2019

HEALTH-BASED DRINKING WATER VALUE RECOMMENDATIONS FOR PFAS IN MICHIGAN

Michigan Science Advisory Workgroup

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Executive Director's Foreword

This report accomplishes a key milestone in Michigan's effort to identify and reduce exposures to per- and polyfluoroalkyl substances (PFAS) contamination. With it, we are now one step closer to developing state drinking water standards for PFAS.

Michigan is a national leader at addressing PFAS contamination. Through our unique, multi-agency approach, Michigan's PFAS Action Response Team (MPART) is systematically identifying sources of PFAS contamination and getting a better understanding of their occurrence throughout our environment.

By using analytical techniques capable of finding PFAS as low as 2 parts per trillion, we have found the presence of PFAS in the drinking water from thousands of private residential wells near contaminated sites. We have also found PFAS in public water supplies across the state. We tested over 1,700 supplies covering all community water supplies plus schools and larger day cares with their own wells. We found PFAS in ten percent of the supplies. While most of the PFAS levels were very low, three percent of the supplies have required follow-up actions, and a few have required an alternate water source.

Unfortunately, we do not have federal drinking water standards, despite knowing they are in our drinking water and that some PFAS have been associated with adverse health effects. Recognizing that the USEPA is still likely several years away from providing any leadership on PFAS drinking water standards, Michigan, like other states, was left to develop our own.

With Governor Gretchen Whitmer's leadership, MPART formed a Science Advisory Workgroup to navigate the science and standards from across the country to advise Michigan on drinking water health-based values for PFAS. These health-based values will be used to inform the next step of the drinking water rule-making process, which includes stakeholder involvement where other factors will be considered.

I could not be more impressed with the thoughtful deliberation of our workgroup and the tireless technical support from our staff. As the information in this report is given to EGLE for consideration during the development of drinking water standards, we all owe them our sincere appreciation for giving us a firm foundation on which to move forward with protecting Michiganders from unacceptable levels of PFAS in their drinking water.

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Michigan PFAS Action Response Team

Michigan Science Advisory Workgroup

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Mr. Kevin Cox
Dr. David Savitz

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Lansing, Michigan
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The Michigan Science Advisory Workgroup

Dr. David Savitz

Dr. David Savitz, who chairs the advisory Workgroup, is a professor of epidemiology in the School of Public Health at Brown University. He also serves as associate dean for research, and holds joint appointments in obstetrics and gynecology, and pediatrics in the Alpert Medical School. His epidemiological research has addressed a wide range of public health issues including environmental hazards in the workplace and community, reproductive health outcomes, and environmental influences on cancer. He has done extensive work on health effects of nonionizing radiation, pesticides, drinking water treatment by-products, and perfluorinated compounds. He is the author of nearly 350 papers in professional journals and editor or author of three books. He was president of the Society for Epidemiologic Research and the Society for Pediatric and Perinatal Epidemiologic Research, and North American regional councilor for the International Epidemiological Association. Dr. Savitz is a member of the National Academy of Sciences Institute of Medicine. From 2013-2017 he served as vice president for research at Brown University. He was a member of the C8 Science Panel that conducted some of the first epidemiologic research on PFAS in the mid-Ohio Valley and has published a number of reports related to potential health effects of PFAS. He recently chaired the Science Panel to advise MPART on the current research related to toxicology, epidemiology, exposure pathways, and remediation of PFAS.
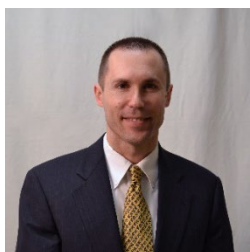
Mr. Kevin Cox

Kevin Cox is a Managing Toxicologist at NSF International. Prior to his current role, Mr. Cox was a Supervising Toxicologist supporting NSF's drinking water additives and dietary supplement certification programs. As an expert in human health risk assessment, Mr. Cox has authored numerous chemical risk assessments evaluating exposure from unregulated drinking water contaminants, dietary supplement ingredients, toy product materials, and pool and spa treatment chemicals. Specific to PFAS, Mr. Cox has conducted a state-of-the-science analysis of published PFAS risk assessments in support of NSF International drinking water programs. This analysis was recently presented to Michigan water management professionals. Mr. Cox received his B.S. in biochemistry and history from the University of Michigan and his MPH in Environmental Health Sciences - Toxicology from the University of Michigan School of Public Health. He is currently an Associate Member of the Society of Toxicology. Mr. Cox also holds a J.D. from the University of Michigan Law School and is a member of the Michigan Bar Association.

Dr. Jamie DeWitt

Dr. Jamie DeWitt is an associate professor in the Department of Pharmacology and Toxicology of the Brody School of Medicine at East Carolina University. Her laboratory's research program explores relationships between biological organisms and their responses after exposure to environmental contaminants, with a specific focus on the immune system and its interactions with the nervous system during development and adulthood. The research program particularly focuses on emerging aquatic contaminants, especially PFAS. With respect to PFAS, DeWitt has published 13 primary research articles, six review articles, two book chapters, and edited a book on PFAS toxicity. She has served as an external reviewer for the United States Environmental Protection Agency (USEPA) health effects assessment of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), the United States National Toxicology Program's immune effects assessment of PFOA and

PFOS, the United States Agency for Toxic Substances and Disease Registry toxicological profile for PFASs, and was a member of the International Agency for Research on Cancer working group for the assessment of the carcinogenicity of PFOA. Her laboratory currently assesses the immunotoxicity of emerging PFAS that have been designed to replace those that have been phased out of production and that are of concern in North Carolina. She double-majored in environmental science and biology for her bachelor's degree from Michigan State University and has doctoral degrees in environmental science and neural science from Indiana University-Bloomington. She completed postdoctoral training in ecotoxicology at Indiana University-Bloomington and in immunotoxicology at the USEPA in partnership with the University of North Carolina at Chapel Hill.

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Executive Summary

Background: The Michigan PFAS Action Response Team (MPART), is a unique, multi-agency proactive approach for coordinating state resources to address per- and polyfluoroalkyl substances (PFAS) contamination. Agencies responsible for environmental protection, public health, natural resources, agriculture, military installations, commercial airports, and fire departments work together to ensure the most efficient and effective response. The work done by MPART on drinking water supports the development of standards now that we have key information, including:

- PFAS have been discovered in drinking water during investigations of contaminated sites and a survey of all of Michigan's public water supplies. Public health responses, such as the provision of alternate water (e.g., point of use filters) have been necessary for thousands of Michiganders based on the strength of the source, location, and the concentrations found.

- The MPART Science Advisory Panel report issued in December 2018 indicated that observational epidemiology literature supports the need for drinking water values below the United States Environmental Protection Agency (USEPA) Lifetime Health Advisory (LHA) level of 70 ppt PFOS and PFOA, individually or in combination, and included a recommendation for establishing state drinking water standards for PFAS.

- The Michigan Department of Health and Human Services (MDHHS)-led MPART Human Health Workgroup developed public health drinking water screening levels for five individual PFAS in February 2019. Those screening levels will prompt further evaluation and public health consultations at numerous public water supplies and residences across the state including where detectable levels of PFOS and/or PFOA are below the USEPA LHA.

On March 26, 2019, Governor Gretchen Whitmer announced that Michigan was establishing enforceable state drinking water standards for PFAS. These standards, otherwise known as Maximum Contaminant Levels (MCLs), under the federal Safe Drinking Water Act have traditionally been established first by the USEPA and then adopted by the states. At this time, however, the USEPA has not initiated its process for establishing PFAS MCLs, and its process could take five or more years to complete. Michigan chose not to wait any longer for federal action.

Governor Whitmer called on MPART to form a Science Advisory Workgroup (Workgroup) to review the existing and proposed PFAS standards from across the country and develop health-based values (HBVs) to inform the initial phase of the rulemaking process for establishing state drinking water standards. The workgroup was given until July 1, 2019 to develop the HBVs. On April 4, 2019, MPART approved a motion to create the Workgroup. The Charge from MPART to the Workgroup is included in Appendix B. The members of the Workgroup were announced on April 11, 2019. The Workgroup was supported by MPART staff.

The Workgroup members are experts in the fields of epidemiology, toxicology, and risk assessment. The composition of the Workgroup matches the typical fields of evaluation for HBV developments. Dr. Jamie DeWitt provided the strong toxicological expertise and up-to-date knowledge on PFAS toxicology as HBVs typically use laboratory animal toxicity studies. Epidemiological information supports the laboratory animal data, and Dr. David Savitz provided his epidemiological expertise in selection of health endpoints and relevance to humans. Tying both toxicology and epidemiology together are risk assessment practices, and Mr. Kevin Cox provided the expertise in that field. Taken together, this Workgroup was able to knowledgably speak on the current state of PFAS health research and provide the scientific expertise needed to efficiently develop HBVs on the requested timeline.

The evaluation and deliberations of the Workgroup occurred over a very limited timeframe (Appendix D), which required frequent interaction. Much of that interaction occurred during 7 web conferences between April 19 and May 29, 2019, culminating in an in-person meeting the weekend of June 1-2, 2019. The Workgroup's final conclusions were presented to MPART on June 27, 2019.

