1) DHHS Drinking Water Advisory Decision Matrix

The Division of Public Health (DPH) within the Department of Health and Human Services does not generally issue guidance on public water supplies (PWS) in North Carolina. PWS are regulated by the EPA Safe Drinking Water Act which is managed by the Department of Environmental Quality (DEQ) in North Carolina. DPH will get involved with PWS during emergency events or when assistance is requested by the PWS, DEQ, or a local health department.

Once DPH becomes involved in evaluating a water supply, private or public, DPH typically uses the methodology established in the North Carolina 2L Groundwater Rules or those established by federal agencies, such as the Environmental Protection Agency (EPA) or Agency for Toxic Substances and Disease Registry (ATSDR) to derive a guidance value. If a contaminant is found to be in exceedance of a guidance value, then DPH would issue water use recommendations. Two examples of recommendations are "do not drink" and "can be used for drinking, cooking, washing, cleaning, bathing and showering." A "boil water" advisory would only be appropriate when dealing with a microbial contamination that exceeds a water quality standard. Most assessments and recommendations done by DPH are for private water supplies, such as wells. Thus, assessments are typically individual consultations and advising in nature and not regulatory.

Occupational and Environmental Epidemiology Specific Processes

The Occupational and Environmental Epidemiology Branch (OEEB) typically provides Health Risk Evaluations for microbial and inorganic testing results of private wells using 15A NCAC 18A.3805 Data Review. OEEB provides information about the contaminants exceeding public drinking water Maximum Contaminant Levels (MCLs), recommendations for water use limitations or treatment options to reduce exposure comparable to meeting public drinking water MCLs, and recommendations about the need for and the frequency of repeat sampling.

By extension, OEEB uses this process for providing information (health risk evaluations) about other types of private well water contaminants including organic chemicals and pesticides.

In agreement with the Division of Waste Management (DWM), North Carolina Department of Environmental Quality (DEQ), OEEB uses the 15A NCAC 02L.0202 process listed below for determining health goals. This process is used to provide consistency among state agencies. Like OEEB, DWM levels are health-based and recommendations for use are similar (suitable/not suitable).

For private well water contaminants without a Maximum Contaminant Level (MCL), OEEB uses the 2L Standards. When there is not a 2L standard, OEEB will use the Interim Maximum Allowable Concentration (IMAC). When there is not a published IMAC, the health goal is typically calculated using a cancer lifetime risk of 10^{-6} and/or a Hazard Quotient (HQ) of 1 for non-cancer endpoints, when there is sufficient health data to inform one or both endpoints. Health goal calculations may also include relative source contribution to account for potential other sources of exposure besides drinking water. For cancer endpoints, this means one potential excess case of cancer per million people exposed. Calculation of cancer risks requires a cancer slope factor (CSF). A **slope factor** is an upper bound, approximating a

95% confidence limit, on the increased **cancer** risk from a lifetime exposure to an agent by ingestion or inhalation.

A **hazard quotient** (HQ) is the ratio of the potential exposure to a substance and the level at which no adverse effects are expected. A HQ is used for non-cancer endpoints and exposures over time (e.g. lifetime). A HQ below 1 means that adverse health effects are not expected. Conversely, a HQ above 1 means that there may be an increased risk of adverse health effects.

For calculations, OEEB uses standard Environmental Protection Agency guidelines, Regional Screening Levels (RSLs), and uncertainty factors. The regional screening levels (RSLs) are risk-based concentrations derived from standardized equations combining exposure information assumptions with EPA toxicity data. RSLs are considered by the EPA to be protective for humans (including sensitive groups) over a lifetime; however, RSLs are not always applicable to a particular geographic site and do not address non-human health endpoints, such as ecological impacts.

