAB meeting via video conference and shared their process for, and considerations in, calculating their GenX water quality standard of 150 ng/L.

DHHS shared further information about the studies used as the basis of their provisional health goal for GenX and discussed the process and calculations relevant to it. Information shared included the considerations of the POD, uncertainty factors (UF) and modifying factors (MF), relative source contribution (RSC) and physicochemical properties. Information was also shared on other states' calculations for other PFAS health goals and the Netherland's calculation for a GenX health goal. Further, DHHS reported that there were sufficient dose-response data to support benchmark dose modeling, but insufficient data to determine a cancer slope factor. The SAB recommended pursuing bench mark dose modeling to identify a point of departure for the health goal calculation more precise than the one generated with the NOAEL-based approach.

During the meeting the U.S. EPA's Office of Water provided an update on their development of a GenX toxicity value. The EPA also noted they would not be developing a cancer slope factor at this time because of the single available carcinogenicity study, which used the rat model. Prior studies suggest rats are less sensitive than mice to adverse effects associated with some PFAS.

March 19, 2018 - The DEQ shared an update of the groundwater investigations around the Chemours site. DEQ also provided information on GenX emissions, stack testing, and rain water testing. DEQ staff had been working on the groundwater assessment related to the Chemours facility in Bladen County. A major component of that work included groundwater sampling of private drinking water wells by both Chemours and DEQ. DEQ has evaluated the current

groundwater data and has looked for sources of the contamination while also evaluating other media that may need further investigation.

DEQ had worked collaboratively with the Departments of Agriculture & Consumer Services (DA&CS) and DHHS to determine next steps regarding other media that may need to be assessed. One component of the collaborative effort included reviewing the literature associated with the presence of perfluorinated compounds in other media.

DEQ presented to the SAB a vegetable garden crops study conducted in the Netherlands (Netherlands 2018). The study was performed at the request of the Netherlands National Institute for Public Health and the Environment per request from the city of Dordrecht. It looked at the presence of GenX in garden crops and addressed: (1) What are the concentrations of GenX and PFOA in selected crops from vegetable gardens in the vicinity of the DuPont Chemours facility in the Netherlands; and (2) Is the allowable daily intake, referred to as the "Tolerable Daily Intake" (TDI), via food from GenX and PFOA exceeded by consumption of vegetable crops in a typical consumption pattern. DEQ staff awaited an English translation of this study, but preliminary information provided indicates that GenX was detectable in home-grown produce grown within 1-kilometer of the Chemours site in the Netherlands, however levels did not exceed health-based limits when looking at average daily intake for individuals. Based on this investigation, health officials in the Netherlands recommended that vegetables within 1-kilometer radius of the plant not be consumed "too often" but recommended no limitations for produce grown beyond a 1-kilometer radius. The results of the Netherlands' produce study do not provide information directly relevant to the North Carolina concern other than as an indication that common home-grown produce may provide an exposure pathway for PFAS released into the environment.

Another study was presented to the SAB by DEQ that had been conducted by the Minnesota Department of Health (Scher et al., 2018). The study began in 2010 in the Minneapolis-St. Paul area where high levels of PFAS were found in drinking water. Sources of drinking water were ultimately utilized for irrigation for residential gardens. The Minnesota study focused on PFOA, PFOS, PFBA, PFBS, PFPeA, PFHxA, and PFHxS[6]. It found uptake and bioaccumulation of PFAS into the terrestrial food chain, represented by home-grown produce, increased as irrigation with PFAS-contaminated water increased. The results confirmed those of other studies indicating that fate and transport of PFAS is predominantly influenced by chain-length and functional group, resulting in the PFAS profile modification as a mixture moves from the source though various environmental compartments, and that short-chain PFAS are more mobile and water soluble than long-chain PFAS. The Minnesota Department of Health (MDH) reported the preferential uptake and bioaccumulation of short-chain PFAS by plants, and that this uptake was PFAS-specific, plant species-specific and plant tissue-specific, with preferential translocation from roots to more distant plant structures generally increasing with decreasing

[6] PFBA CASN 375-22-4, PFBS CASN 375-73-5, PFPeA CASN 2706-90-3, PFHxA CASN 307-24-4, and PFHxS CASN 355-46-4

chain-length. MDH reported that the home-grown produce in their study area may constitute a "measurable" contribution to overall PFAS exposure for high-level produce consumers in areas where irrigation is with PFAS-contaminated groundwater. These risk evaluations are specific to the exposure conditions and populations included in the MDH study and do not provide information directly relevant to risks specific to North Carolina populations.