Conclusions: The Workgroup undertook a methodical approach to evaluate existing and proposed standards from across the country for the 18 PFAS analytes considered under USEPA Method 537.1 (Appendix C). They focused on those PFAS that they determined had enough peer reviewed studies on which to base their conclusions. What they considered, and the logic behind their approach, has been carefully documented in individual chemical summaries for each compound that has a derived HBV in the following table:

Summary Table of Drinking Water Health-Based Values

Specific PFAS	Drinking Water Health-based Value	Chemical Abstract Services Registry Number (CASRN)
PFNA	6 ng/L (ppt)	375-95-1
PFOA	8 ng/L (ppt)	335-67-1
PFHxA	400,000 ng/L (ppt)	307-24-4
PFOS	16 ng/L (ppt)	1763-23-1
PFHxS	51 ng/L (ppt)	355-46-4
PFBS	420 ng/L (ppt)	375-73-5
GenX	370 ng/L (ppt)	13252-13-6

The Workgroup also recommended MPART and water supply operators screen analytical results for other long-chain PFAS (eight carbons and above for carboxylates and six carbons and above for sulfonates) included in USEPA Method 537.1 at the lowest concentration proposed for any of the compounds, which is 6 ppt. Based on the similarity in toxicity for the long-chain PFAS, the Workgroup recommends use of the HBV for PFNA (6 ng/L [ppt]) as a screening level for all other long-chain PFAS included on the USEPA Method 537.1 analyte list for which the Workgroup did not develop an individual HBV. Those other long-chain PFAS included in USEPA Method 537.1 are: NEtFOSAA (CASRN: 2991-50-6); NMeFOSAA (CASRN: 2355-31-9); PFDA (CASRN: 335-76-2); PFDoA (CASRN: 307-55-1); PFTA (CASRN: 376-06-7); PFTrDA (CASRN: 72629-94-8); and PFUnA (CASRN: 2058-94-8). While there is not enough information available at this time to support HBVs and drinking water standards for them, these compounds are expected to produce similar health effects. Additional monitoring, research for potential sources, notification of the public, and efforts to reduce exposure are warranted.

The Workgroup recognizes that their conclusions in some cases deviate modestly from those of other organizations. Evolving science and professional judgement can account for the variation. The variation is not substantial, however, and the values are trending lower nationally over time.

Approach

Workgroup Interpretation of the Charge

The Workgroup was conscience of the importance and responsibility placed upon its efforts to identify public health toxicity values for certain PFAS as described within the Charge. Prior to initiating its efforts, the Workgroup sought and received clarification on the scope of the Charge. Given the relatively short timeframe for which to accomplish the tasks set forth within Charge, the Workgroup confirmed that the focus of the effort was to utilize the existing and proposed national- and state-derived PFAS assessments to inform its decision-making process as opposed to conducting a full systematic review of the available scientific literature on PFAS.

Additionally, as one of the outputs of the Charge is to inform State of Michigan on drinking water health-based values for PFAS, it was important to understand if the State of Michigan had any paradigms in place that the Workgroup must follow when deriving drinking water health-based values. The response received from the State of Michigan indicated that the Workgroup was only limited to applying a scientifically defensible approach as described within the Charge. With these issues clarified, the Workgroup approached the tasks set forth in the charge in the following manner:

1) Initially, PFAS analytes were identified within USEPA Method 537.1 for which published or externally peer reviewed PFAS drinking water criteria or reference doses (RfDs) existed and the derivation of such values was done in a scientifically defensible manner. This approach resulted in the selection of PFOA, PFOS, PFHxS, PFHxA, PFBS, PFNA and GenX as PFAS analytes for which the Workgroup would then develop individual public health toxicity values. The remaining PFAS values within USEPA Method 537.1 were later considered as to whether a class-based or group-based public health toxicity value could be applied.

2) For each of the selected PFAS analytes, the Workgroup evaluated the identified points of departure (defined as the point on a toxicological dose-response curve corresponding to an estimated low effect level or no effect level) and rationale from published risk assessments and assessed the underlying key studies that served as the basis for the published values. From this review, the merits of each available point of departure was discussed among the Workgroup and critical studies and points of departures for each of the seven identified PFAS analytes were identified to form the basis of public health toxicity values described further herein.

3) With critical studies and points of departure identified for each individual PFAS, the Workgroup then identified appropriate uncertainty factors to derive public health toxicity values. From these public health toxicity values, the Workgroup recommended specific drinking water exposure paradigms, accounting for sensitive sub-populations, and applied selected relative source contribution factors to derive the drinking water health-based values described further herein.

4) Lastly, consideration was given to the remaining PFAS analytes from USEPA Method 537.1 that were not selected for the development of individual criteria as to whether a class-based or grouping-based evaluation approach would be appropriate. As described

below, the Workgroup concluded that a screening level approach was valid to assess longer-chain PFAS based on the lowest derived drinking water health-based values.

Based on guidance from the Director of EGLE's Drinking Water and Environmental Health Division, PFAS chemical summary sheets were used to capture the necessary information for the MCL rulemaking process. The Workgroup and MPART staff used this format to provide maximum transparency on the decisions and rationale for drinking water health-based value development for each PFAS.

The chemical summary sheets describe:

- The critical study or studies, point of departure from each study, and conversion to a human equivalent dose;

- Uncertainty factors and a calculated toxicity value;

- Exposure parameters, and methodology for calculation of a drinking water health-based value.

Challenges and Limitations

The premises for the Workgroup's efforts to provide evidence-based conclusions for informing the regulation of PFAS in drinking water are compelling. Policy needs to provide clarity on what levels of specific chemicals are believed to be protective of public health and develop a mechanism to monitor and mitigate pollutants such as PFAS where needed. The Workgroup identified and made optimal use of the scientific evidence that is available to provide guidance, drawing on its knowledge of research methods and quantitative risk assessment. Furthermore, the Workgroup approached the issue free of bias, and as a panel, has a wide range of expertise and familiarity with the research on PFAS. However, the nature of this process is inherently subject to uncertainty and other equally qualified experts presented with the same scientific data the Workgroup drew upon might well make somewhat different conclusions. A number of other organizations have been through a similar exercise in providing guidance on acceptable drinking water contaminant levels, and while there are not extreme differences, there is not complete convergence either. As described in some detail below, a series of inputs were needed to derive the Workgroup's estimates and make that sequence of decisions as transparent as possible for those who wish to compare these conclusions to those made by other agencies. Like all the others, they are based exclusively on toxicology studies given the ability to quantify exposure-response relationships with great precision, but there is a loss of certainty in applying these estimates to free-living human populations. In most cases, there is epidemiologic evidence pertaining to the same health endpoints used in toxicology, and where there is such convergent evidence (e.g., immune function, development), confidence in the applicability of the experimental studies to human populations is enhanced. Finally, it should be noted that the scientific evidence on PFAS is expanding rapidly and that with new studies, the guidelines may well need to be revised. While it would be inefficient to do so frequently, on some periodic basis of several years, it would be useful to repeat the process that generated this report to determine where changes may be needed.

Process

Selection of Toxicity Values

Adverse health effects reported following exposure to PFAS in laboratory animal models and epidemiological studies have been summarized in myriad peer-reviewed and publicly available documents, including those generated by other state agencies. Most recently, the Agency for Toxic Substances and Disease Registry (ATSDR), compiled a toxicological profile for 14 PFAS that comprehensively summarizes evidence from publicly available published studies (ATSDR, 2018). This, and other summary documents, as well as the published studies themselves, were relied on to determine points of departure, as well as the toxicity values that protect the most sensitive populations and reflect a level that is unlikely to lead to adverse health effects if those sensitive populations are exposed over a lifetime or during a sensitive period (i.e., during development). The toxicity values are therefore designed to be protective of all exposed populations. For all of the PFAS examined, points of departure were selected from studies with laboratory animal models. This approach does not negate findings associated with epidemiological studies, but reflects that humans experience uncontrolled and imperfectly documented rather than controlled, precisely measured exposures. Additionally, these points of departure reflect adverse health effects that occur at low doses and that are supported by the weight-of-evidence across endpoints and between findings in humans and laboratory animal models. Therefore, the process to select points of departure used the available scientific evidence to identify an adverse health effect that occurred at a low dose, was supported by findings in other studies, was relevant to humans, and would be protective of sensitive populations.

Uncertainty Factors

In deriving the toxicity values for PFAS, the selected points of departure are divided by uncertainty factors. Uncertainty factors are applied in order to account for:

1. Variation in susceptibility among the human population (intraspecies uncertainty);

2. Uncertainty in extrapolating animal data to humans (interspecies uncertainty);

3. Uncertainty in extrapolating from data obtained from a study with a less-than-lifetime exposure (subchronic to chronic uncertainty);

4. Uncertainty in extrapolating from a lowest observed adverse effect level (LOAEL) as opposed to a no observed adverse effect level (NOAEL); and

5. Uncertainty associated with an incomplete toxicity database. Uncertainty factors assigned for each of these five categories are typically 1x, 3x ($10^{0.5}$x), or 10x with the default value being 10x, which represents greater uncertainty.

For both interspecies and intraspecies uncertainty factors, the variability in response to a toxicant may result from differences in toxicokinetics and/or toxicodynamics. Toxicokinetics refers to the absorption, distribution, biotransformation and excretion of the toxicant following exposure. Toxicodynamics refers to the molecular, biochemical and physiological effects of the toxicant or its metabolites leading to the toxic response. Therefore, the interspecies and intraspecies uncertainty factors are divided into subparts representing the toxicokinetic factor and the toxicodynamic factor. In evaluating the interspecies uncertainty for the selected PFAS, in each

case the toxicokinetic subfactor was able to be reduced to 1x on account of adjustments based on serum half-lives or allometric scaling. Due to lack of data to depart from the default the toxicodynamic subfactor 3x ($10^{0.5}$x), the resulting interspecies uncertainty factor is 3x ($10^{0.5}$x).

When considering the subchronic to chronic uncertainty, the relevant consideration is whether the selected point of departure may differ if the duration of exposure were to be increased. For PFAS, a weight of evidence approach was used to assess the subchronic to chronic uncertainty factor, including, but not limited to, duration of the key study, potential impact of duration on the selected point of departure, as well as availability of chronic repeat-dose toxicity data.

For the NOAEL to LOAEL uncertainty factor, use of a NOAEL (or lower confidence limit on the benchmark dose [BMDL]) allows for an uncertainty factor of 1x. If the point of departure is based on a LOAEL, the uncertainty factor is either 3x ($10^{0.5}$x) or 10x depending on the severity and/or reversibility of the critical effect.