An Uncertainty Factor (UF) is a mathematical adjustment used for reasons of safety when knowledge is incomplete. Scientists use uncertainty factors when they have some, but not all, the information from animal or human studies to decide whether an exposure will cause harm to people. Uncertainty Factors are also sometimes called a safety factors. UFs are used to account for factors such as variations in people's sensitivity (intraspecies variability), for differences between animals and humans (interspecies variability), and for differences between a Lowest-observed-adverse-effect-level (LOAEL) and a No-observed-adverse-effect-level (NOAEL).

If information needed for the calculations is not complete, OEEB will consult Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), EPA Health Advisories (HA), other EPA risk assessment data, and other relevant, published health risk assessment data, and scientifically valid peer-reviewed published toxicological data.

Additional procedural steps taken by OEEB:

- OEEB will include life-stage calculations to determine the most health protective goal for the most vulnerable population(s) such as bottle-fed infants, children, pregnant women, lactating mothers, etc. This is often bottle-fed infants due to their higher water consumption per body weight.

- Where a standard level or concentration is outdated or new information is available, OEEB will provide a revised health goal for risk.

- When there is no information about a contaminant, OEEB will reach out to federal agencies for guidance.

- For public health assessments of specific sites, OEEB uses Agency for Toxic Substances and Disease Registry (ATSDR), Centers for Disease Control and Prevention (CDC) guidelines. OEEB has a cooperative agreement with CDC regarding evaluation of site-specific contamination and is obligated to use these guidelines for public health assessments.

For private well contaminants detected above the health goal, OEEB recommends not to use the water. Water ingestion uses considered include drinking, cooking, and formula preparation. For some

contaminants, bathing showering, washing, and cleaning uses are considered. Where data are available, fish consumption, gardening and irrigation uses may be considered.

Again, all assessments, health goals, and recommendations generated by OEEB are not regulatory. A role of OEEB is to provide public health information.

2) List of Studies, Research and Reports used in GenX health goal calculation

Beekman M, Zweers P, Muller A, de Vries W, Janssen P, Zeilmaker M. 2016. RIVM Report 2016-0174: Evaluation of substances used in the GenX technology by Chemours, Dordrecht. http://www.rivm.nl/Documenten_en_publicaties/Wetenschappelijk/Rapporten/2016/december/Evaluation_of_substances_used_in_the_GenX_technology_by_Chemours_Dordrecht.

ECHA Toxicological Summary for Ammonium 2,3,3,3-Tetrafluoro-2-(Heptafluoropropoxy)Propanoate. https://echa.europa.eu/registration-dossier/-/registered-dossier/2679/7/1

Ferreira et al. Comparing the potency in vivo of PFAS alternatives and their predecessors. Abstract. March 2017. http://su.diva-portal.org/smash/record.jsf?pid=diva2%3A1085755&dswid=5295#sthash.Iofa5rDn.dpbs

Gannon et al. Absorption, distribution, metabolism, excretion, and kinetics of 2,3,3,3-tetrafluoro-2(heptafluoropropoxy)propanoic acid ammonium salt following a single dose in rat, mouse, and cynomolgus monkey. Toxicology 340 (2016) 1–9. http://dx.doi.org/10.1016/j.tox.2015.12.006

Hoke et al. Aquatic hazard, bioaccumulation and screening risk assessment for ammonium 2,3,3,3tetrafluoro-2-(heptafluoropropoxy)-propanoate. Chemosphere 149 (2016) 336-342. http://dx.doi.org/10.1016/j.chemosphere.2016.01.009

Rae et al. Evaluation of chronic toxicity and carcinogenicity of ammonium 2,3,3,3-tetrafluoro-2(heptafluoropropoxy)-propanoate in Sprague–Dawley rats. Toxicology Reports. June 2015. https://doi.org/10.1016/j.toxrep.2015.06.001

Sun et al. Legacy and Emerging Perfluoroalkyl Substances Are Important Drinking Water Contaminants in the Cape Fear River Watershed of North Carolina. Environmental Science & Technology Letters. Nov 2016. DOI: 10.1021/acs.estlett.6b00398.