DHHS provided information on the Peroxisome Proliferator-Activated Receptor alpha (PPARα) mode of action (MOA) and PPARα-mediated outcomes associated with PFAS in animal studies and the relevance of this mode of action to human health. DHHS described findings that some cancer outcomes in animal studies of PFAS may be mediated by activation of PPARα and may not be relevant to human outcomes. DHHS also noted that PPARα activation has not been confirmed for the hepatocellular necrosis endpoint selected by DHHS as the critical effect for the RfD and calculation of the drinking water provisional health goal. DHHS shared information from the EPA's PFOA and PFOS Lifetime Health Advisories (EPA 2016a, EPA 2016b) and the U.S. Centers for Disease Control and Prevention's (CDC) Agency for Toxic Substances and Disease Registry (ATSDR) draft Toxicology Profile for PFAS (ATSDR 2012) which finds evidence of interspecies difference in levels of PPARα expression and responsiveness, and PPARα-independent mechanisms involved in PFOA and PFOS toxicity in non-cancer endpoints such as liver toxicity, including hepatocellular necrosis.

DHHS reported that the U.S. EPA Office of Water and Office of Pollution Prevention and Toxics is working on a GenX reference dose and that DHHS is in communication with EPA as they continue their work.

DHHS presented their progress on the benchmark dose modeling. DHHS staff received training on use of benchmark dose modeling software from U.S. EPA staff. DHHS presented the first stage of the work, which included data tables with each statistically significant endpoint for GenX from the seven available GenX oral toxicity studies (DHHS 2018). The SAB provided guidance on appropriate and significant endpoints relevant to human health and response levels for each endpoint. Recommendations informed what DHHS would use in the benchmark dose modeling and input into the benchmark dose modeling software to provide options for a point of departure.

April 30, 2018 - DEQ presented an update on the continuing investigation of environmental contamination, bioaccumulation, and potential sources of exposure. Well water, groundwater, and soil testing continue. Rain water testing had expanded to a 7-mile radius from the Chemours plant. The full extent of contamination has still not been determined. As part of a pilot study, granulated activated carbon (GAC) filters were to be installed to evaluate the efficacy of this treatment method for PFAS removal. Fish tissue, water, and sediment samples had been collected from a private lake near the facility and were being tested as part of the continuing investigation into environmental contamination and bioaccumulation of GenX and other PFAS.

DHHS reported that it had consulted with U.S. EPA and a member of the SAB and is continuing to work on benchmark dose modeling.

June 18, 2018 - DHHS presented a summary report on the benchmark dose modeling of the available GenX animal studies (DHHS 2018). DHHS requested that the SAB consider the results as they make recommendations about GenX health and regulatory levels in North Carolina. The DHHS noted that the U.S. EPA continued to work toward releasing a GenX RfD this summer.

DEQ, DHHS and DA&CS have continued to collaborate in gathering information related to the presence of perfluorinated compounds in other media. DEQ presented sediment and fish tissue data to the SAB from a preliminary PFAS study of a privately-owned artificial lake near the Chemours-Fayetteville facility (DEQ 2018)**.** Surface water, sediment and three species of fish had been collected in March and April 2018. Fish filet tissue samples were prepared. All samples were analyzed for 33 PFAS. Twenty PFAS were detected in the study, including GenX in the surface water, sediment and one species of fish, Redear Sunfish. DEQ classifies adult Redear Sunfish classified as an insectivorous species (DEQ 2014) and they are noted as opportunistic feeders, foraging mostly on aquatic clams and snails in native habitats (WRC 2018). The same 16 PFAS, the highest number of PFAS detected in the sampled media, were detected in the lake surface water and water collected from a surface spring that flows into the lake. The 16 PFAS detected in the water samples included PFOA and PFOS, as well as short-chain and long-chain PFAS. GenX was the only PFAS detected in the lake sediment. PFOS was also detected in the Redear Sunfish 7-fish composite and two composite samples of Largemouth Bass, each made-up of fish of a different size range (a 5-fish composite of smaller fish and a 2-fish composite of larger, presumably older, fish). Four additional long-chain "legacy" PFAS (11, 12, 13 and 14-chain PFAS) were detected in the two Largemouth Bass samples and a sample from a single Blue Catfish.

