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massachusetts water works association

www.masswaterworks.org

July 18, 2019

Ms. Elizabeth Callahan
Director of Policy & Program Planning
Massachusetts Department of Environmental Protection
Bureau of Waste Site Cleanup, 6th Floor
One Winter Street
Boston, Massachusetts 02108

RE: Comments on Proposed Changes to the Massachusetts Contingency Plan (MCP)
Via email to bwsc.information@mass.gov

Dear Ms. Callahan:

Massachusetts Water Works Association (MWWA) is submitting the following written comments to the Massachusetts Department of Environmental Protection (MassDEP) on proposed changes to the MCP regulations, 310 CMR 40.0000. MWWA is a non-profit membership organization representing over 1,200 drinking water professionals throughout the Commonwealth of Massachusetts. MWWA members are committed to protecting public health and providing a safe and sufficient supply of drinking water to consumers.

Our Public Water Systems are operated by licensed professionals who work each day to provide this essential service at a reasonable cost. Like other sectors of government, our Public Water Systems are facing resource constraints at a time when regulatory programs are increasing, infrastructure is aging, and revenues are declining. Despite these resource constraints, Massachusetts' Public Water Systems still must meet their mandate to provide clean, safe drinking water and to protect public health.

MWWA understands that MassDEP intends to use information received during the public comment process on the MCP revisions to "inform" potential revisions to the current Office of Research and Standards Guideline (ORSG) for Per- and Polyfluoroalkyl Substances (PFAS), which includes five compounds: perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), perfluorononanoic acid (PFNA),

perfluorohexanesulfonic acid (PFHxS), and perfluoroheptanoic acid (PFHpA). We have been informed that the ORSG and MCP efforts will be used in the development of a Massachusetts Maximum Contaminant Level (MMCL) for PFAS. For this reason, MWWA provides comments in this letter relative to those initiatives, even though they are not formalized, nor out for public comment at this time.

PFAS is an example of an emerging and unregulated contaminant which poses daunting challenges for Public Water Systems on every conceivable front, including, but not limited to, the introduction of unfamiliar and unforgiving sampling protocols, a paucity of reliable analytical resources, water treatment uncertainties, and most notably unprecedented cost, funding, and risk communication obligations. Despite the existence of only a "non-enforceable" Health Advisory Level for PFAS, there are several Public Water Systems which have detected these compounds and are voluntarily conducting emergency public notification and outreach efforts and multi-million-dollar mitigation activities which have included the distribution of alternative drinking water methods (i.e. provision of bottled water, point of use treatment….) and greatly accelerated planning, design and construction services required to proceed with rapid installation of expensive treatment systems. These Public Water Systems and their consulting engineers are to be commended for all they are doing to address the challenges posed by an unregulated contaminant and for providing transparent communications to their customers in light of evolving scientific discovery and real-time regulatory oversight. It remains to be seen if these herculean efforts will represent the exception or the rule for water suppliers across the Commonwealth.

MWWA has considerable experience in evaluating and commenting on proposed initiatives under the Safe Drinking Water Act, MassDEP drinking water regulations and policies, Water Management Act regulations and guidelines, drought management and more recently on Conservation Law Foundation's Petition for Rulemaking on PFAS Treatment Techniques. We embrace our role as a stakeholder in the MMCL development process and on Representative Hogan's proposed PFAS Task Force. MWWA and its members are very comfortable offering our expertise and opinions as they relate to the very real impact that new drinking water standards will have on our operations and related services. Our ability to offer comments and opinions on more nuanced toxicological principles is well beyond our area of expertise. As we are becoming increasingly aware of the impact and importance that this specific standard setting process will have on our industry, we have reached out to scientists, toxicologists, risk assessors, LSPs, and engineers for a better understanding of some of the underlying public health issues. Specifically, we have reached out to experts from Sanborn Head & Associates, Green Toxicology and the several of the engineering firms that have been working on PFAS treatment for the impacted municipalities. We have reviewed their assessments and believe that we would be well served if MassDEP not only acknowledge these comments but address them before establishing any standard, most notably those comments submitted by Sanborn Head & Associates and Green Toxicology. Based upon our assessment of their work, we are very concerned that any standard that would be established based upon the "abundance of caution" principle will

not only be overly protective, but given the very real and practicable impacts that we can anticipate within the drinking water industry, would be untenable and irresponsible.

MWWA wants to be very clear that protection of public health is the core mission of all our members. To this end, water system managers and operators must ensure compliance with the Safe Drinking Water Act requirements. MWWA supports the development of an appropriate Federal MCL for PFAS if the process follows properly established, transparent, science-based health standards and takes into consideration available analytical methods, reasonable sampling protocols, appropriate sample result analysis, viable treatment options, full consideration of a cost benefit analysis, scientifically proven health effects, and sufficient due process for stakeholders.

MWWA supports a PFAS cleanup standard under the MCP. That will be a necessary step in the regulatory process. That being said, it is premature to be moving ahead with regulatory standards before there is a better understanding of expected background levels and sources, an understanding of the extent of PFAS prevalence in the Commonwealth, and most importantly, a better understanding of the real potential human health impacts at the low levels that are being detected and potentially regulated in drinking water within Massachusetts.

There is anecdotal evidence that PFAS is being found at levels of "concern" in surface waters, groundwaters and soils throughout Massachusetts. Before regulating these compounds through the MCP or an MMCL, MassDEP needs to have a much more comprehensive database of occurrence, in addition to data on health effects and at what levels those health effects occur. It would be irresponsible to move forward with regulating at exceedingly low concentrations without knowing the likelihood of it being detected and requiring subsequent response actions. MWWA had recommended at the last PFAS stakeholder meeting that MassDEP should begin sampling the groundwater wells in the climate response network used by the MA Department of Conservation and Recreation. Many of these wells have been termed "unimpacted" and would be a good place for MassDEP to begin their data collection.

PFAS is not just a Massachusetts issue; it is a national issue. PFAS is not just a drinking water issue; it requires a comprehensive approach to address air, food, and consumer product sources. Costs of mitigation and management across all these sectors are expected to be formidable. Research, particularly on toxicity and health effect is ongoing and the scientific understanding of these compounds on human health continues to evolve. Even while human health toxicity uncertainties exist, significant investments are being made by many communities to install treatment systems to remove PFAS compounds. For these reasons, it is important that MassDEP take a deliberative approach based on sound science, and not overly conservative politics, to any regulatory initiatives related to PFAS.

In terms of the MCP and development of a clean-up standard, MWWA urges MassDEP to identify specific areas where PFAS has been found, the general types of industry and human activities associated with PFAS and identify the responsible parties contributing

to that contamination. Treatment options for Public Water Systems not only are prohibitively expensive in capital cost, but also significantly add to each community's operating costs going forward. It is unfair to expect water system ratepayers alone to bear the burden of the costs associated with treatment. Pursuing cost recovery against sources of PFAS is also very expensive and will take years of legal battles, a cost that may be prohibitive for communities spending millions for immediate water treatment or for permitting alternative sources of drinking water.

MassDEP also needs to consider establishing a strict timeframe for investigation into where contamination is coming from and then a much quicker response for the responsible party(ies) to implement remediation at a site, as well as contaminated drinking water sources. If Public Water Systems detect PFAS above the ORSG, MassDEP has required them to immediately take action to provide finished water below the ORSG. The same urgency does not seem to exist for responsible parties to remediate the source of contamination and this must be changed.

We offer the following specific comments on the proposed regulations:

Definition of Containerized Waste: The proposed amendment to the definition of Containerized Waste is intended to clarify that contaminated media, i.e., contaminated soil or groundwater, that is not otherwise a hazardous waste does not become Containerized Waste as a result of being placed in a container for off-site disposal. MWWA does not believe that the amended language provides adequate clarification. MassDEP should revisit the definition to provide more clarity.

Definition of Current Drinking Water Source Area: MWWA disagrees with the proposed language to exclude Zone A around emergency sources from the requirements for protection from contamination as a drinking water source. Under the Drinking Water Regulations, it may make sense that the Public Water System isn't required to provide the same level of protection as it does to its active or inactive sources, however the same argument does not hold under the MCP regulations where the standards are designed to protect future sources. Emergency sources have been activated in the past and therefore should remain protected in case they are needed as a potential future source. MWWA asks that the proposed language be stricken.

Definition of Non-potential Drinking Water Source Areas (NPDWSA): MWWA supports this change which would make the MCP regulations consistent with the Drinking Water regulations prohibiting the siting of permitted landfills and wastewater residuals "monofills" within the Zone II or III of a water supply. MWWA does question whether this change will impact existing water supplies that are located near closed landfills?

Definition of Rail Right-of-way: MWWA suggests that MassDEP amend this language to clarify that this could be either a current or former railway. If an abandoned railway has been transformed into another use, like a rail-trail, MWWA does not want to see that area lose designation from clean-up if necessary.

40.0317(20): MWWA supports this amendment which expands the existing notification exemption for releases that are the result of leakage and discharges of water from a public water supply or public water supply distribution system to include, in addition to chloroform, the other trihalomethanes (bromodichloromethane, dibromochloromethane and bromoform) that may be present in drinking water as the result of chlorination. Haloacetic acid compounds and other disinfection by-products found in drinking water should also be included.

40.0362: Reportable Concentrations of Oil and Hazardous Material in Groundwater: At the public forum in Harvard, MA on June 19, 2019, Paul Locke made brief mention of "background" in the context of private drinking water wells and potential influence on those wells from septic systems. MWWA believes MassDEP needs to give more thought to the issue of background levels of PFAS in this regulation package. The MCP establishes the concept of background from anthropogenic factors, but nowhere is it determined what an acceptable level of background for PFAS might be. Given the ubiquitous nature of PFAS in so many consumer products and in products used in the water works industry, MWWA fears that Public Water Systems might be put in a position to have a "Reportable Concentration" if the limit is in the low parts per trillion. MWWA believes clarification is necessary in this section of the regulations to prevent drinking water sources from being classified as waste sites if they find PFAS upon initial sampling. Perhaps it could be made clear that subsequent sampling would need to occur over a specified period to prove that the compounds are no longer present. This issue also needs to be discussed by the Drinking Water Program as they need to consider that products commonly used in the water supply industry (but without NSF 61 approval) should not be considered a significant contribution, as often there is too small a quantity of compounds in use, as well as too low a contact time to leach.