USEPA. Drinking Water Health Advisories for PFOA and PFOS. https://www.epa.gov/ground-water-anddrinking-water/drinking-water-health-advisories-pfoa-and-pfos

USEPA. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000). https://nepis.epa.gov/Exe/ZyPDF.cgi/20003D2R.PDF?Dockey=20003D2R.PDF

USEPA. Reference Dose (RfD): Description and Use in Health Risk Assessments. https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments

USEPA. TSCA Non-Confidential Business Information for 8EHQ-06-16478. https://assets.documentcloud.org/documents/2746960/GenX8eFilings.pdf

3) Description of GenX health goal calculation

Calculation of the Preliminary Assessment

The European Chemical Agency (ECHA) information (ECHA; Beekman et. al., 2016) included a Derived No Effect Level (DNEL) of 0.01 mg/kg body weight (bw)/day for oral exposures. The DNEL reported by ECHA was calculated using a No observed-adverse-effect-level (NOAEL) (1.0 mg/kg body weight (bw)/day) from a 2-year rat chronic toxicity/carcinogenicity study (Rae et. al., 2015) as the point of departure (POD) and applying default uncertainty factors, as described below:

- No-observed-adverse-effect-level (NOAEL) = 1.0 mg/kg body weight (bw)/day
- Total default uncertainty factors (UF) = 100
  (interspecies variability = 10; intraspecies variability = 10)
- Formula: NOAEL/UF = DNEL
  (1.0 mg/kg bw/day)/100 = 0.01mg/kg/day=DNEL

NC DHHS calculated a drinking water equivalent level (DWEL) for GenX as follows:

- Derived No Effect Level (DNEL) = 0.01 mg/kg bw/day
- Body Weight = 7.8 kg (infant)
- Intake = 1.1 L/day (infant)
- Relative Source Contribution (RSC) = 1.0 (assumption made that 100% of Gen X exposure was through drinking water)
- Unit Conversion = 10^6 ng/mg
- Formula: DNEL (mg/kg bw/day) X body weight (kg)/intake (L/day) X RSC X Unit Conversion = DWEL

(0.01 mg/kg/day) X 7.8kg/(1.1L/day) X 1.0 X 10^6 ng/mg = 71,000 ng/L (parts per trillion, ppt)

The values used for body weight and drinking water intake were based on infants (in order to be maximally health protective) since infants consume the highest amount of water in relation to their body weight.

Calculation of the updated Health Assessment

After consultation with EPA, the following were updated:

- The EPA directed DPH staff to a different study (ECHA Repeated dose toxicity: oral, ~~Key~~ Supporting study 005) that had sufficient data to support the use of a lower no-observed-adverse-effect-level (NOAEL) as a point of departure (POD) for the assessment. This NOAEL (0.1 mg/kg/day) is 10-fold lower than the NOAEL used in the preliminary assessment (1.0 mg/kg body weight (bw)/day) and is based on effects on the liver in mice. EPA indicated this was the study and POD they used in their 2008 Standard Review Risk Assessment and they indicated they will be using the same POD for their re-assessment of GenX.

- An additional uncertainty factor of 10 was included in the calculations because this point of departure is based on a subchronic toxicity study rather than a chronic toxicity study. This factor is intended to account for the uncertainty involved in extrapolating from less than chronic

NOAELs to chronic NOAELs, and is consistent with EPA's IRIS guidelines for the use of uncertainty factors in deriving reference doses.

- Based on the US EPA guidance in Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (Figure 4-1), the relative source contribution (RSC) was changed from 100% to 20% to account for potential exposure to GenX from other routes like air, soil, dust, and food. The RSC lowers the acceptable concentration in water due to the potential for other exposure routes and is recommended when insufficient data exists to characterize the likelihood of exposure to other relevant sources.