Section 5 – Adoption of a Non-Cancer Approach to GenX Health Effects

As stated above, DHHS noted there were insufficient data from the available toxicology studies to quantitatively assess a cancer endpoint related to GenX exposures. There exists a single 2-year rat carcinogenicity study. Rats have been observed to be less sensitive to some PFAS-associated adverse effects than mice. DHHS used non-cancer endpoints identified in the available animal studies, which are assumed to have a threshold below which there are no observable adverse effects due to homeostatic and adaptive mechanisms. The U.S. EPA Integrated Risk Information System (IRIS)[7] program provides a discussion of the approach for assessing risks for health effects other than cancer and gene mutations from chronic chemical

[7] IRIS is the U.S. EPA's Integrated Risk Information System. The IRIS Program supports EPA's mission is to protect human health and the environment by identifying and characterizing the health hazards of chemicals found in the environment. Available at: https://www.epa.gov/iris

exposures[8]. EPA states, "*Chemicals that give rise to toxic endpoints other than cancer and gene mutations are often referred to as "systemic toxicants" because of their effects on the function of various organ systems. In addition, chemicals that cause cancer and gene mutations also commonly evoke other toxic effects (i.e., systemic toxicity). Based on our understanding of homeostatic and adaptive mechanisms, systemic toxicity is treated as if there is an identifiable exposure threshold (both for the individual and for populations) below which there are no observable adverse effects. This characteristic distinguishes systemic endpoints from carcinogenic and mutagenic endpoints, which are often treated as nonthreshold processes.*"

The Board identifies that the appropriate approach to determining a safe concentration for a chemical in drinking-water depends on how it causes harm. The Board determined that data were insufficient to establish whether GenX is a human carcinogen. The Board judged that based on the available evidence the most sensitive endpoint for GenX observed in multiple studies is a non-cancer endpoint (hepatocellular single cell necrosis), i.e., that there is some level of exposure below which does not represent a non-cancer risk to human health, and recommends that the U.S. EPA approach for assessing threshold non-cancer risks be applied.

Section 6 – Derivation of the GenX Reference Dose

It is necessary to identify the daily oral exposure amount below which a chemical would not cause adverse health effects if consumed for a lifetime. This is called the reference dose (RfD). The EPA defines a reference dose as "*An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's non-cancer health assessments*."[9]

To calculate a reference dose, DHHS reviewed seven repeat oral dose studies in rodents of 28 days or longer that were provided by Chemours/DuPont during the U.S. EPA Toxic Substances Control Act (TSCA)[10] review process (DHHS 2018). DHHS focused on repeat oral dose studies because this is most applicable to long-term human exposure from drinking water. DHHS consulted with toxicologists and risk assessors at U.S. EPA, the National Institute of Environmental Health Sciences (NIEHS), and ATSDR to identify applicable toxicology information and risk assessment procedures.

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[8] Accessed at https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments

[9] Source: U.S. EPA IRIS Glossary, accessed at: https://iaspub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&vocabName=IRIS%20Glossary#formTop

[10] Under the Toxic Substances Control Act (TSCA) and the Pollution Prevention Act, EPA evaluates potential risks from new and existing chemicals and finds ways to prevent or reduce pollution before it gets into the environment. U.S. EPA TSCA program web-page available at: https://www.epa.gov/chemicals-under-tsca

The first step in calculating a RfD is to identify a point of departure (POD). DHHS released an initial assessment of GenX in drinking water that used a no observed adverse effect level (NOAEL) of 1.0 mg/kg-day from a 2-year chronic study in rats as the POD (DHHS 2017). After further review of the repeat oral dose studies and conversation with experts at U.S. EPA, an updated assessment was provided in July 2017 that identified the NOAEL of 0.1 mg/kg-day for liver toxicity endpoints from two sub-chronic studies in mice (28-day study and a reproductive screen) as a more appropriate POD for calculation of a provisional health goal (PHG) for GenX in drinking water (DHHS 2017). The sub-chronic studies were chosen as the critical studies because they demonstrated adverse effects at the lowest doses tested and the effects were seen across multiple studies at the same or similar doses. DHHS subsequently used the NOAEL of 0.1 mg/kg-day as the POD for calculations of the RfD.