40.0993(3): MWWA supports this amendment which is intended to clarify that the requirements of 310 CMR 22 for the evaluation of drinking water in public water supplies includes both numerical water quality standards and procedural requirements that must be met even when the assessment is being conducted as part of an MCP site. Specifically, MWWA supports the proposed change which cites the drinking water provisions for site-specific risk assessment so that the MCP Method 3 assessment will also meet the drinking water requirements.

40.0317 (13) Releases and Threats of Release Which Do Not Require Notification: MWWA has concern regarding transfer of soil from one area to another without notification to the water supplier where is it being deposited, especially if it is in a designated water supply area. Further, we would suggest that any soil reuse project containing or potentially containing OHM or meeting criteria for RCS-1 but below RCS-2 should require a much higher level of scrutiny and control if it is located within the watershed of a surface water supply (ORW) or in the Zone II of a groundwater supply.

40.0461(9): This language is intended to clarify that Other Persons conducting Utility-related Abatement Measures are not required to tier classify the disposal site where they are conducting the URAM or achieve site closure if they have not otherwise

assumed responsibility for MCP response actions beyond the utility work under the URAM, but they do need to follow the procedures at 310 CMR 40.0170(9) (notify the Department and provide a Status Report) when discontinuing work. MWWA does not believe the included language clarifies this point and contends MassDEP needs to add clarifying language to address materials that may be moved off the disposal site and later be deemed to pose a risk.

40.0974: Identification of Applicable Groundwater Standards in Method 1 (GW-1):
In the draft MCP regulations, MassDEP is seeking input on specific questions it raised relative to PFAS evaluation and regulation, and while some of the questions posed related directly to a GW-1 standard, many will inform future decisions regarding an MMCL, so MWWA is responding with that in mind.

At 20 ppt as a sum of six PFAS, the proposed GW-1 standards, which are likely to become MMCLs, are significantly lower than the Lifetime Health Advisory (LHA) issued by the United States Environmental Protection Agency (EPA) in 2016. The EPA has stated more than once that the LHA is considered a "safe level" and that concentrations below 70 ppt are not of concern based on their review of the available health studies. In addition, an LHA is defined as the level which does not result in "any adverse noncarcinogenic effects for a lifetime of exposure" (EPA, 2018, 2018 Edition of the Drinking Water Standards and Health Advisors, EPA 822-F-18-001). Further, the LHA document states that the LHA is protective of cancer effects for PFOA and PFOS (EPA, 2016, Drinking Water Health Advisory for PFOA, EPA 822-R-16-003; EPA, 2016 Drinking Water Health Advisory for PFOS, EPA 822-R-16-004). Therefore, any level below 70 ppt for drinking water standards is unnecessarily below the "safe level" established by the EPA in the LHA and provides no additional benefit to a drinking water standard set at 70 ppt. Furthermore, EPA can issue an updated LHA if it chooses to do so, and the fact that it has not done so indicates a lack of compelling scientific evidence to merit such a change.

With respect to MassDEP's proposed revision of EPA's Reference Doses (RfD), we understand that EPA's RfD, upon which the MassDEP relies, has (i) not been subject to peer-review and (ii) stands at odds with acceptable intakes set by other reputable, national, regulatory agencies. For example, just last year, Health Canada set drinking water guidelines for PFOA[1] and PFOS[2] of 200 parts per trillion (ppt) and 600 ppt, respectively. These two guidelines have been derived using standard, highly health-protective methods, and are better justified than the methods used to date by EPA for setting their PFOS/PFOA guidelines. EPA's RfDs for both PFOA and PFOS are based not on effects in either humans or other primates, but instead on very minor, reversible, effects in laboratory rodents. Good practice suggests that when dose-response data

[1] https://www.canada.ca/content/dam/hc-sc/documents/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-technical-document-perfluorooctanoic-acid/document/PFOA_2018-1130-eng.pdf

[2] https://www.canada.ca/content/dam/canada/health-canada/migration/healthy-canadians/publications/healthy-living-vie-saine/guidelines-canadian-drinking-water-quality-guideline-technical-document-perfluorooctane-sulfonate/PFOS%202018-1130%20ENG.pdf

from studies in humans and/or nonhuman primates are available, these should take precedence for purposes of predicting risks to public health. For both PFOA and PFOS, there are data from human studies, lab monkey studies, and "humanized," genetically engineered mouse studies. Some of these studies were not available when EPA derived their overly conservative RfDs for PFOA and PFOS. There is a considerable degree of safety built into the EPA LHA. We urge MassDEP to consider the comments on this topic submitted by Sanborn Head & Associates. Basically, the Reference Dose for PFOA/PFOS contains three factors of safety that are arguably unnecessary to protect human health, and hence all represent protective biases that suggest 70 ppt is a safe level. These factors more than compensate for the additional safety factor of 4 proposed by MassDEP as an adjustment to the EPA value. For these reasons, MassDEP should not be adding additional uncertainty factors to the RfDs.

MassDEP has stated that they are proposing a standard of 20 ppt given new information released by the Agency for Toxic Substances and Disease Registry (ASTDR). ASTDR released draft toxicological profiles for PFAS in June of 2018. It is important to acknowledge that they are not yet final. We believe that comments[3] submitted by Dr. Laura Green and Dr. Edmund Crouch from Green Toxicology regarding ASTDR's draft Toxicological Profile for PFAS should be considered in MassDEP ORS's evaluation of the scientific studies. We have attached their analyses to these comments for MassDEP's review. Drs. Green and Crouch point out many concerns with the interpretation of certain studies in deriving the toxicological profiles. Comments such as the ones made by Drs. Green and Crouch should cause changes to ASTDR's final profiles; therefore, MassDEP should not be relying on ASTDR's profiles until they are published as final.

If MassDEP moves forward with setting specific standards for a GW-1 or an MMCL, MassDEP should develop compound-specific standards for each of the PFAS compounds and not employ a cumulative approach. The compounds should not be combined because of different toxicity endpoints, different uncertainty factors between humans and mammal toxicities, different reference dosages, differences in half-lives, bioaccumulation, etc. Summing the six PFAS compounds has the effect of regulating any detection of PFAS as an exceedance of the GW-1 since the typical laboratory reporting limit for the six PFAS is approximately 5 ppt, and adding in non-detects at half detection limits will push six PFAS sum to near or above 20 ppt. Since the compounds being regulated are the most commonly detected compounds, it is likely that more than one PFAS will be detected in many samples. Therefore, in effect based on the added decision to have the sum of the six compounds also be regulated at 20 ppt, the proposed GW-1 is actually 5 ppt or effectively the practical quantitation limit (PQL) for each compound. At a recent PFAS stakeholder meeting, MassDEP pointed out that this has the practical effect of regulating PFAS to non-detect. This is not only inappropriate but also impractical and will significantly increase response action costs by water systems and their customers without providing any additional known health benefit.

[3] Comments on ATSDR's *Toxicological Profile for Perfluoroalkyls,* Edmund A. C. Crouch, Ph.D. and Laura C. Green, Ph.D., D.A.B.T, August 20, 2018; Docket ATSDR-2015-0004

In addition to the analytical challenges associated to the potential standards being close to or at minimum reporting limits for individual PFAS, the potential for drinking water being out of compliance for the presence of individual PFAS in single-digit levels may require many more municipalities to install treatment systems than one may expect, especially considering PFAS levels in the Commonwealth's drinking water are not known. In the Unregulated Contaminants Monitoring Rule (UCMR) 3 study completed by EPA in 2016, less than 1% of public drinking water systems (serving more than 10,000 customers) had PFOA (0.3%) or PFOS (0.9%) at concentrations above the LHA of 70 ppt. However, review of the same data shows a significant increase in the number of water systems above 20 ppt for PFOA and 40 ppt for PFOS (the reporting limits in the UCMR3 study) at 2.4% for PFOA and 1.9% for PFOS. This will substantially increase the number of water systems that will be required to treat to standards that are lower than the LHA which EPA states is protective for both non-cancer and cancer effects, significantly increasing the cost of response actions but providing no additional benefit. Further, since the reporting limit for PFOS was elevated above the proposed GW-1 of 20 ppt, the percentage of water systems above 20 ppt for PFOS would be expected to be higher, further increasing costs to water systems and their customers without providing any additional benefit.

A cumulative-regulatory approach also ignores the complexities of selecting, implementing and operating the appropriate and affordable PFAS treatment solutions. There are a limited number of the drinking water treatment technologies that are known to be effective for PFAS removal. However, there is no one-size-fits-all solution. Depending on several site-specific factors, such as the levels and types of PFAS present in water, general water quality, and existing treatment processes, treatment technologies may show different removal effectiveness depending on several factors, such as the carbon chain length and attached functional group.

If a cumulative approach is taken by MassDEP, the potential for drinking water being out of compliance for the presence of individual PFAS in single-digit levels may also impose significant operational challenges for running PFAS treatment systems; increased spent adsorptive media will be generated requiring disposal or incineration. With adsorptive media technologies that are commonly used for PFAS treatment, such as granular activate carbon (GAC) and anion exchange (AIX) resin systems, water is sampled from the different media bed depths to detect a breakthrough of PFAS, along with monitoring of the finished water level. When the breakthrough of the media is approaching the PFAS standard, the system requires a change-out with new media. Media change-outs are costly (although hopefully infrequent in well-designed systems), and therefore should be based on accurate analytical results. MWWA is concerned that at such low parts per trillion accuracy will be difficult and may cause inefficient use of resources such as requiring an excessive number of PFAS samples to ensure accurate results.