Updated calculation:

- No-observed-adverse-effect-level (NOAEL) = 0.1 mg/kg body weight (bw)/day
- Total default uncertainty factors (UF) = 1000 (interspecies variability = 10; intraspecies variability = 10; and subchronic to chronic extrapolation = 10)
- Formula: NOAEL/UF = Reference Dose (RfD)
  (0.1 mg/kg bw/day)/1000 = 0.0001mg/kg/day

NC DHHS calculated a drinking water equivalent level (DWEL) for GenX as follows:

- Dose (RfD) = 0.0001 mg/kg bw/day
- Body Weight = 7.8 kg (bottle-fed infant)
- Intake = 1.1 L/day (bottle-fed infant)
- Relative Source Contribution = 0.2
- Unit Conversion = 10^6 ng/mg
- Formula: dose (mg/kg bw/day) X body weight (kg)/intake (L/day) X RSC X Unit Conversion = DWEL
  (0.0001 mg/kg/day) X 7.8kg/(1.1L/day) X 0.2 X 10^6 ng/mg = 140 ng/L (parts per trillion, ppt)

The values used for body weight and drinking water intake were based on bottle-fed infants (in order to be maximally health protective) since infants consume the highest amount of water in relation to their body weight. The DWEL was used to set a provisional health goal for the most sensitive population (bottle-fed infants).

References

Beekman M, Zweers P, Muller A, de Vries W, Janssen P, Zeilmaker M. 2016. RIVM Report 2016-0174: Evaluation of substances used in the GenX technology by Chemours, Dordrecht. http://www.rivm.nl/Documenten_en_publicaties/Wetenschappelijk/Rapporten/2016/december/Evaluation_of_substances_used_in_the_GenX_technology_by_Chemours_Dordrecht.

ECHA Toxicological Summary for Ammonium 2,3,3,3-Tetrafluoro-2-(Heptafluoropropoxy)Propanoate. https://echa.europa.eu/registration-dossier/-/registered-dossier/2679/7/1

Ferreira et al. Comparing the potency in vivo of PFAS alternatives and their predecessors. Abstract. March 2017. http://su.diva-portal.org/smash/record.jsf?pid=diva2%3A1085755&dswid=5295#sthash.Iofa5rDn.dpbs

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Rae et al. Evaluation of chronic toxicity and carcinogenicity of ammonium 2,3,3,3-tetrafluoro-2(heptafluoropropoxy)-propanoate in Sprague–Dawley rats. Toxicology Reports. June 2015. https://doi.org/10.1016/j.toxrep.2015.06.001

Sun et al. Legacy and Emerging Perfluoroalkyl Substances Are Important Drinking Water Contaminants in the Cape Fear River Watershed of North Carolina. Environmental Science & Technology Letters. Nov 2016. DOI: 10.1021/acs.estlett.6b00398.

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USEPA. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000). https://nepis.epa.gov/Exe/ZyPDF.cgi/20003D2R.PDF?Dockey=20003D2R.PDF

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USEPA. TSCA Non-Confidential Business Information for 8EHQ-06-16478. https://assets.documentcloud.org/documents/2746960/GenX8eFilings.pdf

4) List of Studies, Research and Reports used in review of Chromium VI health goal
The health goal was set by N.C. DEQ Division of Waste Management and reviewed for accuracy by DPH. Here is a list of resources used to review the cancer slope factor used in the derivation of the health goal:

U.S. EPA. Regional Screening Levels (RSLs). https://www.epa.gov/risk/regional-screening-levels-rsls

N.J. Department of Environmental Protection. Derivation of Ingestion-Based Soil Remediation Criterion for Cr^{+6} Based on the NTP Chromic Bioassay Data for Sodium Dichromate Dihydrate. April 2009. http://www.state.nj.us/dep/dsr/chromium/soil-cleanup-derivation.pdf
(Cited in EPA RSLs)

U.S. EPA. Toxicological Review of Hexavalent Chromium: In Support of Summary Information on the Integrated Risk Information System (IRIS) – External Review Draft. September 2010. https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=221433

Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Public Health Goal for Hexavalent Chromium (CrVI) in Drinking Water. July 2011. https://oehha.ca.gov/media/downloads/water/public-health-goal/cr6phg072911.pdf