DHHS used the default uncertainty factors (UFs) recommended by U.S. EPA to derive a RfD from the POD. An expanded discussion of default U.S. EPA uncertainty factors is provided in Appendix A. DHHS did not apply a modifying factor (MF) because NOAELs from multiple studies were identical, or within the same order of magnitude, with similar health endpoints (liver toxicity). Additionally, DHHS staff concluded that the uncertainty factors discussed below adequately addressed the uncertainties of the database. The default uncertainty factors used were the following:

- Sub-chronic to chronic uncertainty factor (UF_S): A factor of 10 to account for the uncertainty involved in extrapolating from less than chronic NOAELs to chronic NOAELs
- Interspecies uncertainty factor (UF_A): A factor of 10 to account for the uncertainty involved in extrapolating from animal data to humans
- Intraspecies uncertainty factor (UF_H): A factor of 10 to account for the variation in sensitivity among the members of the human population

The RfD was calculated to be 0.0001 mg/kg-day by dividing the point of departure by the uncertainty factors.

$$\text{RfD, mg/kg-day} = (\text{POD, mg/kg-d}) / (UF_S \times UF_A \times UF_H)$$

$$0.0001 \text{ mg/kg-day} = 0.1 \text{ mg/kg-d} / (10 \times 10 \times 10)$$

DHHS presented the process used to calculate the provisional health goal for GenX in drinking water to the SAB during the October 23, 2017 meeting. In response to a request from the Board, DHHS compiled data from the seven repeat oral dose studies to be used in benchmark dose (BMD) modeling to potentially refine the point of departure (DHHS 2018). The benchmark dose approach conveys more dose-response information than the NOAEL-approach and applies EPA's BMD software for the analysis and modeling of dose-response relationships to identify dose levels corresponding to specific response levels near the low-end of the observable range of the data (EPA 2012). The benchmark dose-response assessment involves defining the POD

and extrapolating from the POD to a response level of relevance for human exposures (the Benchmark Response, BMR). Benchmark dose lower bound (BMDL) values may be used rather than NOAELs or lowest observed adverse effect levels (LOAELs) as the point of departure for derivation of toxicity values such as a reference dose. Benchmark dose modeling work was completed by DHHS in May 2018 and presented to the SAB during the June 18, 2018 meeting.

The modeled BMDLs for selected endpoints were presented by DHHS, while they cautioned that some of these values may be inappropriate to consider as a POD since the endpoints had very large BMD-to-BMDL ratios, indicating poor model fit and a large confidence interval on the BMD and perhaps inadequate data for modeling these endpoints (EPA 2012). The Board recommended refining the modeled BMDL ranges to exclude those with BMD-to-BMDL ratios >20. The refined range of BMDLs modeled by DHHS is 0.0492 to 25.3 mg/kg-day for selected hematology endpoints, 0.151 to 5.55 mg/kg-day for selected hepatic endpoints, and 3.06 to 635 mg/kg-day for selected developmental endpoints. A full report of the benchmark dose modeling efforts, results and limitations can be found in a separate document provided to the SAB on May 26, 2018 (DHHS 2018).

Based on available evidence, and calculations undertaken by DHHS staff on the request of the Board, the Board recommends the provisional reference dose (RfD) of 0.0001 mg/kg-day. The Board considers this is a reasonable health-based target action level for the state. The benchmark dose modeling effort generated a range of POD that were consistent with the NOAEL approach. As additional studies on the health effects associated with GenX become available, and the U.S. EPA's development of a GenX toxicity value is completed, review and refinement of the RfD and the drinking water provisional health goal (PHG) should be undertaken by the agencies.

Section 7 – Calculation of the DHHS GenX Provisional Health Goal for Drinking Water

To be protective of sensitive life-stages DHHS used the 95th percentile water intake and average body weight for a bottle-fed infant for calculation of a provisional health goal for GenX in drinking water. Bottle-fed infants drink more water compared to their body weight than other age groups and are therefore considered a sensitive sub-group for drinking water exposures.

In calculating health goals for exposure from drinking water, it is necessary to consider other routes of potential exposure, including air and food for example. GenX has been measured in samples of food (specifically fish) and rainwater in North Carolina, however data on the extent of exposure from these other routes is limited. DHHS used a relative source contribution (RSC) of 20% to account for other possible routes of exposure, consistent with EPA guidance (EPA 2000) when data on the extent of exposure from other routes are few. Use of this relative source contribution allocates 80% of a person's GenX exposure to sources other than drinking water.