The database uncertainty factor is based on the ability of the existing data to support a scientific judgment of the likely critical effect from exposure to the compound. In assessing the database completeness, the types of toxicity data (e.g., human, animal, mode of action) as well as data gaps that may have improved the derived risk values should be emphasized. This approach should take into consideration issues such as the types of endpoints evaluated, life-stages evaluated, duration, timing, route of exposure, and the potential for latent effects and/or reversibility of effects (USEPA, 2002). For the selected PFAS, each database was unique; however, common concerns were lack of appropriate characterization of immune, endocrine or neurodevelopmental effects.

Relative Source Contribution

Relative source contribution (RSC) is the percentage of a person's exposure to a chemical that comes from drinking water. For example, an RSC of 20 percent assumes that the other 80 percent of a person's exposure to a chemical comes from non-drinking water sources. The USEPA (2000) provides guidance on the selection of an RSC value using an exposure decision tree that takes into account specific populations of concern, whether these populations are experiencing exposure from multiple sources, and whether levels of exposure or other circumstances make apportionment of the toxicity value or POD/UF desirable. The most conservative RSC is established at 20 percent, and the RSC can reach a ceiling of 80 percent as more information is available about exposure pathways and the source of exposure.

Drinking Water Health-Based Value Derivation

The traditional risk assessment approach using simple equations based on body weight, water intake rate and RSC to calculate drinking water HBVs is not adequate to address the bioaccumulative nature and known or presumed developmental toxicity of PFAS. These traditional equations do not consider the PFAS body-burden at birth or any transfer of maternal PFAS through breastmilk. To better address these concerns, and to also account for higher early-life intake rates, the Goeden et al. (2019) simple one-compartment toxicokinetic model was used where the data were available for the individual PFAS. The resulting drinking water HBVs are considered protective for an infant exclusively breast-fed for 12 months, followed by drinking contaminated water through life. Additionally, these drinking water HBVs also protective for formula-fed infants. Where data were not available to derive drinking water HBVs using the model, traditional equations were used.

Confidence Statement

Following USEPA guidance (2002), risk assessments may contain a narrative description of the overall confidence in the derived health-effects based values. Confidence in the risk assessment would be low if there is a high degree of scientific uncertainty and would be high if there is a low degree of scientific uncertainty. Major elements of scientific uncertainty may be considered to include, but not limited to, the following; database completeness, quality of key study(ies), severity and relevance of the critical effect, quality of the dose-response analysis and consideration of sensitive subpopulations. (NRC, 2009; Beck et al., 2016).

For the selected PFAS for which quantitative values were derived there remains significant scientific uncertainty. Health outcomes due to PFAS exposure that warrant additional study include, but are not limited to, endocrine disruption, immunological and neurodevelopmental effects as well as cancer. Further information is needed on the mode of action as well as the cumulative risk of exposure to multiple PFAS. Overall, the present evaluation of the selected PFAS is based on sound science and current practices in risk assessment; however, the Workgroup recognizes that the science of PFAS is constantly evolving and new information may come to light that requires a re-evaluation of the drinking water HBVs established herein.

PFAS Chemical Summary Sheets

Chemical Summary for PFNA

	Decision Point	Rationale/justification
Critical study	Das KP, Grey BE, Rosen MB, et al. 2015. Developmental toxicity of perfluorononanoic acid in mice. *Reproductive Toxicology* 51:133-144.	The Workgroup reviewed the available evaluations and focused on the assessments by ATSDR and New Jersey. Das et al. (2015) was selected by both ATSDR (2018) and NJDEP (2015).
Description of the critical study	Timed-pregnant CD-1 mice were administered 0, 1, 3, 5 or 10 mg/kg PFNA by daily oral gavage from gestational day (GD) 1 to 17. Maternal toxicity and reproductive outcomes were investigated. Postnatal toxicity, liver gene expression and developmental effects were evaluated in mouse offspring. *Body weight endpoints* – Decreased body weight gain in mouse pups *Developmental endpoints* – Delayed eye opening, preputial separation, and vaginal opening in mouse pups	The Workgroup reviewed the health endpoints investigated in Das et al. (2015) and identified the developmental endpoints as more relevant than liver endpoints.
Point of Departure (POD)	A NOAEL of 1 mg/kg/day was identified for developmental effects. The average serum concentration for NOAEL (1 mg/kg/day) was estimated (6.8 mg/L) in dams using an empirical clearance model (Wambaugh et al., 2013). The estimated time-weighted average serum concentration corresponding to the NOAEL was 6.8 mg/L.	The Workgroup decided that serum-based points of departure were appropriate for PFAS.
Human equivalent dose (HED)	The time-weighted average serum concentration of 6.8 mg/L was converted to the HED using the below equation. $NOAEL_{HED}$ = (TWA serum x k_e x V_d) = 0.000665 mg/kg/day Ke = 0.000489165 (4.8 x 10^{-4}) based on a human serum half-life of 1417 days (calculated from Zhang et al. [2013] as described above) Vd = 0.2 L/kg (ATSDR [2018]; Ohmori et al. [2003])	The Workgroup discussed the human serum half-lives available from Zhang et al. (2013), which were an arithmetic mean of 2.5 years (913 days) for 50 year old or younger females and 4.3 years (1570 days) for females older than 50 years old and all males. An average of 3.9 years (1417 days) was calculated based on those averages. The Workgroup selected the calculated average as it would better represent the entire population.
Uncertainty factors	A total uncertainty factor of 300: • 1 for LOAEL to NOAEL • 10 for human variability • 3 ($10^{0.5}$) for animal to human variability • 1 for subchronic to chronic • 10 for database deficiencies was used.	The Workgroup discussed the uncertainty factors selected by ATSDR (2018) and agreed that those selected were appropriate.

Toxicity value	2.2 ng/kg/day (2.2 x 10^{-6} mg/kg/day) which corresponds to a serum concentration of 0.023 mg/L Serum levels used in development of these toxicity levels are not meant to indicate a level where health effects are likely. These serum levels are calculated to be at a point where no or minimal risk exists for people drinking water with a certain PFAS.	Human equivalent dose or serum level divided by the total uncertainty factors = toxicity value
Exposure parameters for drinking water screening HBVs	Breast-fed infant, which is also protective of a formula-fed infant Placental transfer of 69% (MDHHS 2019) Breastmilk transfer of 3.2% (MDHHS 2019) Half-life = 1417 days (3.9 years) (calculated from Zhang et al. [2013] as described above) Volume of distribution = 0.2 L/kg (ATSDR [2018]; Ohmori et al. [2003]) 95th percentile drinking water intake, consumers only, from birth to more than 21 years old (Goeden et al. [2019]) Upper percentile (mean plus two standard deviations) breast milk intake rate (Goeden et al. [2019]) Time-weighted average water ingestion rate from birth to 30-35 years of age (to calculate maternal serum concentration at delivery) (Goeden et al. [2019]) Relative Source Contribution of 50% (0.5) Based on NHANES 95th percentiles for 3-11 (2013-2014) and over 12 years old (2015-2016) participants (CDC 2019)	The Workgroup discussed the Goeden et al. (2019) model which considered full life stage exposure, from fetal exposure, to infant exposure through breastfeeding, and into adulthood. While the model was also developed for a formula-fed infant, the breastfed infant scenario is protective of a formula-fed infant. The Workgroup selected this model for developing drinking water HBVs when the needed inputs were available.
Drinking water HBV	6 ng/L (ppt)	Numeric HBV derived and justified using the above information

	Decision point	Rationale/justification
Critical study	Onishchenko N, Fischer C, Wan Ibrahim WN, Negri S, Spulber S, Cottica D, Ceccatelli S. 2011. Prenatal exposure to PFOS or PFOA alters motor function in mice in a sex-related manner. Neurotox. Res. 19(3):452-61. Koskela A, Finnilä MA, Korkalainen M, Spulber S, Koponen J, Håkansson H, Tuukkanen J, Viluksela M. 2016. Effects of developmental exposure to perfluorooctanoic acid (PFOA) on long bone morphology and bone cell differentiation. Toxicol. Appl. Pharmacol. 301:14-21.	The Workgroup reviewed the available evaluation and selected the ATSDR (2018) critical studies. The Workgroup concluded that the ATSDR position was defensible with respect to range and sensitivity of health endpoints identified and considered in ATSDR (2018).
Description of the critical study	Onishchenko et al.: Pregnant C57BL/6 mice were exposed to 0 or 0.3 mg PFOA/kg/day throughout pregnancy. The critical effects considered were Neurobehavioral effects (decreased number of inactive periods, altered novelty induced activity) at 5-8 weeks of age. Koskela et al.: Pregnant C57BL/6 mice were exposed to PFOA mixed with food at the dose of 0 or 0.3 mg PFOA/kg/day throughout pregnancy. Group of five offspring (female) were sacrificed at either 13 or 17 months of age. The critical effects considered were skeletal alteration such as bone morphology and bone cell differentiation in the femurs and tibias.	The Workgroup selected these developmental delays as most appropriate health endpoint as the mammary gland effects may represent a delay that may not be considered adverse. However, the mammary gland effects may be representative of endocrine effects at doses below the selected POD.
Point of Departure	The average serum concentration was estimated in the mice (8.29 mg/L) using a three-compartment pharmacokinetic model (Wambaugh et al. 2013) using animal species-, strain-, sex-specific parameters.	The Workgroup decided that serum-based points of departure were appropriate for PFAS.
Human equivalent dose	The time-weighted average serum concentration of 8.29 mg/L was converted to the HED using the below equation. $LOAEL_{HED} = (TWA\ serum \times k_e \times V_d) = 0.001163\ mg/kg/day$ $Ke = 0.000825175\ (8.2 \times 10^{-4})$ based on a human serum half-life of 840 days (Bartell et al. 2010) $Vd = 0.17\ L/kg$ (Thompson et al. 2010)	The Workgroup selected the PFOA serum half-life of 840 days (2.3 years) as more relevant for exposure to the general population as this half-life corresponds to data from Bartell et al. (2010) in which 200 individuals (100 men, 100 women) were exposed by drinking PFOA-contaminated water. The Workgroup selected the volume of distribution based on human data, when available.