The State of New Hampshire just released their final MCL values and have selected different levels for each of the four individual compounds they will be regulating, which

are PFOA, PFOS, PFNA, and PFHxS. MWWA also notes that many other states have proposed to follow a similar approach as NHDES, including New Jersey that proposed and adopted the country's first individual PFAS MCLs for PFNA, PFOA, and PFOS; Minnesota has individual health risk values for PFOA, PFOS, and PFHxS; and California enforces individual notification levels for PFOA and PFOS only.
The State of Michigan just released a report and also has separate values for each compound it intends regulate through an MCL (copy of report attached).

MassDEP asked if PFHpA and PFDA should be included, excluded or treated separately, and MWWA would like to point out that New Hampshire is not regulating PFHpA and PFDA at this time. Because, as it admits, there is a dearth of toxicity, epidemiology and pharmacokinetic data on PFHpA and PFDA, MWWA believes it would be premature for MassDEP to regulate these compounds at this time.

We would request that MassDEP tighten the standards that are being proposed for the GW-3 standard for PFAS. At the low parts per trillion that are being proposed, the sooner we are able to identify and remediate the source of contamination, the better chance we have of protecting our water sources from being contaminated.

MWWA is quite concerned about analytical controls and capabilities to reliably and accurately quantify the compounds when looking at very low parts per trillion. MassDEP is suggesting that laboratories should be capable of identifying a minimum reporting level (MRL) of 5 ppt for each respective compound. MassDEP is further suggesting that anything between 1/3 the MRL and the MRL be considered as ½ the MRL. MWWA believes that anything detected below MRL should not be governed by an arbitrary rule assuming a certain level exists; such an interpretation is not scientific. Values below the MRL should not be reportable nor counted towards anything at these low parts per trillion levels. We note that in other areas of the Drinking Water Program, it is explicit that all values below the MDL be recorded as zero, as seen in the line below from the MassDEP "Stage 2 Disinfection By-Products Rule (DBPR) Quarterly Compliance Worksheet." Why would PFAS be treated differently?

Note: Record and calculate all ND or < MDL results as the number 0 (zero).

It is concerning that EPA does not currently have an approved method for soil evaluation or detection in other matrices aside from finished drinking water, so we wonder how MassDEP will reliably and accurately evaluate PFAS concentrations in soil?

It is also important to note that advances in analytical techniques have allowed laboratories to detect substances at lower and lower levels. Substances found at low levels do not always correlate to health impacts. There needs to be robust toxicological studies conducted on the human health impacts of PFAS at the levels being detected. Further, because there is a real difference in the way in which mice and humans react to chemical influence, Drs. Green and Crouch have urged that guinea pigs might be a

better study animal than mice. MWWA is attaching to our comments a paper[4] written by Drs. Green and Crouch which outlines their reasoning. MWWA urges MassDEP to conduct a thorough evaluation of existing toxicological studies and perhaps fund future studies to better understand how these levels specifically impact human health.

Proposed Development of an MMCL:

With respect to establishing an MMCL, MWWA firmly believes that any new drinking water standard must be developed through a transparent process that:

- Follows a clearly documented and transparent legal process
- Relies on a strong scientific foundation, which includes studies that are peer-reviewed, comprehensive, and repeatable
- Involves key stakeholders
- Evaluates the cost-benefit of the proposal, and
- Evaluates the effectiveness of the regulatory action in achieving better health outcomes

The EPA is responsible for oversight of the Safe Drinking Water Act and is tasked with setting drinking water quality standards on a national basis. MassDEP has been delegated the authority (otherwise known as primacy), to oversee the Safe Drinking Water Act in Massachusetts. The issue of emerging contaminants is one to which EPA pays close attention. For public health protection, EPA has a rigorous process for evaluating contaminants of concern in drinking water and deciding whether regulation is warranted. EPA employs experts who derive protective health-based standards (e.g., toxicologists and health risk assessors), economists who produce cost and benefit analysis, and chemists and engineers who can determine lab and treatment capabilities.

EPA regularly mandates water systems of a certain size to test for substances on their Contaminant Candidate List (CCL) through the Unregulated Contaminant Monitoring Rule. This process allows EPA to assess the prevalence of a substance throughout the country. There were several PFAS substances included in the last round of the UCMR sampling (UCMR 3) and several more are proposed for UCMR 5.

EPA has already completed a PFAS Action Plan[5] which outlines the concrete steps the agency is taking to address PFAS and protect public health. This plan:

- *Demonstrates the agency's critical national leadership by providing both short-term solutions and long-term strategies to address this important issue.*
- *Provides a multi-media, multi-program, national research, and risk communication plan to address this emerging environmental challenge.*
- *Responds to the extensive public input the agency has received over the past year during the PFAS National Leadership Summit, multiple community engagements, and through the public docket.*

[4] Advancing the ball: Using guinea pigs to study perfluorinated alkyl substances (PFAS)
Laura C. Green, Ph.D., D.A.B.T. and Edmund A.C. Crouch, Ph.D., January 5, 2019

[5] https://www.epa.gov/sites/production/files/2019-02/documents/pfas_action_plan_021319_508compliant_1.pdf

EPA is committed to proposing a national drinking water regulatory determination for PFOA and PFOS and has begun that process. American Water Works Association and the National Association for Water Companies both advocate for an MCL to be developed by EPA at the National level and not at the state level.

As we stated earlier in our comments, setting drinking water standards involves a multi-step process. The toxicity level (in particular, with respect to humans) of the substance or contaminant must be determined. The prevalence of the substance must be evaluated. The ability to reliably detect and quantify the substance must be determined. The feasibility of treating to remove the substance must be evaluated. The cost to the affected parties must be assessed. The benefits to the environment and human health of reaching the standard must be quantified. We are not sure that MassDEP has enough information on each of the above steps to properly develop an MMCL right now.

MWWA has always believed that it is in the best interest of the public for EPA to take the lead on setting health-based drinking water standards, so there is a consistent protocol and messaging for all water suppliers across the nation. In the past, Massachusetts has imposed regulatory controls on Perchlorate and Manganese before the national process was complete. Jumping out ahead of the EPA puts Massachusetts water suppliers in the untenable position of complying with standards of uncertain value and places a burden on the water suppliers and their customers before the public health benefits have been completely evaluated. Perchlorate is a perfect illustration of this, as EPA just put a proposed standard out for public comment which is significantly higher than the MMCL established back in 2003. When states act independently and have differing standards for particular substances, it causes confusion and concern among the public. It is critical that MassDEP understand this contaminant at the levels being discussed; it will have an enormous financial impact on the entire state, both public and private sectors. MWWA urges MassDEP not to act based on what other states may do. Further, MassDEP should not apply an excessive conservative factor to a number not supported by sound science. MWWA suggests that MassDEP closely follow the EPA process on PFAS and implement standards only after the scientific and public health merits of doing so have been methodically and carefully considered.

Implementation Considerations:

MassDEP needs to carefully consider implementation challenges for Public Water Systems from regulatory efforts related to PFAS. Water sources are not quickly or easily treated or replaced. There is significant engineering effort and cost that goes into selection of the appropriate treatment technologies for a given water system. Site-specific testing, either bench-scale or pilot-scale, that evaluates the effectiveness of the treatment technologies with the actual contaminated water conditions and the follow-up cost analysis are critical for 1) identifying the appropriate treatment solution for that specific water and existing treatment processes; 2) selecting the cost-effective alternative; and 3) identifying and avoiding any potential unintended consequences that

are inherently possible when any new water treatment process is added (e.g. although this is a very infrequent occurrence, coal-based carbon has been observed to release arsenic under certain water conditions). While such testing provides critical design parameters and potentially cost-saving measures, it takes time. Engineering the design of the permanent PFAS treatment facility, assuming timely approval from MassDEP, local permitting, and constructing it can be a lengthy process. Renting temporary treatment equipment not only is very costly but also takes time. These considerations should be taken into account in MassDEP's timeframe for enforcing PFAS standards.

In some instances, Massachusetts Public Water Systems have been advised to take sources out of service so that finished water is below the ORSG; this will not be possible for most water systems. In addition, some water systems have limited sources and those sources may be constrained by other regulatory programs, such as the Water Management Act. Flexibility for limited use of impacted sources during peak demand periods may be necessary for public safety (adequate pressure and fire protection) or to maintain reasonable operating costs while permanent solutions are implemented. Interconnections with neighboring communities to provide an alternative water source may pose challenges in terms of cost and time required to design and construct the needed infrastructure, as well as potential incompatibility with that water. It is also recommended that MassDEP streamline their new technology review process to more quickly grant approvals.

MWWA is also concerned that Public Water Systems may face procurement challenges if new drinking water standards are put in place. MassDEP needs to give some consideration as to whether statutory changes are needed to enable water systems to more quickly procure treatment technologies or if procurement thresholds need to be raised to avoid prolonged bidding processes. MWWA is also concerned that certain treatment components may become harder to procure if demand for treatment increases. The state may consider whether it should make some bulk purchases and stockpile certain common treatment equipment so that components will be more readily available to water systems if needed, or MassDEP must allow a reasonable amount of time for water systems to fund and procure treatment (if required).

MWWA would also like to reiterate a concern we raised back when the petition to regulate PFAS was initially filed and that is time and effort needs to be spent by the Commonwealth on a communication strategy so that water suppliers are not left on their own to individually figure out how to handle the risk communication. Thus far there have been many questions raised by residents at public forums in the communities grappling with PFAS contamination, especially about potential impacts to health, with very few direct answers from MassDEP and the Massachusetts Department of Public Health. MassDEP needs to be better prepared to answer questions and address mounting fears of residents, and to assist Public Water Systems who are often the first line of defense for questions from their customers.

Finally, MWWA strongly encourages MassDEP to establish and maintain communications with Administration and Finance, the Clean Water Trust, and the

Legislature regarding how to provide more funding to communities facing PFAS contamination. There is obvious attention to the initial capital costs that Public Water Systems will incur to install treatment. In some situations, the responsible party may pay for the capital costs. In most cases, municipalities will need to front the costs and chase the responsible part(ies) for reimbursement. It is likely that the majority of contaminated water supplies may not have an easily identifiable source or responsible party. There will be ongoing costs for sampling, operation, and maintenance of the treatment system. Who will be responsible for these ongoing costs? Ratepayers should not have to bear this burden for harms caused by others.