Applying these factors, the DHHS provisional health goal for GenX in drinking water was calculated as 140 ng/L (DHHS 2017). This level is not a boundary line between a "safe" and "dangerous" level of a chemical but represents the concentration of GenX in drinking water at which no adverse non-cancer health effects would be anticipated over an entire lifetime of exposure. The provisional health goal for GenX in drinking water is subject to change based on new information but was calculated with the best currently available information and using default factors when specific information is limited. For more details and information on the calculation of the provisional health goal, see https://ncdenr.s3.amazonaws.com/s3fs-public/GenX/NC%20DHHS%20Risk%20Assessment%20FAQ%20Final%20Clean%20071417%20PM.pdf.

140 ng/L PHG = (0.0001 mg/kg-day RfD x 7.8 kg BW_{infant})/1.1 L/day IR_{infant} x 1E06 ng/mg x 0.2 RSC

Where:

PHG = DHHS drinking water Provisional Health Goal, nanograms per liter, protective of bottle-fed infants
RfD = Reference dose in milligrams GenX per kilogram body weight per day
BW_{infant} = Body weight, 7.8 kilograms for a bottle-fed infant (birth to 12 months of age)
IR = Intake rate of drinking water for a bottle-fed infant, 1.1 liters per day
1E06 = 1,000,000 nanograms per milligram conversion factor
RSC = Relative Source Contribution, proportion of total GenX exposure from drinking water, 0.2
RSC = U.S. EPA drinking water default value

The DHHS GenX PHG of 140 ng/L relates to the 150 ng/L water quality standard for GenX developed by the Netherlands Institute for Public Health and the Environment and presented to the Board at the January 29, 2018 meeting. The Netherlands group noted they used a 0.1 mg/kg-day point of departure from a chronic study in rats as it was the longest exposure study available. The study reported effects to the liver, changes in albumin level and the albumin/globulin ratio at the lowest effect level (LOAEL). The Netherlands agency applied an additional safety factor to adjust for possible toxicokinetic differences between humans and the GenX study test species, as to reflect difference reported for PFOA. The toxicokinetics adjustment factor was calculated as the difference in the elimination half-life of PFOA in humans to monkeys. The Netherlands agency staff stated application of the toxicokinetics factor was supported by the chemical similarity of PFOA and GenX, the similarity in toxicological effects for the two chemicals and indications of half-life differences among humans and other species reported for other PFAS compounds. Other factors applied in their calculation included a factor of 10 for human population sensitivity variation (interspecies variability) and a 20% factor for the total allowed daily uptake for water (2 liters per day for a 70 kg adult).

The Board noted the exposure of an adult consuming drinking water contaminated with GenX at the provisional health goal concentration of 140 ng/L and assuming EPA-referenced default exposure parameters (70 kg body weight and 2 liters per day water intake) and 100% of the

GenX exposure from drinking water indicates an adult exposure dose equal to 1/25th of the reference dose (0.0001 mg/kg-day GenX RfD) calculated by DHHS. This calculation indicates an additional margin of safety for an adult consumer ingesting drinking water contaminated with GenX at the PHG level, as the PHG was calculated to be protective of a bottle-fed infant representing the population group with the highest water intake per body weight.

$$(140 \text{ ng/L GenX} \times 2 \text{ L/day } IR_{adult})/70 \text{ kg } BW_{adult} \times 1E06 \text{ ng/mg} = 4E\text{-}06 \text{ mg/kg-day adult dose}$$

$$(1E\text{-}04 \text{ mg/kg-day RfD})/(4E\text{-}06 \text{ mg/kg-day adult dose}) = 25$$

Where:

IR_{adult} = Intake rate of drinking water for an adult, 2 liters per day
BW_{adult} = Body weight, 70 kilograms for an adult

The Board judges that the U.S. EPA default assumption that 20% of exposure be attributed to drinking-water is appropriate and common U.S. EPA default values for consumption and body weight were also used for the calculation of the GenX point of departure, reference dose and the drinking water provisional health goal. The Board judges that protection of the most susceptible segment of the population, that is the group with the greatest water intake to body weight, bottle-fed infants, is appropriate.