Uncertainty factors	A total uncertainty factor of 300: • 3 ($10^{0.5}$) for LOAEL to NOAEL • 10 for human variability • 3 ($10^{0.5}$) for animal to human variability • 1 for subchronic to chronic • 3 ($10^{0.5}$) for database deficiencies (endocrine effects)	The Workgroup discussed the use of an uncertainty factor of 3 for use of a LOAEL. They noted that a NOAEL for immune effects was similar to the LOAEL selected and that the selected LOAEL represented less severe effects. The Workgroup concluded that use of the 3 ($10^{0.5}$) would be sufficiently protective. The Workgroup added a database uncertainty factor of 3 ($10^{0.5}$) for deficiencies the database regarding endocrine effects. The Workgroup noted that the mammary gland effects may signal a concern for other low dose endocrine effects.
Toxicity value	3.9 ng/kg/day (3.9 x 10^{-6} mg/kg/day) which corresponds to a serum concentration of 0.028 mg/L Serum levels used in development of these toxicity levels are not meant to indicate a level where health effects are likely. These serum levels are calculated to be at a point where no or minimal risk exists for people drinking water with a certain PFAS.	Human equivalent dose or serum level divided by the total uncertainty factors = toxicity value
Exposure parameters for drinking water HBVs	Breast-fed infant, which is also protective of a formula-fed infant Placental transfer of 87% (MDH 2017) Breastmilk transfer of 5.2% (MDH 2017) Human Serum half-life of 840 days (Bartell et al. 2010) Volume of distribution of 0.17 L/kg (Thompson et al. [2010]) 95th percentile drinking water intake, consumers only, from birth to more than 21 years old (Goeden et al. [2019]) Upper percentile (mean plus two standard deviations) breast milk intake rate (Goeden et al. [2019]) Time-weighted average water ingestion rate from birth to 30-35 years of age (to calculate maternal serum concentration at delivery) (Goeden et al. [2019]) Relative Source Contribution of 50% (0.5) Based on NHANES 95th percentiles for 3-11 (2013-2014) and over 12 years old (2015-2016) participants (CDC 2019)	The Workgroup discussed the Goeden et al. (2019) model which considered full life stage exposure, from fetal exposure, to infant exposure through breastfeeding, and into adulthood. While the model was also developed for a formula-fed infant, the breastfed infant scenario is protective of a formula-fed infant. The Workgroup selected this model for developing drinking water HBVs when the needed inputs were available.
Drinking water HBV	8 ng/L (ppt)	Numeric HBV derived and justified using the above information

Chemical Summary for PFHxA

	Decision point	Rationale/justification
Critical study	Klaunig, J.E., Shinohara, M., Iwai, H., Chengelis, C.P., Kirkpatrick, J.B., Wang, Z., Bruner, R.H., 2015. Evaluation of the chronic toxicity and carcinogenicity of perfluorohexanoic acid (PFHxA) in Sprague-Dawley rats. Toxicol. Pathol. 43 (2), 209–220.	The Workgroup reviewed the Luz et al. (2019) compiled information and development of a toxicity value. The Workgroup was in agreement with Luz et al. (2019) on selection of the chronic study (Klaunig et al. 2015) for toxicity value development.
Description of the critical study	PFHxA was administered to male and female Crl:CD rats (n=60-70/sex/dose) via daily oral gavage for up to 104 weeks. Males: 0, 2.5, 15, and 100 mg/kg/day. Females: 0, 5, 30, and 200 mg/kg/day. Functional observational battery, locomotor activity, ophthalmic, hematology, serum chemistry, and tissue and organ histopathology endpoints were evaluated.	The Workgroup also considered the developmental effects observed in Loveless et al. (2009) one generation reproductive assay. Pup body weight was significantly reduced in the 500 mg/kg/day, resulting in NOAEL of 100 mg/kg/day. Data were not available for Benchmark Dose Modeling for further evaluation.
Point of Departure	Critical effect renal tubular degeneration and renal papillary necrosis in female rats – $BMDL_{10}$ 90.4 mg/kg/day (Luz et al., 2019).	The Workgroup noted that the Benchmark Dose approach is preferred over the use of a NOAEL/LOAEL.
Human equivalent dose	Therefore, the BMD was adjusted by $(80kg/0.45 kg)^{1/4} = 3.65$. The resulting POD_{HED} (90.4 mg/kg/day divided by 3.65) = 24.8 mg/kg/day. (Luz et al., 2019).	The Workgroup discussed the description of the Benchmark Dose modeling conducted by Luz et al. (2019) and concluded the modeling was adequate for use. The Workgroup did not conduct their own Benchmark Dose modeling. The Workgroup took into consideration the available serum half-life data presented in Russell et al. (2013) and concluded that, unlike most PFAS, allometric scaling could be supported.
Uncertainty factors	Total uncertainty factor of 300: • 1 for LOAEL to NOAEL • 10 for human variability • 3 ($10^{0.5}$) for animal to human variability • 1 for subchronic to chronic • 10 for database deficiencies – lack of additional chronic toxicity studies and no additional developmental data in a second species, and immune and thyroid endpoints	The Workgroup discussed the uncertainty factors and selected an uncertainty factor of 10 for database deficiencies. Several items noted were that the available studies were largely in one species, with no mouse or non-human primate data, and that there was insufficient information addressing immune or thyroid endpoints.
Toxicity value	83,000 ng/kg/day (8.3 mg/kg/day)	Human equivalent dose divided by the total uncertainty factor = toxicity value

Exposure parameters for drinking water HBVs	95th percentile of water intake for consumers only (direct and indirect consumption) for adults (>21 years old) of 3.353 L/day, per Table 3-1, USEPA Exposure Factors Handbook, 2019. An adult body weight of 80 kilograms was used (Table 8-1, USEPA 2011b). A default Relative Source Contribution of 20% was included.	The Workgroup discussed the use of an upper percentile water intake. The 95th percentile for consumers only was selected as it would protect those drinking larger amounts of water. As no human serum data were available to assess the population's exposure to PFHxA from sources other than drinking water, a default Relative Source Contribution of 20% was selected consistent with USEPA (2000) guidance. The Workgroup evaluated the protectiveness of the renal tubular degeneration and renal papillary necrosis in relation to the reduced pup weights observed in Loveless et al. (2009). Available data did not support Benchmark Dose Modeling for further evaluation of Loveless et al. (2009) data.
Drinking water HBV	400,000 ng/L (ppt) (400 micrograms per Liter or parts per billion)	Numeric HBV derived and justified using the above information in the following equation: $$HBV = \frac{RSC \times Toxicity\ value \times Body\ weight}{Water\ intake}$$

	Decision point	Rationale/justification
Critical study	Dong GH, Zhang YH, Zheng L, Liu W, Jin YH, He QC. (2009). Chronic effects of perfluorooctanesulfonate exposure on immunotoxicity in adult male C57BL/6 mice. Arch Toxicol. 83(9):805-815.	The Workgroup discussed the available evaluations, particularly MDH (2019) and New Jersey Department of Environmental Protection (NJDEP) (2018), and selected a critical study with an immune system functional assay rather than observational data.
Description of the critical study	Adult male C57BL/6 mice were exposed to PFOS daily via oral gavage for 60 days with 0, 0.5, 5, 25, 50 or 125 mg/kg total administered dose, equivalent to 0 or approximately 0.008, 0.08, 0.4, 0.8 or 2.1 mg/kg/day. The NOAEL for suppression of plaque forming cell response and increase in liver mass was 0.5 mg/kg total administered dose which corresponded to a serum concentration of 0.674 mg/L.	The Workgroup acknowledged that immune effects in mice were seen at lower doses in Peden-Adams et al. (2008). Serum concentrations from Peden-Adams et al. (2008) were well below both the NOAEL and LOAEL serum concentrations measured from several other studies as described by Pachkowski et al. (2019) and may be an outlier in the database.
Point of Departure	The NOAEL for suppression of plaque forming cell response and increase in liver mass was 0.5 mg/kg total administered dose which corresponded to a serum concentration of 0.674 mg/L.	The Workgroup decided that serum-based points of departure were appropriate for PFAS.
Human equivalent dose	The serum concentration of 0.674 mg/L was converted to the HED using the below equation (based on ATSDR 2018). $NOAEL_{HED} = (TWA\ serum \times k_e \times V_d) = 0.0000866$ mg/kg/day $K_e = 0.000558539$ (5.5×10^{-4}) based on a human serum half-life of 1241 days (Li et al. 2018) $V_d = 0.23$ L/kg (Thompson et al. 2010)	The Workgroup selected the serum half-life from a non-occupationally exposed population as it is closer to the general population's exposure. The Workgroup selected volume of distributions based on human data, when available.
Uncertainty factors	A total uncertainty factor of 30: • 1 for LOAEL to NOAEL • 10 for human variability • 3 ($10^{0.5}$) for animal to human difference (toxicodynamics) • 1 for subchronic to chronic • 1 for database deficiencies	The Workgroup reviewed the uncertainty factors selected by MDH (2019) and adjusted the database uncertainty factor to 1 based on the critical study selection. With consideration of the selected immunotoxicity endpoint, the database uncertainty factor of 1 was supported by the assessments by USEPA (2016), NJDEP (2018), ATSDR (2018) and New Hampshire (2019).