Thank you for the opportunity to provide these comments. MWWA respectfully requests that MassDEP publish a response to comments prior to finalizing the final MCP regulations. That response to comments should be available for review by the public prior to MassDEP moving forward with any other regulatory initiatives related to PFAS (either revisions to the ORSG or development of an MMCL).

As mentioned previously and throughout this letter, public water suppliers understand the importance of ensuring that the drinking water that reaches their customers meet Safe Drinking Water Act requirements and protect the public health. Water suppliers work hard each day to meet these goals and satisfy their customers' expectations. As we have all come to be keenly aware, the issue of emerging contaminants is a huge challenge. Our members will be tasked with meeting any and all regulatory requirements and standards set; therefore, MassDEP has an obligation to determine what the real human risk exposure is, and then, when and if the science dictates, move towards standards that will achieve desired public health outcomes. EPA has its national strategy for PFAS and MWWA recommends and encourages MassDEP to follow that process closely. We look forward to working collaboratively with MassDEP as this process moves forward.

Sincerely,

Jennifer A. Pederson
Executive Director

Enclosures
cc: Martin Suuberg, Commissioner, MassDEP
Stephanie Cooper, Deputy Commissioner, MassDEP
Kathleen Baskin, Assistant Commissioner, MassDEP
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Comments on ATSDR's *Toxicological Profile for Perfluoroalkyls*

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Introduction and Overview

The ATSDR *Toxicological Profile for Perfluoroalkyls* (Draft for Public Comment, June 2018) offers provisional minimal risk levels (MRLs) for four perfluoroalkyl substances (PFAS): perfluorooactanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS).

These MRLs are, in general, more restrictive than analogous reference values set by U.S. EPA or other agencies. For example:

- U.S. EPA's proposed reference dose for PFOA is 2×10^{-5} mg/kg/day;
- Health Canada's tolerable daily intake for PFOA is similar (at 2.5×10^{-5} mg/kg/day); and
- ATSDR's provisional MRL for PFOA is an order of magnitude more restrictive, at 3×10^{-6} mg/kg/day.

Unfortunately, ATSDR's provisional MRLs are no more justifiable than previously proposed guideline-values, and cannot be said to be reliable. Among other issues, the provisional MRLs for these four PFAS:

- Are not based on evidence of adverse effects in humans;
- Are sometimes based on questionable "principal studies";
- Do not reflect known or reasonably anticipated differences in sensitivities between and among laboratory rats, laboratory mice, and humans; and
- Fail to account for many recent, relevant studies.

With regard to the first point, it remains the case that epidemiologic and/or clinical evidence has so far failed to demonstrate that any PFAS harms human health. Notably, cancer patients in a phase 1 trial have been dosed with massive amounts of PFOA (up to 1.2 grams per patient per week), as an experimental chemotherapeutic drug, with no apparent harm to their livers

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(the organ most clearly and adversely affected by PFOA in laboratory rodents) or other organs (Convertino et al., 2018).[1]

Of course, high-level exposures to various PFAS, including PFOA, clearly *do* harm the health of laboratory animals, and it is entirely appropriate to base health-protective guidelines on exposure-response data derived from laboratory animal studies.

However, doing so requires considerable toxicological judgment — both in choosing which "principal studies" and dose-response data-sets to use, and deciding how to use them. The principal studies must be well-designed and executed, and the results should have been replicated. As explained below, for some of its four provisional MRLs, ATSDR's choice of principal studies is questionable; while for others, the data-sets are reliable enough, but ATSDR's use of them appears to be unjustified.

This is especially unfortunate because the text of the *Profile* itself is often quite informative and insightful. However, none of this insight is carried over into the derivation of the MRLs. Indeed, the latter — which are derived in Appendix A — are essentially uninformed by the almost 700 pages of text that precede them. This perplexing disconnect should not carry through to the final version of the *Profile* and its MRLs.

In this draft version, Appendix A assumes, by default, and without justification, a combined "uncertainty factor" of 300 (in three cases, a factor 10 of this is termed a "modifying factor") for each of its four provisional MRLs. So doing, Appendix A fails to conform with modern, human health risk assessment practice that, among other things, encourages the application (or at least consideration) of "chemical-specific adjustment factors" to provide more biologically-based, predictive, and still protective guidance values (see, for example, Meek et al., 1999, 2002 & 2011; Edler et al., 2002; WHO/IPCS, 2005; US EPA, 2014; Bhat et al., 2017).

For example, for each of its four provisional MRLs, the Agency simply applies a default factor of 10 to account for "human variability," but fails to justify this value. Of course, humans do vary

[1] As is typical for cancer chemotherapeutic drugs, these large doses did cause fatigue, nausea, vomiting, and diarrhea, which were considered tolerable by the patients. The draft *Profile* does not cite this paper, but should. The Convertino et al. (2018) paper was available five months prior to the release of the *Profile*; and ATSDR was aware of this clinical trial of PFOA, since the *Profile* cites a 2011 poster session abstract that describes it (MacPherson et al., 2011), and the poster *per se* is included in comments to U.S. EPA (Dupont, 2014). This information is especially important for the exposure assessment sections of the *Profile*, which at present indicate that it is manufacturing workers, and perhaps people drinking highly contaminated water, who are the groups receiving the largest doses of PFAS. For PFOA, at least, that is not the case. PFOS also has anti-tumor activity (Wimsatt et al., 2016), although we know of no clinical trials using PFOS.

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with regard to their sensitivities to the adverse effects of chemicals; but whether a factor of 10 is appropriate for accounting for populational variability *depends on the chemical and end-point at issue*.

For these four chemicals, interindividual differences in metabolic rate need not be accounted for, since these PFAS are not metabolized by either laboratory animals or humans.

Also, three of the four provisional MRLs are based on developmental effects associated with PFAS exposures of fetuses *in utero* and/or of neonates through lactational exposures. Of course these life stages are uniquely sensitive to the effects of developmental toxicants. There is no need to account for the possibility of some greater sensitivity of older children or of the elderly, for example, since for all other such subpopulations, development has already occurred.

In what senses, then, is a factor of 10 for "human variability" the "correct" value for these four PFAS MRLs? The Agency does not say, but it should. In several cases, the variability due to variation in elimination rates is known, and substantially less than a factor of 10; what would remain is only variability due to potentially differing sensitivities within the chosen, already most sensitive sub-population.

Also important, but also ignored in the derivation of the MRLs, are the *qualities* of the principal studies upon which the provisional MRLs are based.

For example, despite the availability of multiple high-quality studies on PFOA (most of which are cited in the *Profile* text), Appendix A relies for its MRL-derivation on results in rodents from a single poor-quality study[2] that fails to conform with internationally accepted study-guidelines, uses too few rodents, tests these rodents at only one dose-level, relies on unverified test-methods, has not been replicated (indeed, has been contradicted by more recent data), is strictly uncontrolled, uses the wrong basic measurement unit, and is otherwise entirely unsuitable. As detailed below, the "final" MRL for PFOA should be based on far more reliable data from guideline-based studies.

The *Profile* is based on literature searches that cover the period up until May 2016, so is now more than two years out-of-date. Had ATSDR searched for more recent literature (even for just papers that cited the principal studies that the Agency has selected), it would have found that the results of the principal study selected for the PFOA MRL, for example, *were not replicated* using standard test-methods.

[2] Two papers are cited as the principal studies (Onishchenko et al., 2001, and Koskela et al., 2016), but the laboratory mice reported on in the latter publication are simply a subset of the mice reported on in the earlier publication.

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In Appendix A, the Agency presents various approaches taken to estimate "human equivalent doses" (HEDs). Oddly, these approaches differ for the different PFAS, and they have been applied in a mutually exclusive fashion. As a result, and without justification, the Agency has ignored various high-quality studies, and relied instead on lower quality studies.

In particular, for PFOA and PFOS, the Agency relies on the use of the Wambaugh et al. (2013) modeled parameters to estimate the average serum concentration in experimental animals, thus ignoring any studies that did not use female CD-1 mice, female C57Bl6 mice, or male Sprague-Dawley rats (Table A-7). The Agency similarly ignores, for PFOS, any studies that did not use female CD-1 mice, female Sprague-Dawley rats, or Cynomolgus monkeys (Table A-15).

This unjustified approach was followed *even in cases where the serum concentrations were measured* in the cited studies, or in other studies using the same animals (but not analyzed in Wambaugh et al., 2013). However, with known dosing schedules, a good approximation to the volume of distribution, and even a single measurement at a known time point, the average serum concentration in experimental animals of PFOA and PFOS can be estimated; and in several of the studies reporting serum concentration measurements, additional information is provided that allows better estimates. The accuracy of this estimation is probably as good, for any single experiment, as the estimate obtained using the Wambaugh et al. (2013) modeled parameters. And, indeed, this approach using measured concentrations is taken for PFHxS and PFNA.

There is no reason to not use the same approach for PFOA and PFOS, relying, if necessary, on estimated parameters from other experiments on the mouse and rat strains not analyzed by Wambaugh et al. (2013). Indeed, if concentration measurements are available for the animals used in any study, then estimates using this approach should be compared with those obtained from the Wambaugh et al. (2013) modeling approach, and any discrepancies described and resolved. In particular, in Table A-7 for PFOA:

- Loveless et al., 2008 — serum PFOA concentrations were not measured in this experiment (which dosed for 29 total days), but a previous, cited experiment (Loveless et al., 2006) using the same animals at the same daily doses included measurements of serum concentration at 14 days. The previous measurements are quite sufficient to estimate average serum concentrations in Loveless et al., 2008.
- Abbot et al., 2007 — measured and reported serum PFOA concentrations.
- Cheng et al., 2013 — no suitable measurements in this report
- Albrecht et al., 2013 — measured and reported serum PFOA concentrations.

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And in Table A-15, for PFOS:

- Long et al, 2013 — no suitable measurements in this report
- Peden-Adams et al, 2008 — measured and reported serum PFOS concentrations.
- Guruge et al., 2009 — measured and reported plasma PFOS concentrations.
- Dong et al., 2009 — measured and reported serum PFOS concentrations.
- Dong et al., 2011 — measured and reported serum PFOS concentrations.
- Onishchenko et al, 2011 — no suitable measurements in this report.
- Wang et al., 2015c — measured and reported serum PFOS concentrations.
- Yahia et al, 2008 — no suitable measurements in this report.