Section 8 – Ecological, Produce and Air Concerns

Ecological implications of GenX exposure are poorly understood in the natural environment because there is very little environmental monitoring data on invertebrate, fish and wildlife receptors. Laboratory studies on GenX accumulation in common carp (28-day bioconcentration factor[11], BCF <30 L/kg-tissue) and toxicity to green algae (72-hour no observed effect concentration (NOEC) >107 mg/L), daphnids (21-day NOEC for reproduction 4.17 mg/L), and fishes including Japanese medaka (96-hour EC50 >100 mg/L)[12], rare gudgeon (96-hour EC50 >150 mg/L) and rainbow trout (90-day reproduction NOEC of 8.9 mg/L) (Hoke et al., 2016) indicate adverse effects at exposures much higher than reported environmental concentrations. There was no effect on bobwhite quail at dietary concentrations up to 100 mg/kg (Newsted et al., 2008). The extent to which these commonly tested species are

[11] A Bioconcentration Factor (BCF) is a proportionality constant relating the chemical concentration in fish to the concentration in water under steady-state conditions. It measures the tendency of a chemical to accumulate in fish. Measurements of BCFs are generally undertaken in a controlled laboratory environment.

[12] EC50 is the "effect concentration" of a test substance that results in specified effect to 50% of the test population. Common measured effects include mortality, reduced growth or reduced reproduction. Source: https://iaspub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&vocabName=IRIS%20Glossary#formTop

adequate surrogates for the diversity of free-living invertebrates, fish, and wildlife in the Cape Fear basin is unknown.

The Board heard in March and April 2018 DEQ collected surface water, sediment and fish from a privately-owned lake less than 1-mile from the Chemours facility for a limited PFAS study (DEQ 2018). The study identified 20 different PFAS in the study samples of the 33 PFAS included in the target analyte list. GenX was detected in the lake surface water (968 ng/L), a surface spring feeding the lake (1160 ng/L) and in the lake surface sediment (1,800 ng/kg dry weight sediment). GenX was also detected in one of three species of fish collected from the lake, the 7-fish Redear Sunfish filet composite (270 ng/kg wet weight tissue). Five other PFAS were also detected in the three-fish species, including the legacy 8-carbon PFOS, as well as the legacy 11, 12, 13 and 14-carbon PFAS compounds PFUdA, PFDoA, PFTrDA and PFTeDA[13] (361 to 2840 ng/kg-wet weight). These data indicate the current-use and historical PFAS are present in environmental compartments in the area near the Chemours facility and may be attributed to releases from the Fayetteville facility.

There is little information on ecological toxicity benchmarks for these and most other PFAS, limiting our ability to assess potential ecological harm related to individual PFAS exposures, or to mixtures of PFAS compounds which may occur in areas where these compounds are manufactured or used in production. There is also inadequate information on the potential for ecological effects associated with additive, long-term exposures to sensitive receptors.

Measured air emissions of the GenX compounds from some of the processes at the Chemours/DuPont plant are significantly higher than previously understood or reported. GenX has also been measured in rainwater as far as 20 miles downwind of the facility, indicating atmospheric transport and deposition of this compound. Testing of private drinking water wells near but upgradient of the Chemours/DuPont plant has shown concentrations of GenX. The combination of environmental measurements and analysis by DEQ strongly indicate a causal link between GenX air emissions and widespread groundwater degradation near the Chemours/DuPont plant.

Section 9 – The Significance of the Circumstances

Board members heard compelling testimony from citizens, some clearly distressed, expressing profound concern for their health and that of their family members and others. The degree of public concern calls for action by the state to promote safe environmental conditions and to give practical guidance to those who are concerned to protect their own health and that of their family and community, especially more vulnerable persons. Large centers of population that are, or have been, exposed (such as those of the Lower Cape Fear Basin), and people with

[13] PFUdA CASN 2058-94-8, PFDoA CASN 307-55-1, PFTrDA CASN 72629-94-8, PFTeDA CASN 376-06-7

high levels and multi-media exposure (such as those living close to the Chemours plant in Fayetteville), are of special concern.

Comprehensive characterization of PFAS present in the environment and identification of all routes of exposure, and the implications of additive exposures are desirable, but the evidence needed to undertake these tasks is not currently available. Agencies and organizations with the capacity to persuade and facilitate the acquisition of this knowledge are urged to do so to enhance protection of human health and the environment. Studies are needed to characterize current and changes to PFAS burdens in nearby environmental matrices that may serve as long-term sources of PFAS to the local and regional environment, even as local emission sources to the environment may be controlled. In circumstances where concentrations observed in environmental matrices may not have implications to the health of non-human ecosystem components, these concentrations may provide long-term sources of exposure to sensitive human receptors through uptake by plants, animals or fishes consumed by humans.