Toxicity value	2.89 ng/kg/day (2.89 x 10^{-6} mg/kg/day) which corresponds to a serum concentration of 0.022 µg/ml Serum levels used in development of these toxicity levels are not meant to indicate a level where health effects are likely. These serum levels are calculated to be at a point where no or minimal risk exists for people drinking water with a certain PFAS.	Human equivalent dose or serum level divided by the total uncertainty and modifying factors = toxicity value
Exposure parameters for drinking water HBV	Breast-fed infant, which is also protective of a formula-fed infant Placental transfer of 43% (MDHHS 2019) Breastmilk transfer of 1.3% (MDHHS 2019) Human serum half-life of 1241 days (3.2 years) (Li et al. 2018) Volume of distribution of 0.23 L/kg (Thompson et al. 2010) 95th percentile drinking water intake, consumers only, from birth to more than 21 years old (Goeden et al. [2019]) Upper percentile (mean plus two standard deviations) breast milk intake rate (Goeden et al. [2019]) Time-weighted average water ingestion rate from birth to 30-35 years of age (to calculate maternal serum concentration at delivery) (Goeden et al. [2019]) Relative Source Contribution of 50% Based on NHANES 95th percentiles for 3-11 (2013-2014) and over 12 years old (2015-2016) participants (CDC 2019)	The Workgroup discussed the Goeden et al. (2019) model which considered full life stage exposure, from fetal exposure, to infant exposure through breastfeeding, and into adulthood. While the model was also developed for a formula-fed infant, the breastfed infant scenario is protective of a formula-fed infant. The Workgroup selected this model for developing drinking water HBVs when the needed inputs were available.
Drinking water HBV	16 ng/L (ppt)	Numeric HBV derived and justified using the above information

Chemical Summary for PFHxS

	Decision point	Rationale/justification
Critical study	NTP 2018 TOX-96: Toxicity Report Tables and Curves for Short-term Studies: Perfluorinated Compounds: Sulfonates and personal communication between MDH and NTP project manager Dr. Chad Blystone (as cited in the HRA Toxicology Review Worksheet for PFHxS, last revised 3/8/2019)	The Workgroup reviewed available evaluations and focused on the ones from Minnesota Department of Health (2019) and ATSDR (2018). In both evaluations, thyroid endpoints were selected. The Workgroup discussed Chang et al. (2018) and concluded that the health outcome (reduction in litter size) was a marginal effect.
Description of the critical study	28-day oral toxicity study in Sprague Dawley rats (NTP, 2018). PFHxS was administered via daily gavage at the following doses for 28 continuous days: Male rats: 0, 0.625, 1.25, 2.5, 5 or 10 mg/kg/day Male rats mean measured plasma levels: 0.102, 66.76, 92.08, 129.0, 161.7, and 198.3 µg/ml Female rats: 0, 3.12, 6.25, 12.5, 25, 50 mg/kg/day Female rats mean measured plasma levels: 0.1754, 37.03, 50.41, 63.82, 83.82, and 95.51 µg/ml n=10/sex/dose Critical effect: decreased serum free thyroxin (T_4) levels was observed in adult male rats at the lowest PFHxS dose administered (0.625 mg/kg/day) Co-critical effects: decreased free and total T_4, triiodothyronine (T_3), and changes in cholesterol levels and increased hepatic focal necrosis	The Workgroup selected this thyroid endpoint as it was a measure of a clinical or functional effect rather than observational.
Point of Departure	POD of 32.4 mg/L serum concentration for male rats based on $BMDL_{20}$. A BMR of 20% was used in the BMD modeling based on clinical and toxicological knowledge regarding adverse outcomes associated with decreases in circulating thyroid hormones. MDH stated that 20% provided a more statistically reliable and biologically significant BMR. (MDH conducted Benchmark Dose modeling and provided modeling run data in the HRA Toxicology Review Worksheet for PFHxS, last revised 3/8/2019.	The Workgroup decided that serum-based points of departure were appropriate for PFAS. Although the Workgroup concluded that the Chang et al. (2018) health outcome was marginal, they did note that the serum concentration at the NOAEL for Chang et al. (2018) was equivalent to the serum concentration at the selected POD.
Human equivalent dose	The POD (32.4 mg/L) was multiplied by a toxicokinetic adjustment based on the chemical's specific clearance rate of 0.000090 L/kg-d (Vd = 0.25 L/kg [Sundstrom et al. [2012], half-life = 1935 days [Li et al. 2018]) for a human equivalent dose of 0.00292 mg/kg/day.	The Workgroup selected the human serum half-life from Li et al. (2018) as it was a non-occupational population drinking water with elevated PFAS.

Uncertainty factors	Total Uncertainty Factor of 300 • 1 for LOAEL to NOAEL • 10 for human variability • 3 ($10^{0.5}$) for animal to human variability (toxicodynamic differences) • 1 for subchronic to chronic • 10 for database deficiencies - to address concerns for early life sensitivity and lack of 2-generation or immunotoxicity studies	The Workgroup reviewed the uncertainty factors used by MDH (2019) and concluded that the database uncertainty factor of 10 was very defensible in this situation, especially for the lack of information on early-life sensitivity.
Toxicity value	9.7 ng/kg/day (9.7 x 10^{-6} mg/kg/day) which corresponds to a serum concentration of 0.11 µg/ml Serum levels used in development of these toxicity levels are not meant to indicate a level where health effects are likely. These serum levels are calculated to be at a point where no or minimal risk exists for people drinking water with a certain PFAS.	Human equivalent dose or serum level divided by the total uncertainty factors = toxicity value
Exposure parameters for drinking water HBV	Breast-fed infant, which is also protective of a formula-fed infant Placental transfer of 80% (MDHHS 2019) Breastmilk transfer of 1.2% (MDHHS 2019) Human serum half-life of 1935 days (Li et al. [2018]) Volume of distribution of 0.25 L/kg (MDH [2019] based on Sundstrom et al. [2012]) 95th percentile drinking water intake, consumers only, from birth to more than 21 years old (Goeden et al. [2019]) Upper percentile (mean plus two standard deviations) breast milk intake rate (Goeden et al. [2019]) Time-weighted average water ingestion rate from birth to 30-35 years of age (to calculate maternal serum concentration at delivery) (Goeden et al. [2019]) Relative Source Contribution of 50% (0.5) Based on NHANES 95th percentiles for 3-11 (2013-2014) and over 12 years old (2015-2016) participants (CDC 2019)	The Workgroup discussed the Goeden et al. (2019) model which considered full life stage exposure, from fetal exposure, to infant exposure through breastfeeding, and into adulthood. While the model was also developed for a formula-fed infant, the breastfed infant scenario is protective of a formula-fed infant. The Workgroup selected this model for developing drinking water HBVs when the needed inputs were available.
Drinking water HBV	51 ng/L (ppt)	Numeric HBV derived and justified using the above information

	Decision point	Rationale/justification
Critical study	Feng, X; Cao, X; Zhao, S; Wang, X; Hua, X; Chen, L; Chen, L. (2017). Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring. Toxicol Sci 155: 409-419.	The Workgroup evaluated available agency decision documents and selected the study associated with the draft USEPA (2018) PFBS toxicity value based on thyroid effects. The kidney effects identified in the draft USEPA (2018) toxicity assessment were identified as a potentially compensatory response. The thyroid effects were identified as having greater functional significance.
Description of the critical study	PFBS was orally administered to pregnant ICR mice (n=30/dose) at doses of 0, 50, 200, and 500 mg/kg/day from gestational day (GD) 1 to GD20. Dams (F0) and female offspring (F1) from each dose group were subsequently evaluated for 1) growth and development, 2) hormone levels, and 3) serum PFBS levels. The critical effect is decreased serum total thyroxine (T_4) in newborn (PND 1) mice. Selection of total T_4 as the critical effect is based on a several key considerations that account for cross-species correlations in thyroid physiology and hormone dynamics particularly within the context of a developmental life stage.	
Point of Departure	A POD of 28.19 mg/kg/day ($BMDL_{20}$) for decreased serum total T_4 in newborn (PND 1) mice was selected	The Workgroup noted that a Benchmark Dose approach is preferable to a NOAEL/LOAEL. The Workgroup noted that the thyroid point of departure would be protective of the kidney effects as well. The draft USEPA (2018) toxicity assessment contained administered doses from the individual studies converted to HED doses using study-specific Dosimetric Adjustment Factors (DAF; not reported for each dosing group) derived using allometric scaling ($BW^{3/4}$) prior to BMD model analysis. An example DAF calculation was provided in Table 8 of the draft USEPA (2018) toxicity assessment: dose x DAF = 200 x 0.149 = 29.9 mg/kg/day, where DAF equals $(BW_{animal}^{1/4})/(BW_{human}^{1/4}) = 0.0399^{1/4} \div 80^{1/4} = 0.149$ The POD_{HED} = 4.2 mg/kg/day for decreased serum total T_4 in newborn (PND 1) mice (USEPA 2018). The USEPA POD_{HED} of 4.2 was divided by 0.149 (USEPA example DAF) to obtain a $BMDL_{20}$ of 28.19 mg/kg/day.

Human equivalent dose	The BMDL$_{20}$-HED is 0.0892 mg/kg/day. The BMDL$_{20}$ of 28.19 mg/kg/day was divided by the Dose Adjustment Factor of 316 (human serum half-life/female mouse serum half-life = 665 hours/2.1 hours = 316) (MDH, 2017).	The Workgroup evaluated the half-life based Dose Adjustment Factor used by the Minnesota Department of Health (MDH) (2017). As that allowed conversion of the point of departure to a human equivalent dose using chemical-specific information, the Workgroup selected this approach over the allometric scaling used in the draft USEPA (2018) PFBS toxicity assessment.
Uncertainty factors	The total uncertainty factor is 300. • 1 for LOAEL to NOAEL • 10 for human variability • 3 ($10^{0.5}$) for animal to human variability • 1 for subchronic to chronic • 10 for database deficiencies, for the lack of neurodevelopmental, immunotoxicological, and chronic studies	The Workgroup discussed the uncertainty factors selected in the draft USEPA (2018) toxicity assessment and supported their use.
Toxicity value	300 ng/kg/day (0.0003 mg/kg/day)	Human equivalent dose or serum level divided by the total uncertainty factors = toxicity value
Exposure parameters for drinking water HBV	95th percentile of water intake for consumers only (direct and indirect consumption) for infants (birth to <1 year old) of 1.106 L/day, per Table 3-1, USEPA Exposure Factors Handbook, 2019. An infant body weight of 7.8 kilograms was used and represents a time-weighted average for birth to 1 year old (Table 8-1, USEPA 2011). A default Relative Source Contribution of 20% was included.	The Workgroup discussed the use of an upper percentile water intake. The 95th percentile for consumers only was selected as it would protect those drinking larger amounts of water. As insufficient human serum data was available to assess the population's exposure to PFBS from sources other than drinking water, a default Relative Source Contribution of 20% was selected consistent with USEPA (2000) guidance.
Drinking water HBV	420 ng/L (ppt)	Numeric HBV derived and justified using the above information in the following equation: $$HBV = \frac{RSC \times Toxicity\ value \times Body\ weight}{Water\ intake}$$