Of course, the lack of measurements *within any particular report* should not end the quest for estimated serum concentrations; it is necessary to search related literature (particularly that published by, or cited by, the same authors) for experiments with serum concentration measurements in the same animals under similar experimental conditions. Why did the Agency fail to perform such a search?

In what follows, we present additional, hopefully constructive criticisms of the four provisional MRLs. We would note that assessing risks to human health for these compounds is not straightforward, and there is no one best approach. Nonetheless, we hope to explain how current evidence can be better used, and how future research may address uncertainties as to whether and how PFAS affect public health.

PFOA

The provisional, intermediate-duration MRL for PFOA is based on work in mice published by Onishchenko et al. (2011) and Koskela et al. (2016). The latter study relied on mice used in the former study, evaluated at a later age and for a different end point.

For at least the reasons detailed below, these "principal studies" fail to provide a sound basis for the derivation of an MRL. These investigations are nominally studies of developmental neurotoxicity (from prenatal exposures to PFOA or PFOS), but their methods are poor, and their results are unreliable. The Agency should choose different studies as the basis for its "final" MRL.

Groups of toxicologists, in regulatory agencies and elsewhere, have worked for decades to standardize the design of laboratory rodent studies (whether of potential drugs or other chemicals) for purposes of human health risk assessment. To investigate developmental

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neurotoxicity, the relevant guideline is *OECD Test Guideline (TG) 426* (OECD, 2007, based on U.S. EPA, 1998). As explained by Beronius et al. (2013):

> Both the US EPA and the OECD guidelines for [developmental neurotoxicity] DNT testing are structured to include investigations of developmental landmarks and behavioral ontogeny, motor activity, motor and sensory function, learning and memory, and neuropathology. For some of these categories several different validated test methods are available and the guidelines are largely flexible regarding which test method to include in the study design.

Unfortunately, the studies chosen by ATSDR for the PFOA provisional MRL fail to conform to the essential elements of the *Guideline*. For example:

- The *Guideline* calls for the use of rats as the study subjects, but Onishchenko et al. (2011) conducted their studies in mice.
- The *Guideline* calls for the use of at least three dose-groups, but Onishchenko et al. (2011) reported on only one dose-group.
- The *Guideline* calls for evaluation of 20 litters per dose-level, but Onishchenko et al. (2011) used only 6 pregnant dams in their exposed group (and 10 dams in their control group).
- The *Guideline* calls for the reporting of clinical observations of the test rodents, but Onishchenko et al. (2011) provide no such reporting.

Next, the Agency is not entirely accurate in its summarizing of the principal studies. For example, reviewing the results of Onishchenko et al. (2011), the Agency writes (page A-23), "Prenatal PFOA exposure was associated with increases in global activity and exploratory activity in adult offspring . . . ", but this is inaccurate. What was reported by the investigators was an increase in activity by male mice both during the first hour (habituation) and subsequently, but a *decrease* by female mice during the first hour of habituation, *with no change thereafter*.

Moreover, it is not known whether these observations, such as they are, in fact represent effects caused by to PFOA. This is because:

- The PFOA-exposed male mice were not matched with their controls. The 6 PFOA-exposed males were housed 3 and 3 in two cages, but the 8 control males were housed as 4 and 4 (these distributions are not explicitly stated, but are the only possibilities given the described experimental design). Activity levels in social groups might well depend on crowding levels.

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- The authors made no correction for their multiple comparisons. A quite large number of comparisons were made (at least 34 initial comparisons[3] can be seen in the reported results) with regard to behavioral-endpoints. Given this large number, the 5 "significant results" (at "$p<0.05$") that Onishchenko et al. (2011) report as being associated with PFOA might well have arisen due to chance alone, and not to any PFOA-induced effect. It is not possible to fully evaluate this problem, since the exact set of tests performed is not described.
- Some of the analysis was clearly performed post-hoc: the authors write, "… signs of altered locomotor activity in the exposed groups prompted us to extend the analysis of behavioral data …", which further compromises any statistics-based conclusions.
- There was no accounting for litter or individual animal effects in the analysis, and, as noted above, too few litters (6 for the experimental group, 10 for the control group; apparently there was no matching on litters) were used in any case to reach valid conclusions. The 5 "significant results" among males are clearly obtained from analyses of the wrong measure. All 5 of them could be due to excess activity by one mouse, for example, which would not correspond to a statistically significant effect. The analytical units here should clearly be mouse and litter, potentially taking into account interaction effects within each cage (since an over-active mouse might induce activity in other mice).
- In a more recent paper, several of the Onishchenko et al. authors (Spulber et al., 2014) state "… we re-analyzed the data we reported earlier [19], focusing on the novelty-induced hyperactivity in mice (Fig. 2 D), and found that mice exposed to 0.3 mg/kg/day PFOS display both less locomotor activity, and faster habituation (larger negative IOC value) as compared to controls and mice exposed to 3 mg/kg/day PFOS (Fig. 2 E)." Reference 19 is to the principal study, Onishchenko et al. (2011). Since Onishchenko et al. (2011) report only on exposure at 0.3 mg/kg/day PFOS, omitting the results subsequently documented at 3 mg/kg/day, this 2014 paper raises the possibility that higher dose(s) of PFOA might have also been tested, with the results similarly omitted from the 2011 report. Importantly, the higher dose (3 mg/kg/day) of PFOS resulted *in no effect* compared with control for at least one of the results reported as positive at 0.3 mg/kg/day, suggesting that the authors of Onishchenko et al. (2011) underestimated the variability in their experiments and/or applied incorrect statistical treatments.
- The apparatus used by Onishchenko et al. (2011) — cited as Trafficage, NewBehavior, Zurich, Switzerland; http://www.newbehavior.com/products/trafficage — is unusual, indeed almost unique (used apparently by only one group), for such studies, and it has not been calibrated against standard measures. A subsequent version of the apparatus (cited as TraffiCage, TSE-Systems, Germany; https://www.tse-systems.com/product-details/trafficage) has distinct differences (6 coils in place of 5) and requires special

[3] Counting males and females together, at least the following: 2 for the locomotor tests, 6 for the novelty comparisons in Figure 2, 10 in Table 2, 12 in Table 3, 2 in Figure 4, 2 in Figure 5.

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computer code to "correct" the measurements (*e.g.* Dudek et al., 2015). No such "corrections" were applied in the cited experiment, or at least none were mentioned.

- There is no reference to a tested protocol that would eliminate potential biases (*e.g.* even if the control and test animals were housed in the same room, they might be differentially sensitive to external influences such as vibrations, even if housed on the same bench, due to resonance locations in the building or support structures) and potential corrections needed (*e.g.* the shielding effect of tissue on the transponders might affect the recorded location of the animal vary with the orientation of the animal within the cage). The need for extensive protocol testing is apparent in the results of tests carried out on similar apparatus for rats (Redfern et al., 2017).
- The manufacturers of both the originally cited and the subsequent version of the TraffiCage apparatus failed to respond to emails from us requesting technical details of their apparatuses, and no such details are provided on their web sites (the first now re-directs to TSE-Systems), so it is not possible to even theoretically evaluate the minimal experimental details provided. The "References" on the TSE-Systems site is simply a Google Scholar search. Certain technical details (the time resolution) of the apparatus used by Onishchenko et al. (2011) are given different values[4] in subsequent publications (Spulber et al. 2014, 2015).

Further doubt on the validity of any causal connection between exposure to PFOA and the effects claimed in Onishchenko et al. (2011) is raised by (i) the complete lack of agreement between effects claimed in male and female mice in the results obtained, and (ii) the subsequent failure to replicate the results (Goulding et al., 2017).

Moreover, the experiments of Abbott et al. (2007) on PPARα-null mice, and of Albrecht et al. (2013) on PPARα-null and PPARα-humanized mice, showed that developmental toxicity in the mouse is dependent on the expression of mouse PPARα and not human PPARα. Thus, even were the effects reported by Onishchenko et al. (2011) in the mouse actually caused by PFOA, *human fetuses and neonates would be expected to be relatively resistant* to such effects.

The second paper (Koskela et al., 2016) selected as the basis for the provisional MRL examined an outcome in the female mice used in Onishchenko et al. (2011) when they had grown to 13 or 17 months old. This experiment was again uncontrolled, in that the dosed and control groups were of different weights, and the outcome measures were such that, as stated by the authors, "[t]he mild effects seen here are probably explained to some degree by increased body weight and thus increased load on the long bones …" although of course without the necessary

[4] 50 ms and 20 ms respectively. However, while the time-stamp provided by the apparatus might provide such resolution, the actual measurements using the RFID transponder types described take somewhat longer, and a full measurement cycle over the 5 coils would take longer still (typically about 60 ms and 500 ms respectively, based on Redfern et al., 2017).

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controls it is impossible to rule out (or rule in) some effect of PFOA exposure. Once again, the observations of Abbott et al. (2007) and Albrecht et al. (2013) on the PPARα-dependence of developmental effects in mice is relevant (Table 2-3 classifies the outcome claimed by Koskela et al., 2016, as developmental).

In neither experiment were the reported outcomes determined, *by ATSDR itself*, to be serious effects. Table 2-3 of the *Profile* classifies the claimed "Increased locomotor activity in adult offspring" listed for Onishchenko et al. (2011) as a "Less serious" effect. Table 2-3 fails to note that this effect was only seen in male offspring, and the opposite effect was transiently seen in female offspring, and only during novelty induced activity. The bone differences seen by Koskela et al. (2016) were also classified in Table 2-3 as "Less serious" effects. Why does Appendix A fail to mention these caveats? Surely MRLs should be based on effects deemed to be seriously adverse: if not, why bother making this distinction throughout the text?