Section 10 - Recommendations in Response to the Board's Charge for GenX

The Board recommends the reference dose developed by DHHS to DEQ as the foundation for establishing health-protective environmental standards including for groundwater and surface water.

The Board recommends the use of the current reference dose and provisional health goal developed by DHHS as the foundation for protecting affected and sensitive populations and providing corresponding risk assessments and advice.

NC DHHS developed a health-protective provisional health goal for drinking water for the most vulnerable population exposed to GenX using the best available science as federal and state standards were not available. DHHS followed the Board's recommendation to further evaluate the provisional health goal developmental process by using benchmark dose modeling to possibly refine the point of departure.

Section 11 – Other Recommendations

GenX is an 'emerging hazard', meaning one about which current scientific studies are few and new information is being produced. The Board judges that the available evidence is adequate to inform the adoption of the reference dose and the provisional health goal described here. Because there is ongoing research in North Carolina, nationally and internationally, and there are likely to be other studies:

- The Board recommends re-opening and updating this document as health values for GenX or other PFAS become available from the U.S. EPA, with consideration of utilizing benchmark dose modeling data to identify a range of risk values applicable.
- The Board counsels that the recommendations made here be reviewed within three years by the Board and Departments with a view to ensuring the adequacy of health protection and the efficacy of control measures. This will require ongoing monitoring and evaluation of environment and health conditions by the Departments.
- That DEQ and DHHS collaborate with the NC Department of Agriculture and Consumer Services and others to improve understanding of the relevance to local populations of exposure to GenX through foodstuffs, in particular with a view to determining whether standards for foodstuffs and/or guidance to local populations on food-related exposures are necessary and can be scientifically justified.
- That GenX and other PFAS releases to the air be characterized to evaluate inhalation exposures for humans, as well as the implications for contamination of soil, surface water, groundwater and the food web.
- That DEQ encourage and support efforts to more fully understand the ecological and environmental impacts of GenX, but also the long-term low-level additive exposures to mixtures of PFAS, including their persistence, environmental fate, and effects on ecological receptors.
- That the Departments recognize the concern of population members that exposure to GenX has occurred concurrent with exposure to other related emissions from the Chemours/DuPont plant and support efforts to understand possible interaction among the toxicity of and exposure to the associated chemicals and potential approaches to their combined regulation.
- That the Departments further recognize the concern of population members about the accumulation of these chemicals in the environment (for example in soils, river sediments and through bioaccumulation in animals) causing continuing human exposure.