	Decision point	Rationale/justification
Critical study	Oral (Gavage) Reproduction/ Developmental Toxicity Study in Mice (OECD TG 421; modified according to the Consent Order) DuPont-18405-1037 (2010) (also contains 90-day toxicity study information and outcomes - that information is not described here)	The Workgroup evaluated the North Carolina Department of Health and Human Services (2017) and draft USEPA (2018) information. The draft USEPA (2018) evaluation was identified as providing a more in-depth and robust analysis and approach.
Description of the critical study	In a combined oral gavage reproductive/developmental toxicity study in mice with HFPO dimer acid ammonium salt, the test compound was administered by oral gavage to Crl:CD1(ICR) mice (25/sex/group) at doses of 0, 0.1, 0.5, or 5 mg/kg/day, according to a modified OECD TG 421. Parental F0 males were dosed 70 days prior to mating and throughout mating through 1 day prior to scheduled termination. Parental F0 females were dosed for 2 weeks prior to pairing and were dosed through LD 20. F1 animals (offspring) were dosed daily beginning on PND 21 through PND 40. At 0.5 mg/kg/day, liver effects (increased absolute and relative weight and histopathologic findings) were reported in both males and females. At 5 mg/kg/day, male and female F1 pups exhibited lower mean BWs at PNDs 4, 7, 14, 21, and 28. Male F1 pups continued to exhibit lower mean BWs at PNDs 35 and 40. The USEPA (2018) identified additional developmental effects (delays in balanopreputial separation and vaginal patency) that occurred at the same dose level, but the biological significance of these effects are equivocal as described. NOAEL (F0) = 0.1; LOAEL (F0) = 0.5 for liver effects (single-cell necrosis in males, and increased relative liver weight in both sexes). NOAEL (F1) = 0.5 for developmental effects (decreased pup weights).	The Workgroup noted that while primarily industry-funded studies are the only ones available, they followed recognized testing guidelines and/or were published following external peer-review. These studies appear to be sufficient for developing values.

Point of Departure	$BMDL_{10}$ = 0.15 mg/kg/day for liver single cell necrosis in parental males (DuPont-18405-1037, 2010).	The Workgroup noted that the Benchmark Dose approach is preferred over the use of a NOAEL/LOAEL. USEPA (2018) evaluated the relevance of this endpoint in humans and noted that, per the Hall criteria (Hall et al., 2012) liver effects accompanied by effects such as necrosis or inflammation, among others, are indicative of liver tissue damage (USEPA, 2018). While some liver effects in rodents are mediated through PPARα and may be less relevant to humans, available information indicates that liver single cell necrosis may be mediated by a number of processes and pathways. In PPARα-mediated rodent hepatocarcinogenesis, liver necrosis is not a key event. (DeWitt and Belcher, 2018)
Human equivalent dose	A candidate POD_{HED} was derived from the $BMDL_{10}$ for liver effects using a $BW^{3/4}$ allometric scaling approach. A BW_a of 0.0372 kg was identified as the mean BW of the F0 male mouse controls. A BW_h of 80 kg for humans was selected. The resulting DAF for the allometric scaling of doses from mice to humans is 0.15. Using the $BMDL_{10}$ of 0.15 mg/kg/day to complete the calculation results in a POD_{HED} for single-cell necrosis of the liver from DuPont-18405-1037 (2010) of 0.023 mg/kg/day (USEPA 2018).	The Workgroup noted that a toxicokinetic adjustment from the point of departure to human equivalent dose would provide a chemical-specific conversion. However, no chemical-specific data on human serum half-life was available that would allow this conversion. Allometric scaling, per USEPA (2011a) guidance, was used.
Uncertainty factors	Total Uncertainty Factor of 300 • 1 for use of a LOAEL to NOAEL • 10 for human variability • 3 ($10^{0.5}$) for animal to human variability • 3 ($10^{0.5}$) for subchronic-to-chronic • 3 ($10^{0.5}$) for database deficiencies, including lack of epidemiological, and developmental and immunotoxicological studies in laboratory animals	The Workgroup evaluated the uncertainty factors selected by USEPA (2018). Given the deficiencies in the database, including a lack of epidemiological studies and developmental and immunotoxicological in laboratory animals, a database uncertainty factor of 3 was retained. In conjunction with the deficiencies covered by the database uncertainty factor, the subchronic to chronic uncertainty factor of 3 was identified as sufficient.
Toxicity value	77 ng/kg/day (7.7 x10-5 mg/kg/day)	Human equivalent dose or serum level divided by the total uncertainty = toxicity value

Exposure parameters for drinking water HBV	95th percentile of water intake for consumers only (direct and indirect consumption) for adults (>21 years old) of 3.353 L/day, per Table 3-1, USEPA Exposure Factors Handbook, 2019. An adult body weight of 80 kilograms was used (Table 8-1, USEPA 2011b). A default Relative Source Contribution (RSC) of 20% was included.	The Workgroup discussed the use of an upper percentile water intake. The 95th percentile for consumers only was selected as it would protect those drinking larger amounts of water. As no human serum data was available to assess the population's exposure to GenX from sources other than drinking water, a default Relative Source Contribution of 20% was selected consistent with USEPA (2000) guidance. The Workgroup evaluated the protectiveness of adult exposure in combination with the point of departure. The NOAEL for developmental effects described above was at a dose five times higher than the NOAEL for liver necrosis effects. As a drinking water value based on the developmental NOAEL would be higher than the level presented below, the Workgroup decided that the drinking water HBV below based on liver effects would be sufficiently conservative to be protective of infant exposure.
Drinking water HBV	370 ng/L (ppt)	Numeric HBV derived and justified using the above information in the following equation: $$HBV = \frac{RSC \times Toxicity\ value \times Body\ weight}{Water\ intake}$$

Rationale for Individual HBVs

While there are on-going discussions regarding the grouping of multiple PFAS into one drinking water value, there is no consensus from the scientific community on which PFAS should be grouped or the basis of that grouping. Grouping methods that have been applied include combining multiple PFAS into one number based on known or assumed toxicity, carbon chain length, and/or biological half-life (simple addition) as well as the use of relative ability of the grouped PFAS to lead to a comparable health endpoint (toxic equivalency); the latter approach being similar to those used for dioxins, furans, and coplanar polychlorinated biphenyls.

There is, however, scientific agreement that the long-chain PFAS (eight carbons and above for carboxylates and six carbons and above for sulfonates) have similar toxicity. Based on the similarity in toxicity for the long-chain PFAS, the Workgroup recommends use of the HBV for PFNA (6 ng/L [ppt]) as a screening level for all other long-chain PFAS included on the USEPA Method 537.1 analyte list for which the Workgroup did not develop an individual HBV. This screening level should not be used to evaluate the risk of developing health effects, but as a screening tool for EGLE/public water supplies to use for decision making.

Adverse health effects of long chain (six-carbon perfluorosulfonic acids or eight-carbon perfluorocarboxylic acids) have been established in epidemiological and laboratory animal model studies. These adverse health effects include kidney and testicular cancer, elevated serum cholesterol, endocrine effects, immune effects, and reproductive effects (ATSDR, 2018). These effects are supported by studies of different human populations exposed to a few or to many PFAS, including those from populations of high PFAS exposure and the general population and demonstrate that many different long-chain PFAS can produce similar adverse health effects in exposed humans. However, while not all long-chain PFAS have robust data available for the development of a HBV, the totality of evidence indicates that long-chain PFAS in drinking water may pose risks of adverse health effects.

While health concerns are based on the total exposure to PFAS across many sources, because drinking water is the predominant source of exposure for many people consuming contaminated water, it remains the focus for health-based regulation based on current knowledge. Therefore, monitoring of drinking water should continue and be based on levels that will be protective for exposure to all PFAS.

At this time, it is recommended that the proposed HBV for PFNA be used as a screening level for the long chain PFAS included in USEPA Method 537.1 that may be found in drinking water that are not covered by an individual PFAS HBVs as presented in the Summary Table of Drinking Water HBVs.

Summary of Conclusions

Specific PFAS	Drinking Water Health-based Value	Chemical Abstract Services Registry Number (CASRN)
PFNA	6 ng/L (ppt)	375-95-1
PFOA	8 ng/L (ppt)	335-67-1
PFHxA	400,000 ng/L (ppt)	307-24-4
PFOS	16 ng/L (ppt)	1763-23-1
PFHxS	51 ng/L (ppt)	355-46-4
PFBS	420 ng/L (ppt)	375-73-5
GenX	370 ng/L (ppt)	13252-13-6

For all other PFAS on the USEPA Method 537.1 analyte list, the Workgroup recommendation is to use the lowest long-chain (eight carbons and above for carboxylates and six carbons and above for sulfonates) HBV of 6 ppt, which is the HBV for PFNA. Those other long-chain PFAS included in USEPA Method 537.1 are: NEtFOSAA (CASRN: 2991-50-6); NMeFOSAA (CASRN: 2355-31-9); PFDA (CASRN: 335-76-2); PFDoA (CASRN: 307-55-1); PFTA (CASRN: 376-06-7); PFTrDA (CASRN: 72629-94-8); and PFUnA (CASRN: 2058-94-8).