PFOS

The Agency chooses to base its provisional MRL for PFOS on "[D]elayed eye opening and decreased pup body weight," as reported in a two-generation rat study by Luebker and colleagues, 2005 (page A-36). This is a questionable choice, given what the study authors themselves write about these two "effects". In particular, Luebker et al. (2005) note (*emphases added*):

> The *slight* delay in eye opening (0.6 days compared to control) in the 0.4 mg/(kg day) dose group *was not considered an adverse outcome*. . . .
>
> *Only transient* reductions in body weights occurred during mid-lactation in the F_2 generation pups at the 0.4 mg/(kg day) dose level. *This observation was not considered toxicologically significant* because the small reductions in pup body weights were associated with minimally larger live litter sizes at birth and on LD 4 pre-culling, as compared with the control group, and body weights in this dose group were comparable to controls at the end of lactation.

Nowhere in its discussion of this "principal study" (pages A-41-A-42) does ATSDR mention these important caveats. Why? If ATSDR maintains this study as the basis for the PFOS MRL, then it should provide experimental evidence (a) that a 0.6 day delay in eye opening is not within normal variability for this strain of rats, and (b) that the larger litter size cannot explain the reductions in body weight.

Not only does ATSDR fail to explain why it disagrees with the study authors concerning the lack of toxicological significance of the relied-upon PFOS-associated effects: the Agency also fails to explain what it believes these effects mean for the development of human infants. Indeed, while eye opening is one developmental milestone in rodents, there is of course no direct

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analogue for humans. Further, there are many other developmental milestones, and/or indications of developmental toxicity, typically measured in two-generation rodent studies; and these are not, apparently, affected by PFOS at the effect-level chosen by ATSDR from Luebker et al (2005). Such typical rodent developmental effects include: olfactory discrimination, swimming performance, nocioception (measured by the tail flick test), sensorimotor gating-prepulse inhibition, exploratory behavior, and social (play) behavior (see, for example, Schneider & Przewlocki, 2005). Is it significant that PFOS, at the point of departure, is not known to affect any of these developmental and/or neurobehavioral endpoints? ATSDR does not say.

Separately, and also perplexingly, ATSDR derives its MRL (based, nominally, on Luebker et al., 2005) by applying a "modifying factor" of 10 to account (page A-42) "for concern that immunotoxicity may be a more sensitive endpoint of PFOS toxicity than developmental toxicity. This seems poorly justified, at best. The Luebker et al. (2005) is not a study of immunotoxicity, and no "modification" of dose-response data from it can be used to predict immunotoxicity even in rats, let alone in humans.

If the Agency believes that PFOS is immunotoxic at or near environmentally-relevant exposures, then it should rely directly on other studies that actually address immunotoxicity. But if the Agency believes instead that such studies are no more than suggestive, then it should discount them.

At the least, the effect-levels in such immunotoxicity studies should be compared with those in the principal, currently selected study: if the effect-levels in the immunotoxicity studies are comparable or larger than those in the principal study, then clearly no further "modifying factor" is necessary; while if the effect-levels are smaller, then any "modifying factor" need not exceed the ratio of the effect-levels (and in this case the immunotoxicity study would effectively become the principal study).

If ATSDR is concerned that PFOS might be immunotoxic at environmentally-relevant exposures, then it should propose specific additional research aimed to uncover such an adverse effect, which, if found, could provide a reliable, relevant data-set for purposes of human health risk assessment.

As it stands, though, the Agency bases its provisional MRL for PFOS on "critical effects" (page A-36) in neonatal rats that the study-investigators themselves deem to be "slight", "transient", and not "toxicologically significant;" and then compounds its questionable choice by dividing by an arbitrary factor of 10 that appears to be more "precautionary" than it is scientific.

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PFNA

The Agency bases its provisional MRL for PFNA on "[D]ecreased body weight and developmental delays" as reported in a two-generation mouse study by Das et al., (2015; page A-57). This study utilized four dose-rates (1, 3, 5, and 10 mg PFNA/kg-day), and 8 to 10 dams per dose-group. The authors report, "Mouse pups were born alive and postnatal survival in the 1 and 3 mg/kg PFNA groups was not different from that in controls." Offspring that had been exposed at 3 mg/kg (but not at 1 mg/kg) gained weight at reduced rates (starting at postnatal day 7); and both eye-opening and vaginal opening separation were delayed in offspring at 3 mg/kg (but not at 1 mg/kg).

With regard to mechanism of action, Das et al. (2015) note the "robust activation of peroxisome proliferator-activated receptor-alpha (PPARα) target genes by PFNA that resembled the responses of PFOA." And as expected and reported by Wolf et al. (2010), PFNA failed to induce these adverse effects in mice that had been genetically engineered to lack this important receptor.

Accordingly, as noted above, human fetuses and neonates would be expected to be *considerably less*, not more, sensitive to these PFNA-induced, PPARα-mediated effects.[5] But again, the Agency derives its MRL by assuming that human offspring could be up to 30 times more sensitive than the "average" mouse. The Agency again fails to even discuss the genuine uncertainties in its 30-fold "uncertainty factor," let alone to justify its choice of this precise and,

[5] PPARs are present throughout the plant and animal kingdoms: many forms of these receptors have so far been identified (see, for example, Tyagi, 2011, for an authoritative review). The specific molecular forms and structures of these receptors differ among rats, mice, monkeys, and humans; and some of these differences profoundly affect how PFAS and other PPAR-agonists affect rodents, for example, as opposed to humans. Tyagi, 2011 note (emphases added):

> PPARs were identified in rodents in 1990 and these belong to a nuclear hormone receptor superfamily containing 48 members. *But, these agents are associated with no proliferation in the human beings*. Structurally, PPARs are similar to steroid or thyroid hormone receptor and are *stimulated in response to small lipophilic ligands*. *In rodents*, a large class of structurally related chemicals including herbicides, industrial solvents, and hypolipidemic drugs lead to significant increase in the number and size of peroxisomes in the liver and may cause liver hypertrophy, liver hyperplasia, hepatocarcinogenesis, and transcription of genes encoding proximal enzymes. PPARs mainly exist in three subtypes; α, β/δ, and γ, each of which mediates the physiological actions of a large variety of FAs and FA-derived molecules. Activated PPARs are also capable of transcriptional repression through DNA-independent protein-protein interactions with other transcription factors such as NFκB signal activators and transducers of transcription STAT-1 and AP-1 signaling.

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based on the evidence, overly large value. This failure should not carry through to the final version of the *Profile*.

Some 10 epidemiological studies have addressed the hypothesis that PFNA affects birth outcomes: results from these studies have generally failed to support this hypothesis.

In particular, PFNA exposure-levels have been found to not correlate with birth weights (Monroy et al., 2008; Chen et al., 2012; Arbuckle et al., 2013; Robledo et al., 2015; Bach et al., 2016; Lee et al., 2016; Lenters et al., 2016; Shi et al. 2017) or with other developmental indices, such as birth length or ponderal index (Bach et al., 2016; Shi et al., 2017). Wang et al. (2016) reported that PFNA and four other PFAS all correlated inversely with the birth weight of girls, but not of boys.

The text of the *Profile* (page 377) does note:

> No consistent associations for alterations in birth weight were found for . . . PFNA . . . Overall, no associations were found between serum PFOA, PFOS, PFHxS, PFNA, or PFUA and increases in the risk of low birth weight or small for gestational age infants. No consistent results for risks of birth defects have been found . . .The available epidemiology data do not suggest associations between perfluoroalkyls and IQ or scholastic achievement for PFOA, PFOS, PFHxS, PFNA, PFDeA, PFUA, or PFDoA. Similarly, no associations were found between PFOA, PFOS, PFHxS, PFNA, or PFDeA and increased risk of ADHD; several studies have found decreased risk of ADHD.

Yet Appendix A, in deriving an MRL for PFNA based on the developmental endpoints in mice noted above, fails to note a lack of support from the rather abundant epidemiologic database. This seems an important omission, and should be rectified in the final version of the *Profile*.

PFHxS

The Agency bases its provisional MRL for PFHxS on "[T]hyroid follicular cell damage" supposedly reported in rats, citing Butenhoff et al. (2009) and Hoberman and York (2003). The 2003 report is unpublished, and although cited several times in the text of the *Profile*, not discussed. It apparently forms the basis of the published, 2009 paper. The agency should provide a reference to this unpublished paper that allows an interested person to locate it: a suitable form would be something such as, "Available in EPA Administrative Record AR-226, copies of which may be requested on CD-ROM from the EPA Docket Office by calling 202-566-0280 or sending an email request to: oppt.ncic@epa.gov."

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For at least two reasons, ATSDR's choice is questionable.

First, there is no evidence that the rats' thyroid follicular cells were "damaged" by PFHxS. Instead, as Butenhoff et al. (2009) note, high doses of PFHxS did, as expected, affect exposed rats' livers – effects that the Agency itself clearly rejects as irrelevant for purposes of human health risk assessment (see page A-49). The effects seen in the thyroid glands of the male (and not female) rats were (i) only indirect, being secondary to induction of the rats' livers' microsomal enzymes and, in any event, (ii) not "damage". The Butenhoff et al. (2009) study makes this point clear: but Appendix A obscures it.

Second, follow up studies in mice (Chang et al., 2018, not cited by ATSDR) found no such effects in the thyroid of either male or female rodents, neither in adults nor in the offspring. The Chang et al. (2018) study examined reproductive and developmental toxicity in CD-1 mice, with additional mice added for toxicokinetic studies. The authors report (emphasis added):

> In the current study of PFHxS, there was no effect on TSH in the adult F_0 mice or in the F_1 pups when serum TSH was measured at multiple times during their development; and, most importantly, there were no effect on thyroid histopathology. Therefore, there is *no evidence to suggest that perfluoroalkyl sulfonates such as PFHxS and PFOS impact thyroid homeostasis*.

This paper is not cited in the *Profile*, but should be.