Figure

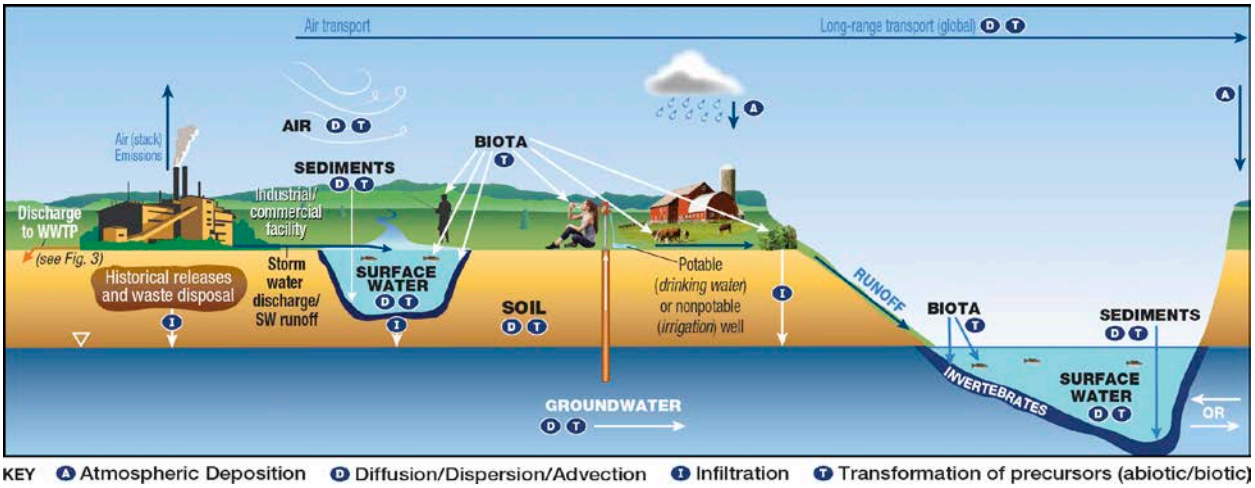

Figure 1. PFAS industrial source conceptual site model. Source: *Environmental Fate and Transport for Per- and Polyfluorinated Substances*. Interstate Technology and Regulatory Council (ITRC), Washington, DC. March 2018. https://pfas-1.itrcweb.org/

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Appendix A

Review of Uncertainty Factors Used in Calculation of the NC DHHS Provisional Drinking Water Health Goal for GenX

Review of Uncertainty Factors (UFs) Used in Calculation of the NC DHHS Provisional Drinking Water Health Goal for GenX

Standard uncertainty factors and modifying factors (Section 1.2.2.2.4: https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments)

i. Intraspecies UF: Factor of 10 to account for the variation in sensitivity among the members of the human population. In general, intraspecies variability in sensitivity to toxic effects can be due to a variety of factors, including age, sex, disease status, nutrition, genetics, etc.

   Used in GenX Provisional Health Goal calculation to account for potential sensitivity differences within the human population. There is no information available to justify use of any number besides the default factor of 10.

ii. Interspecies UF: Factor of 10 to account for the uncertainty involved in extrapolating from animal data to humans. Interspecies differences in sensitivity to toxic effects can be due to a variety of factors such as difference in metabolism and kinetics.

   Used in GenX Provisional Health Goal calculation (only rat and mice studies available). There is a large interspecies difference in half-life of legacy PFAS such as PFOS and PFOA, but there is not enough information to determine if this large interspecies variability would also occur with GenX. In the absence of data on the human half-life for GenX, DHHS used the default interspecies uncertainty factor of 10.

   DHHS was recently made aware that in the absence of PBPK modeling or chemical-specific data, EPA accounts for interspecies differences in calculating oral reference doses using allometric scaling, as outlined in a guidance document titled "Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose". This approach uses a dosimetric adjustment factor and a reduced interspecies uncertainty factor to replace the former default interspecies uncertainty factor of 10. DHHS is including this information in the interest of providing the SAB with all information needed to make fully informed recommendations.

iii. Sub chronic-chronic UF: Factor of 10 to account for the uncertainty involved in extrapolating from less than chronic NOAELs to chronic NOAELs. It is generally assumed that longer exposure times would result in adverse effects at lower concentrations due to accumulation of the toxicant or inability of an organism to repair injury from the substance.

   Used in GenX Provisional Health Goal calculation because the NOAEL from 28-day mice study and a reproductive screen in mice with a sub-chronic exposure duration was used as opposed to a NOAEL from a chronic (ex: 2 year) study. Sub-chronic

studies were used because adverse effects were observed at lower doses, and these effects were consistently seen across multiple studies at the same or similar doses (ex: the 90-day study in mice and the 90-day study in rats). To be health protective, studies with adverse effects at the lowest doses tested were used as the critical studies for determining the point of departure.

iv. LOAEL-NOAEL UF: Factor of 10 to account for the uncertainty involved in extrapolating from LOAELs to NOAELs.

Not used in GenX Provisional Health Goal calculation because NOAELs were available so an additional uncertainty factor was deemed unnecessary.

v. Modifying factor: additional uncertainty factor that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above; e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

Not used in GenX Provisional Health Goal calculation. Professional judgement from DHHS staff determined that a modifying factor was not necessary based on the following justification: Seven repeated dose oral studies ≥ 28 days in duration in two rodent species were reviewed, including a 2-year chronic study in rats and a reproductive/developmental toxicity screen in mice. NOAELs from several studies were identical or within the same order of magnitude with identical or similar health endpoints (liver toxicity). Additionally, DHHS staff concluded that the uncertainty factors discussed above adequately addressed the uncertainties of the database.

Appendix B

Benchmark Dose Modeling Report for GenX

NC DHHS

May 26, 2018

Appendix C

Benchmark Dose Modeling Report for GenX Supplemental Documentation

NC DHHS

June 8, 2018