As shown in Figure 1 (below), the drinking water values for PFOS and PFOA have gone down over time. This is a reflection of the evolving science, both the ever-increasing knowledge gained from published toxicology and epidemiology studies and the risk assessments for development of toxicity values and drinking water values. Information continues to become available on multiple PFAS and as there are thousands of PFAS, new information will likely become available for many years to come. It is quite possible that the same trend demonstrated in Figure 1 will be seen for other PFAS, where drinking water values become lower over time and that new values could be developed within a few years' time. As described in the Challenges and Limitations section, along with use of current scientific data, development of drinking water values includes a certain amount of scientific judgement informed from the scientific knowledgebase. It is that combination of scientific judgement and data that ultimately informs the development of drinking water values. With emerging contaminants like PFAS, rapid availability of data drives public health protective actions and drinking water values.
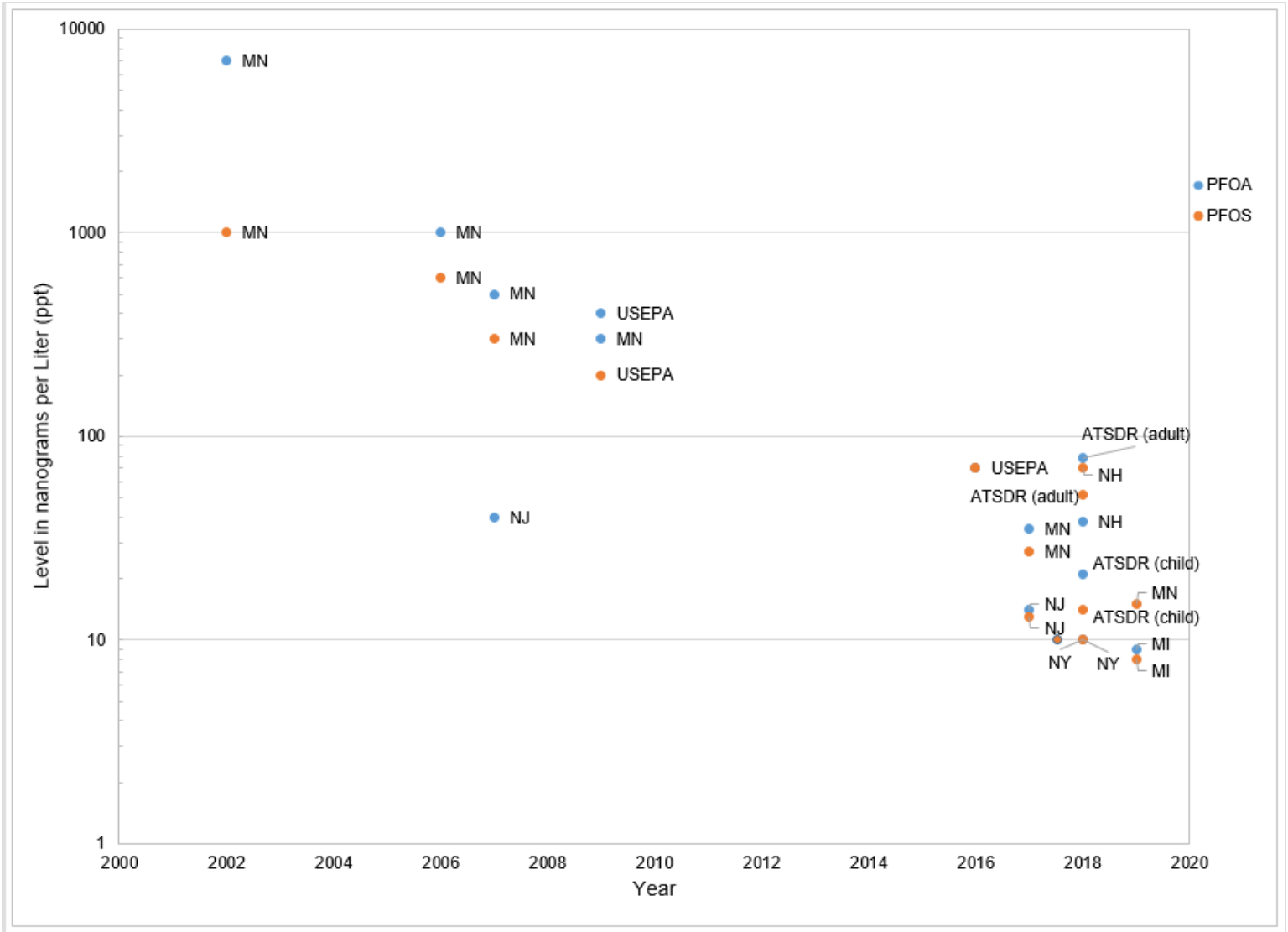
PFOS and PFOA

Figure 1: Screening Levels, Health-Based Values, and Regulatory Standards for PFOS and PFOA Over a 20-Year Timeframe.

The numbers in Figure 1 are the various screening levels, HBVs, and regulatory standards developed by various agencies and states over time as of June 2019. It does not include the agencies that include multiple PFAS into a single value. This should not be considered an exhaustive list of all PFAS drinking water values available, and values may be updated, and additional values will likely become available. The Michigan values included in Figure 1 are the MPART Human Health Workgroup public health drinking water screening levels.

Concluding Remarks

The Workgroup would like to commend the State of Michigan for addressing PFAS concerns with unusual rigor, openness, and reliance on independent scientific guidance. From the beginning of the recognition of environmental and public health issues related to PFAS, the State of Michigan has been at the forefront nationally in assessing the scope of the contamination, intervening to mitigate exposure, and monitoring the evidence to guide policy. The statewide survey of drinking

water supplies was highly unusual if not unique relative to other areas, and the process of developing Maximum Contaminant Levels as rigorous as any in the nation. By engaging experts from outside the state agencies to complement the considerable expertise of the staff in the Michigan Departments of Health and Human Services and Environment, Great Lakes, and Energy, they have demonstrated their commitment to following the evidence through to developing sound policy.

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Appendix A: Acronym List

ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	lower confidence limit on the benchmark dose
BMR	benchmark response
BW	body weight
BWa	body weight animal
BWh	body weight human
CDC	Centers for Disease Control and Prevention
DAF	dosimetric adjustment factor
EGLE	Environment, Great Lakes, and Energy (Michigan Department of)
GD	gestational day
GenX	perfluoro-2-propoxypropanoic acid
HBV	health-based value
HED	human equivalent dose
HFPO	hexafluoropropylene oxide
HRA	health risk assessment
kg	kilogram
L	liter
LD	lactation day
LHA	lifetime health advisory
LOAEL	lowest observed adverse effect level
MCL	Maximum Contaminant Level
MDH	Minnesota Department of Health
MDHHS	Michigan Department of Health and Human Services
mg	milligram
MI	Michigan
ml	milliliter
MPART	Michigan PFAS Action Response Team
µg	microgram
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NJDEP	New Jersey Department of Environmental Protection
NOAEL	no observed adverse effect level
OECD	Organization for Economic Co-operation and Development
PFAS	per- and polyfluoroalkyl substances
PFBS	perfluorobutane sulfonic acid
PFHxA	perfluorohexanoic acid
PFHxS	perfluorohexane sulfonic acid
PFNA	perfluorononanoic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonic acid
PND	postnatal day
POD	point of departure
POD_{HED}	point of departure human equivalent dose
PPAR	peroxisome proliferator-activated receptor
ppt	parts per trillion
RfD	reference dose
RSC	relative source contribution
TWA	time weighted average
UF	uncertainty factor
USEPA	United States Environmental Protection Agency

Motion

Motion to establish a Science Advisory Workgroup with the Charge described below, comprised of external members with expertise in toxicology, epidemiology, and risk assessment, and further to authorize the chairperson of MPART to finalize the appointments in consultation with MPART members.

Preamble

On March 26, 2019, Governor Whitmer directed the Michigan PFAS Action Response Team (MPART) to further protect public health and the environment, by forming a Science Advisory Workgroup to "review both existing and proposed health-based drinking water standards from around the nation to inform the rule making process for appropriate Maximum Contaminant Levels for Michigan..." Toward this objective, the Science Advisory Workgroup shall make numeric recommendation(s) to MPART for those per- and polyfluoroalkyls substances (PFAS) for which adequate information exists.

Charge

The Science Advisory Workgroup shall:

1. For the PFAS listed in USEPA Method 537.1, review all existing and proposed national- and state-derived PFAS drinking water standards and identify the most scientifically defensible non-cancer or cancer-based public health toxicity values available for each individual PFAS chemical family member, or combination thereof, for which the Science Advisory Workgroup determines that adequate information exists. Provide written justification that shall include, but not be limited to, the basis for the selection of the primary study, critical effect identification, point of departure determination, evaluation of all uncertainty and/or modification factors applied, and the non-cancer or cancer-based toxicity value derivation.
2. Review all existing and proposed national- and state-derived PFAS drinking water standards and identify the most scientifically defensible exposure assessment and risk evaluation methodology for each individual PFAS chemical family member, or combination thereof, for which the Science Advisory Workgroup determines that adequate information exists. Provide written justification that shall include, but not be limited to, selection of the most appropriate receptor(s) and identification of all appropriate exposure assumptions for the receptor(s).
3. Identify the most appropriate and scientifically defensible combination of each specific PFAS toxicity value and exposure assessment and risk evaluation methodology, including consideration of relative source contribution, from which to derive a health-based drinking water value for each individual PFAS chemical family member, or combination thereof, for which the Science Advisory Workgroup determines that adequate information exists.
4. Provide to MPART no later than July 1, 2019, a report recommending scientifically-defensible numeric health-based values to inform the rulemaking process for Maximum Contaminant Levels for each individual PFAS chemical family member, or combination thereof, with written justification for the calculation methodology and each input into used in the methodology by the Science Advisory Workgroup.