In estimating an HED from the study of Butenhoff et al. (2009), the Agency used the half-life derived by Olsen et al. (2007) in 26 retired occupationally exposed workers, only two of whom were women (both likely past menopause). The Profile should note that Li et al. (2017a,b) have derived half-lives for PFOS, PFHxS, and PFOA in 106 members of the general population, with separate estimates for men and women ages 15–50. For PFHxS (and for PFOS), the half-life for younger women was significantly less than for men, with menstrual blood loss potentially accounting for some of that difference. If the final MRL were to be based on reproductive effects, then the extrapolation to humans should be based on this smaller half-life, since women of child-bearing age would be the susceptible population. Of course, HEDs for other end-points in the rodents should be compared, and use of a longer half-life might be appropriate for estimating HEDs for such other end-points.

We note that Ramhøj et al. (2018) examined the effect of PFHxS and a mixture of PFHxS and twelve endocrine disrupting chemicals on reproductive toxicity in Wistar rats, but the F_0 generation was limited to the dams. Evaluation of these studies should be added to the *Profile*.

Overall, though, there are so far rather few published toxicologic studies on PFHxS. Perhaps deriving *any* MRL for this specific PFAS is premature? Alternatively, perhaps additional,

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unpublished studies could be located (and made publicly available): if relevant and reliable, could they be used to derive a more reliable MRL?

Additional observations

This set of compounds is typically referred to as "perfluorinated alkyl substances," and so abbreviated as PFAS. The Agency chooses instead to refer to them as "perfluorinated alkyls," which is both nonstandard and ungrammatical, the correct term in chemistry being, for example, "alkyl group". Why did ATSDR make this odd choice? We recommend against it.

We noted two typos in Appendix A in connection with PFHxS. At page A-9, the paragraph beginning "PFHxS," at line 3, the estimated half-life given by Olsen et al. (2007) was 3,109 days, not 3,102; and at line 5, the highest final concentration was 791 ng/mL, not 1,740 ng/mL (which was the highest final concentration of PFOS, not PFHxS).

Concluding remarks

Through no fault of the Agency's, ATSDR's *Toxicological Profiles*, and especially its MRLs, often stir controversy. The current *Profile* and set of MRLs are no exception. Even mainstream science news reports contained headlines and stories such as (*E&E News*, Jun. 20, 2018):

> ***After controversy, U.S. releases report showing elevated health risks from nonstick chemicals***
>
> President Donald Trump's administration has released a politically charged toxicology report about nonstick chemicals showing they can endanger human health at significantly lower levels than the Environmental Protection Agency (EPA) has previously called safe. . . .

Of course, the statements are inaccurate, in several respects, but perhaps that is to be expected. Press releases from various activists' groups were more alarmist still.

Because of their importance, the Agency's MRLs, even just the "provisional" MRLs, must be strongly evidence-based. Moreover, the ATSDR must take special care to succinctly and transparently convey the many uncertainties that surround its MRLs: U.S. EPA does this with regard to its reference dose-values; but ATSDR's standard explanations of its MRLs fall short.

For example, ATSDR must make plain, to the public, which of its MRLs are based directly on evidence from human studies, and which (all four in this case) are instead extrapolated solely from evidence in laboratory rats and/or mice. Perhaps a simple designation could be devised to mark the MRLs: such as, "Acute MRL; based on human studies"; or "Chronic MRL; based on studies in rats."

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As detailed herein, the Agency's provisional MRLs for all four PFAS should be revised. In some cases, as noted above, the Agency chose unreliable studies as their sole basis for an MRL. The Agency should choose differently going forward. In other cases, the chosen studies are reliable, but the Agency's uses of them are questionable.

We expect that ATSDR has many constraints, resource-wise and otherwise, and recognize that objective analysts may differ among themselves as to the "correct" way to assess risks to human health from given chemical contaminants. Nonetheless, there is now considerable scientific knowledge regarding at least PFOA and PFOS, if not the other two PFAS. ATSDR can and should do better as it works to finalize its MRLs.

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References

Abbott BD, Wolf CJ, Schmid JE, Das KP, Zehr RD, Helfant L, Nakayama S, Lindstrom AB, Strynar MJ, Lau C. Perfluorooctanoic acid–induced developmental toxicity in the mouse is dependent on expression of peroxisome proliferator–activated receptor-alpha. Toxicological Sciences. 2007 May 7;98(2):571–581.

Albrecht PP, Torsell NE, Krishnan P, Ehresman DJ, Frame SR, Chang SC, Butenhoff JL, Kennedy GL, Gonzalez FJ, Peters JM. A species difference in the peroxisome proliferator-activated receptor α-dependent response to the developmental effects of perfluorooctanoic acid. Toxicological Sciences. 2013;131(2):568–582.

Arbuckle, T.E., Kubwabo, C., Walker, M., Davis, K., Lalonde, K., Kosarac, I., Wen, S.W., Arnold, D.L., 2013. Umbilical cord blood levels of perfluoroalkyl acids and pol-ybrominated flame retardants. Int. J. Hyg. Environ. Health 216, 184e194.

Bach CC, Bech BH, Brix N, Nohr EA, Bonde JP, Henriksen TB. Perfluoroalkyl and polyfluoroalkyl substances and human fetal growth: a systematic review. Crit Rev Toxicol. 2015 Jan;45(1):53-67.

Beronius A, Hanberg A, Heimeier R, Håkansson H. Risk assessment of developmental neurotoxicity: Evaluation of the OECD TG 426 test guideline and guidance documents. Karolinska Institute, Stockholm. 2013. https://ki.se/sites/default/files/2013-1.pdf.

Bhat VS, Meek ME, Valcke M, English C, Boobis A, Brown R. Evolution of chemical-specific adjustment factors (CSAF) based on recent international experience; increasing utility and facilitating regulatory acceptance. Critical Reviews in Toxicology. 2017 Oct 21;47(9):733–753.

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Butenhoff JL, Chang SC, Ehresman DJ, York RG. Evaluation of potential reproductive and developmental toxicity of potassium perfluorohexanesulfonate in Sprague Dawley rats. Reproductive Toxicology. 2009 Jun 1;27(3-4):331–341.

Chang S, Butenhoff JL, Parker GA, Coder PS, Zitzow JD, Krisko RM, Bjork JA, Wallace KB, Seed JG. Reproductive and developmental toxicity of potassium perfluorohexanesulfonate in CD-1 mice. Reproductive Toxicology. 2018 Jun 1;78:150–168.

Chen, M., Ha, E., Wen, T., Su, Y., Lien, G., Chen, C., Chen, P., Hsieh, W., 2012. Per-fluorinated compounds in umbilical cord blood and adverse birth outcomes. PloS One 7, e42474.

Cheng, Y., Cui, Y., Dang, Z.C., Xie, W.P., Li, H.S., Yin, H.H., Chen, H.M., 2012. Effects ofCheng J, Fujimura M, Zhao W, Wang W. Neurobehavioral effects, c-Fos/Jun expression and tissue distribution in rat offspring prenatally co-exposed to MeHg and PFOA: PFOA impairs Hg retention. Chemosphere. 2013 May 1;91(6):758–764.

Convertino M, Church TR, Olsen GW, Liu Y, Doyle E, Elcombe CR, Barnett AL, Samuel LM, MacPherson IR, Evans TR. Stochastic Pharmacokinetic-Pharmacodynamic Modeling for Assessing the Systemic Health Risk of Perfluorooctanoate (PFOA). Toxicological Sciences. 2018 Feb 16;163(1):293–306.

Das KP, Grey BE, Rosen MB, Wood CR, Tatum-Gibbs KR, Zehr RD, Strynar MJ, Lindstrom AB, Lau C. Developmental toxicity of perfluorononanoic acid in mice. Reproductive toxicology. 2015 Jan 1;51:133–144.

Dong GH, Liu MM, Wang D, Zheng L, Liang ZF, Jin YH. Sub-chronic effect of perfluorooctanesulfonate (PFOS) on the balance of type 1 and type 2 cytokine in adult C57BL6 mice. Archives of Toxicology. 2011 Oct 1;85(10):1235–1244.

Dong GH, Zhang YH, Zheng L, Liu W, Jin YH, He QC. Chronic effects of perfluorooctanesulfonate exposure on immunotoxicity in adult male C57BL/6 mice. Archives of Toxicology. 2009 Sep 1;83(9):805–815.

Dudek M, Marcinkowska M, Bucki A, Olczyk A, Kołaczkowski M. Idalopirdine–a small molecule antagonist of 5-HT 6 with therapeutic potential against obesity. Metabolic Brain Disease. 2015 Dec 1;30(6):1487–1494.

Dupont, 2014. Comments on U. S. EPA Office of Water February 2014 Draft “Health Effects Document for Perfluorooctanoic Acid (PFOA)”. EPA-HQ-OW-2014-0138-0016. [Contains the full MacPherson 2011 poster].

Edler L, Poirier K, Dourson M, Kleiner J, Mileson B, Nordmann H, Renwick A, Slob W, Walton K, Würtzen G (2002) Mathematical modelling and quantitative methods. Food and Chemical Toxicology, 40: 283–326.

Goulding DR, White SS, McBride SJ, Fenton SE, Harry GJ. Gestational exposure to perfluorooctanoic acid (PFOA): alterations in motor related behaviors. Neurotoxicology. 2017 Jan 1;58:110–119.

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Koskela A, Finnilä MA, Korkalainen M, Spulber S, Koponen J, Håkansson H, Tuukkanen J, Viluksela M. Effects of developmental exposure to perfluorooctanoic acid (PFOA) on long bone morphology and bone cell differentiation. Toxicology and Applied Pharmacology. 2016 Jun 15;301:14–21.

Lee ES, Han S, Oh JE. Association between perfluorinated compound concentrations in cord serum and birth weight using multiple regression models. Reprod Toxicol. 2016 Jan;59:53-9.

Lenters V, Portengen L, Rignell-Hydbom A, Jönsson BA, Lindh CH, Piersma AH, Toft G, Bonde JP, Heederik D, Rylander L, Vermeulen R. Prenatal Phthalate, Perfluoroalkyl Acid, and Organochlorine Exposures and Term Birth Weight in Three Birth Cohorts: Multi-Pollutant Models Based on Elastic Net Regression. Environ Health Perspect. 2016 Mar;124(3):365-72.