End

Appendix C: USEPA Method 537.1 Analyte List

Analyte Name*	Acronym	Fluorinated Carbon Chain Length	Chemical Abstract Services Registry Number (CASRN)
Perfluorotetradecanoic acid	PFTeA	C_{14}	376-06-7
Perfluorotridecanoic acid	PFTriA	C_{13}	72629-94-8
Perfluorododecanoic acid	PFDoA	C_{12}	307-55-1
Perfluoroundecanoic acid	PFUnA	C_{11}	2058-94-8
Perfluorodecanoic acid	PFDA	C_{10}	335-76-2
Perfluorononanoic acid	PFNA	C_9	375-95-1
Perfluorooctanoic acid	PFOA	C_8	335-67-1
Perfluoroheptanoic acid	PFHpA	C_7	375-85-9
Perfluorohexanoic acid	PFHxA	C_6	307-24-4
Perfluorooctanesulfonic acid	PFOS	C_8	1763-23-1
Perfluorohexanesulfonic acid	PFHxS	C_6	355-46-4
Perfluorobutanesulfonic acid	PFBS	C_4	375-73-5
2-(N-Ethylperfluorooctanesulfonamido) acetic acid	N-EtFOSAA	C_8	2991-50-6
2-(N-Methylperfluorooctanesulfonamido) acetic acid	N-MeFOSAA	C_8	2355-31-9
Hexafluoropropylene oxide dimer acid	HFPO-DA (GenX)	C_6	13252-13-6[a]
11-chloroeicosafluoro-3-oxaundecane-1-sulfonic acid	11Cl-PF3OUdS	C_{10}	763051-92-9[b]
9-chlorohexadecafluoro-3-oxanone-1-sulfonic acid	9Cl-PF3ONS	C_8	756426-58-1[c]
4,8-dioxa-3H-perfluorononanoic acid	ADONA	C_7	919005-14-4[d]

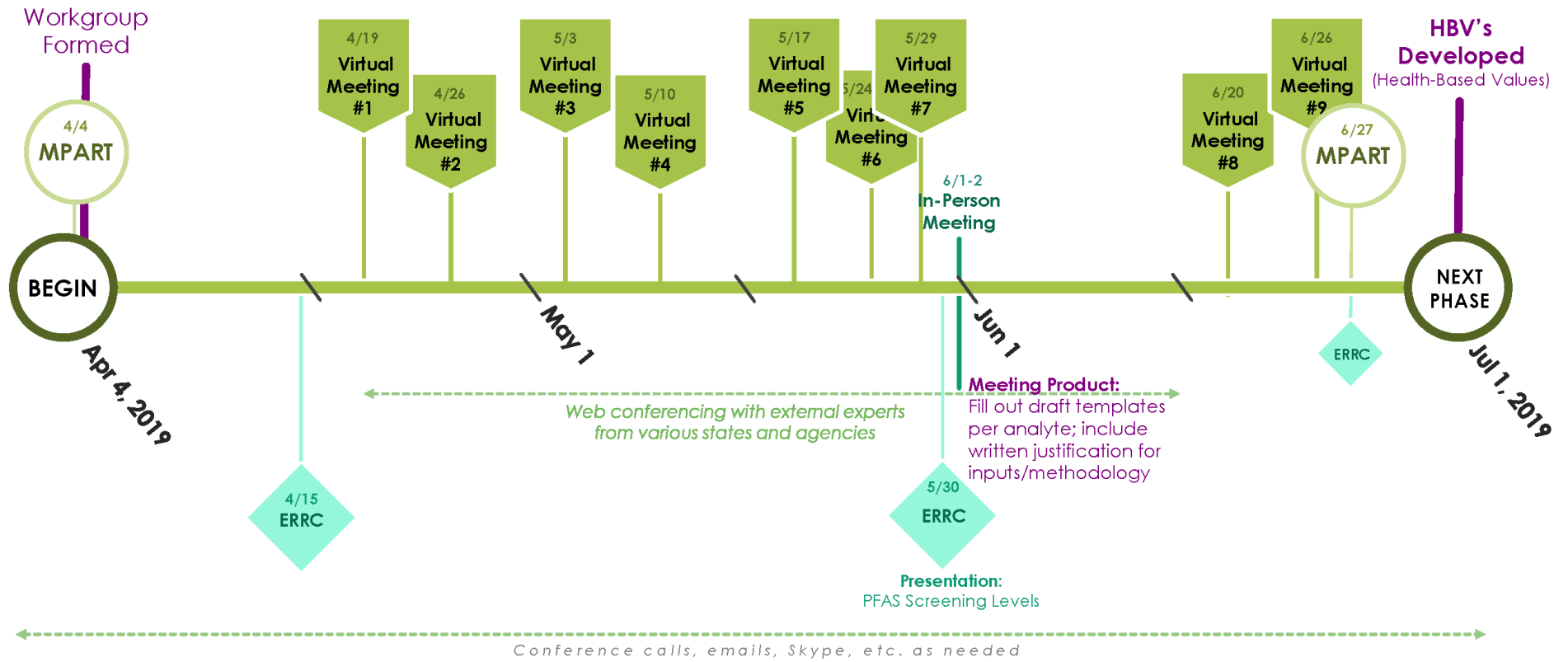[a] HFPO-DA is one component of the GenX processing aid technology.
[b] 11Cl-PF3OUdS is available in salt form (e.g. CASRN of potassium salt is 83329-89-9).
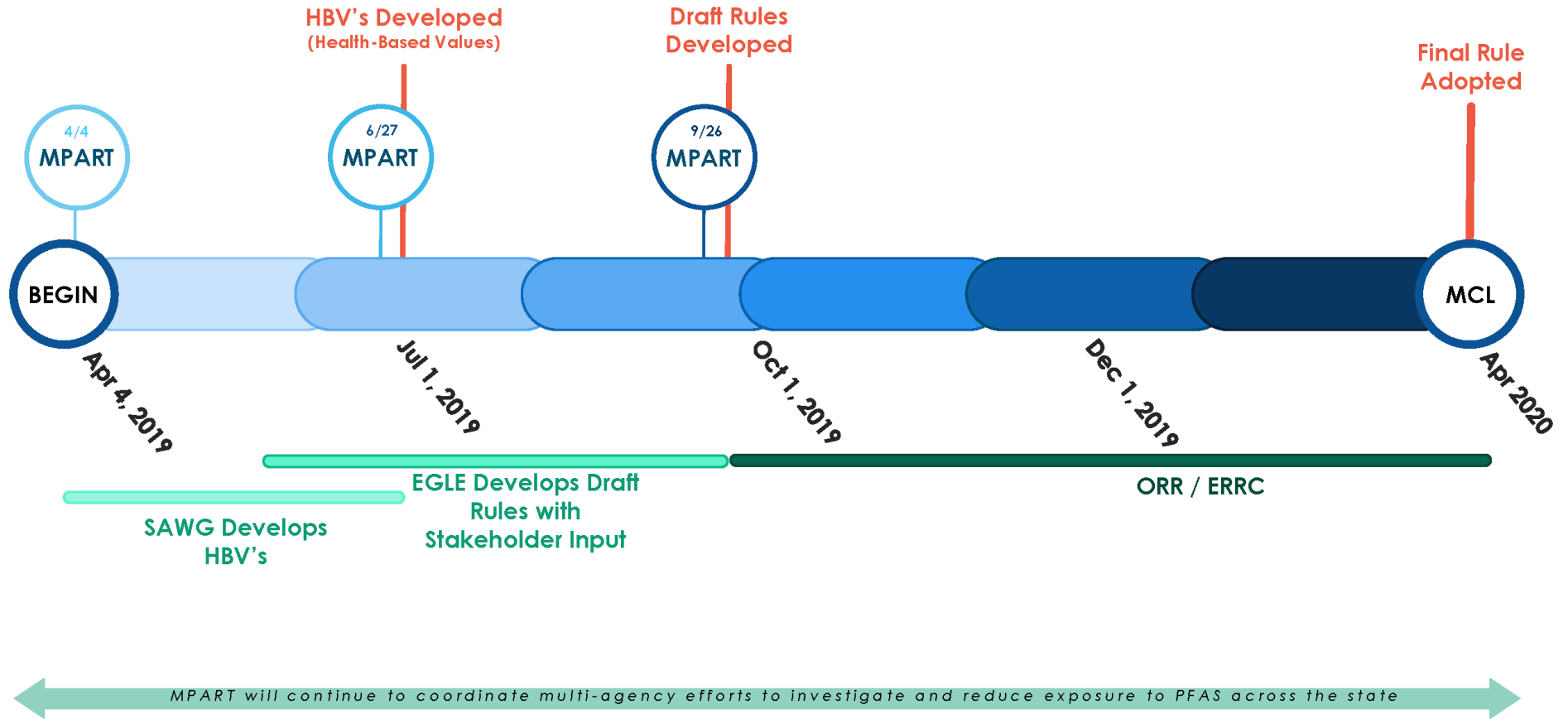[c] 9Cl-PF3ONS analyte is available in salt form (e.g. CASRN of potassium salt is 73606-19-6)
[d] ADONA is available as the sodium salt (no CASRN) and the ammonium salt (CASRN is 958445-448).
* Some PFAS are commercially available as ammonium, sodium, and potassium salts. This method measures all forms of the analytes as anions while the counterion is inconsequential. Analytes may be purchased as acids or as any of the corresponding salts.

Appendix D: Timeline for the Science Advisory Workgroup's Development of Drinking Water HBVs

Workgroup Formed

HBV's Developed
(Health-Based Values)

4/4 MPART

BEGIN

Apr 4, 2019

4/15 ERRC

4/19 Virtual Meeting #1

4/26 Virtual Meeting #2

May 1

5/3 Virtual Meeting #3

5/10 Virtual Meeting #4

5/17 Virtual Meeting #5

5/24 Virtual Meeting #6

5/29 Virtual Meeting #7

6/1-2 In-Person Meeting

5/30 ERRC

Presentation: PFAS Screening Levels

Web conferencing with external experts from various states and agencies

Jun 1

Meeting Product:
Fill out draft templates per analyte; include written justification for inputs/methodology

6/20 Virtual Meeting #8

6/26 Virtual Meeting #9

6/27 MPART

ERRC

NEXT PHASE

Jul 1, 2019

Conference calls, emails, Skype, etc. as needed

v.7

ERRC = Environmental Rules Review Committee

Appendix E: Timeline of the Maximum Contaminant Level Development Process

MPART will continue to coordinate multi-agency efforts to investigate and reduce exposure to PFAS across the state

v . 5