Li Y, Fletcher T, Mucs D, Scott K, Lindh CH, Tallving P, Jakobsson K. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup Environ Med. 2017a;75(1)46–51.

Li Y, Mucs D, Scott K, Lindh C, Tallving P, Fletcher T, Jakobsson K. 2017b. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Report No 2:2017, Occupational & Environmental Medicine in Gothenburg, The Sahlgrenska Academy Institute of Medicine, Goteborgs Universitet.

Long Y, Wang Y, Ji G, Yan L, Hu F, Gu A. Neurotoxicity of perfluorooctane sulfonate to hippocampal cells in adult mice. PLoS one. 2013 Jan 30;8(1):e54176.

Loveless SE, Finlay C, Everds NE, Frame SR, Gillies PJ, O'Connor JC, Powley CR, Kennedy GL. Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO). Toxicology. 2006 Mar 15;220(2-3):203–217.

Loveless SE, Hoban D, Sykes G, Frame SR, Everds NE. Evaluation of the immune system in rats and mice administered linear ammonium perfluorooctanoate. Toxicological Sciences. 2008 Jun 16;105(1):86–96.

Luebker DJ, Case MT, York RG, Moore JA, Hansen KJ, Butenhoff JL. Two-generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. Toxicology. 2005 Nov 5;215(1–2):126–148.

MacPherson M, Bissett D, Tait B., Samuel LM, MacDonald J, Barnett AL, Wolf CR, Elcombe CR, Jeynes-Ellis A, Evans TRJ. A phase I Clinical trial of CXR1002 in patients (pts) with advanced cancer. Eur J Cancer Suppl. 2010 Nov;8(7)124. DOI:10.1016/S1359-6349(10)72098-X. (Poster session, 22nd EORTC – NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics Programme and Abstract Book).

MacPherson IR, Bissett D, Petty RD, Tait B, Samuel LM, MacDonald J, Smith M, Birse-Archbold JA, Barnett AL, Wolf CR, Elcombe CR, Jeynes-Ellis A, Evans TRJ. A first-in-human phase I clinical trial of CXR1002 in patients (pts) with advanced cancer. Journal of Clinical

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Oncology. 2011 May 20;29(15_suppl):Abstract 3063. DOI: 10.1200/jco.2011.29.15_suppl.3063.

Meek ME, Ohanian E, Renwick A, Naumann B, Lake B, Vu V, Dourson M. 1999. Guidelines for application of data-derived uncertainty factors in risk assessment. Report of a Meeting by Toxicology Excellence for Risk Assessment for US EPA/Health Canada, Washington, March 25th–26th.

Meek ME, Renwick A, Ohanian E, Dourson M, Lake B, Naumann BD, Vu V. 2002. Guidelines for application of chemical-specific adjustment factors in dose/concentration-response assessment. Toxicology. 181- 182:115–120.

Meek ME, Boobis AR, Crofton KM, Heinemeyer G, Van Raaij M, Vickers C. 2011. Risk assessment of combined exposure to multiple chemicals: a WHO/IPCS framework. Regul Toxicol Pharmacol. 60:S1–S14.

Monroy, R., Morrison, K., Teo, K., Atkinson, S., Kubwabo, C., Stewart, B., Foster, W.G., 2008. Serum levels of perfluoroalkyl compounds in human maternal and umbilical cord blood samples. Environ. Res. 108, 56e62.

OECD Guideline for the testing of chemicals (2007) Developmental Neurotoxicity study, TG 426.

Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, Zobel LR. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environmental health perspectives. 2007 Sep;115(9):1298–1305.

Onishchenko N, Fischer C, Ibrahim WN, Negri S, Spulber S, Cottica D, Ceccatelli S. Prenatal exposure to PFOS or PFOA alters motor function in mice in a sex-related manner. Neurotoxicity Research. 2011 Apr 1;19(3):452–461.

Peden-Adams MM, Keller JM, EuDaly JG, Berger J, Gilkeson GS, Keil DE. Suppression of humoral immunity in mice following exposure to perfluorooctane sulfonate. Toxicological Sciences. 2008 Mar 20;104(1):144–154.

Ramhøj L, Hass U, Boberg J, Scholze M, Christiansen S, Nielsen F, Axelstad M. Perfluorohexane Sulfonate (PFHxS) and a Mixture of Endocrine Disrupters Reduce Thyroxine Levels and Cause Antiandrogenic Effects in Rats. Toxicological Sciences. 2018 Mar 6;163(2):579–591.

Redfern WS, Tse K, Grant C, Keerie A, Simpson DJ, Pedersen JC, Rimmer V, Leslie L, Klein SK, Karp NA, Sillito R. Automated recording of home cage activity and temperature of individual rats housed in social groups: The Rodent Big Brother project. PloS One. 2017 Sep 6;12(9):e0181068. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0181068.

Robledo CA, Yeung E, Mendola P, Sundaram R, Maisog J, Sweeney AM, Barr DB, Louis GM. Preconception maternal and paternal exposure to persistent organic pollutants and birth size: the LIFE study. Environ Health Perspect. 2015 Jan;123(1):88-94.

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Schneider T, Przewłocki R. Behavioral alterations in rats prenatally exposed to valproic acid: animal model of autism. Neuropsychopharmacology. 2005 Jan;30(1):80-9.

Shi Y, Yang L, Li J, Lai J, Wang Y, Zhao Y, Wu Y. Occurrence of perfluoroalkyl substances in cord serum and association with growth indicators in newborns from Beijing. Chemosphere. 2017 Feb;169:396-402.

Spulber S, Conti M, DuPont C, Raciti M, Bose R, Onishchenko N, Ceccatelli S. Alterations in circadian entrainment precede the onset of depression-like behavior that does not respond to fluoxetine. Translational Psychiatry. 2015 Jul;5(7):e603.

Spulber S, Kilian P, Ibrahim WN, Onishchenko N, Ulhaq M, Norrgren L, Negri S, Di Tuccio M, Ceccatelli S. PFOS induces behavioral alterations, including spontaneous hyperactivity that is corrected by dexamfetamine in zebrafish larvae. PloS One. 2014 Apr 16;9(4):e94227. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0094227.

Tyagi S, Gupta P, Saini AS, Kaushal C, Sharma S. The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. J Adv Pharm Technol Res. 2011 Oct;2(4):236-40.

US EPA (1998) US Environmental Protection Agency Health Effects Test Guidelines. OPPTS 870.6300. Developmental Neurotoxicity Study.

US EPA (2014). Guidance for applying quantitative data to develop data-derived extrapolation factors for interspecies and intraspecies extrapolation. Risk Assessment Forum. EPA/100/R-14/002F. Washington (DC) 20460.

Wambaugh JF, Setzer RW, Pitruzzello AM, Liu J, Reif DM, Kleinstreuer NC, Wang NC, Sipes N, Martin M, Das K, DeWitt JC. Dosimetric anchoring of in vivo and in vitro studies for perfluorooctanoate and perfluorooctanesulfonate. Toxicological Sciences. 2013 Sep 17;136(2):308–327.

Wang Y, Liu W, Zhang Q, Zhao H, Quan X. Effects of developmental perfluorooctane sulfonate exposure on spatial learning and memory ability of rats and mechanism associated with synaptic plasticity. Food and Chemical Toxicology. 2015 Feb 1;76:70–76.

Wang Y, Adgent M, Su PH, Chen HY, Chen PC, Hsiung CA, Wang SL. Prenatal Exposure to Perfluorocarboxylic Acids (PFCAs) and Fetal and Postnatal Growth in the Taiwan Maternal and Infant Cohort Study. Environ Health Perspect. 2016 Nov;124(11):1794-1800.

WHO/IPCS (World Health Organization/International Programme on Chemical Safety). 2005. Chemical-Specific Adjustment Factors (CSAF) for interspecies differences and human variability: guidance document for the use of data in dose/concentration-response assessment. (IPCS harmonization project document no. 2). WHO/IPCS/01.4, 1-96. Geneva, Switzerland.

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Wolf CJ, Zehr RD, Schmid JE, Lau C, Abbott BD. Developmental effects of perfluorononanoic acid in the mouse are dependent on peroxisome proliferator-activated receptor-alpha. PPAR Research. 2010;2010:282896.

Yahia D, Tsukuba C, Yoshida M, Sato I, Tsuda S. Neonatal death of mice treated with perfluorooctane sulfonate. The Journal of Toxicological Sciences. 2008 May 1;33(2):219–226.

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2019

HEALTH-BASED DRINKING WATER VALUE RECOMMENDATIONS FOR PFAS IN MICHIGAN

Michigan Science Advisory Workgroup

DR. JAMIE DEWITT
MR. KEVIN COX
DR. DAVID SAVITZ

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.

Steve Sliver,
Executive Director,
Michigan PFAS Action Response Team

Michigan Science Advisory Workgroup

Dr. Jamie DeWitt
Mr. Kevin Cox
Dr. David Savitz

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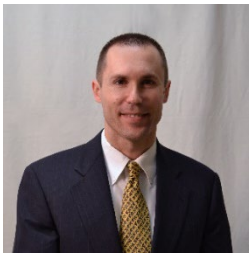
Report developed for the Michigan PFAS Action Response Team,
Lansing, Michigan
June 27, 2019

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.

Table of Contents

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 (4.8×10^{-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

Chemical Summary for PFOA

	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, Håkanss on 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 x k_e x V_d) = 0.001163 mg/kg/day Ke = 0.000825175 (8.2×10^{-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 $(80kg/0.45\ kg)^{¼}$ = 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: $$HBV = \frac{RSC \times Toxicity\ value \times Body\ weight}{Water\ intake}$$

Chemical Summary for PFOS

	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 x k_e x V_d) = 0.0000866 mg/kg/day Ke = 0.000558539 (5.5×10^{-4}) based on a human serum half-life of 1241 days (Li et al. 2018) Vd = 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

Chemical Summary for PFBS

	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: $$HBV = \frac{RSC \times Toxicity\ value \times Body\ weight}{Water\ intake}$$

Chemical Summary for GenX

	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

Summary Table of Drinking Water HBVs

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.

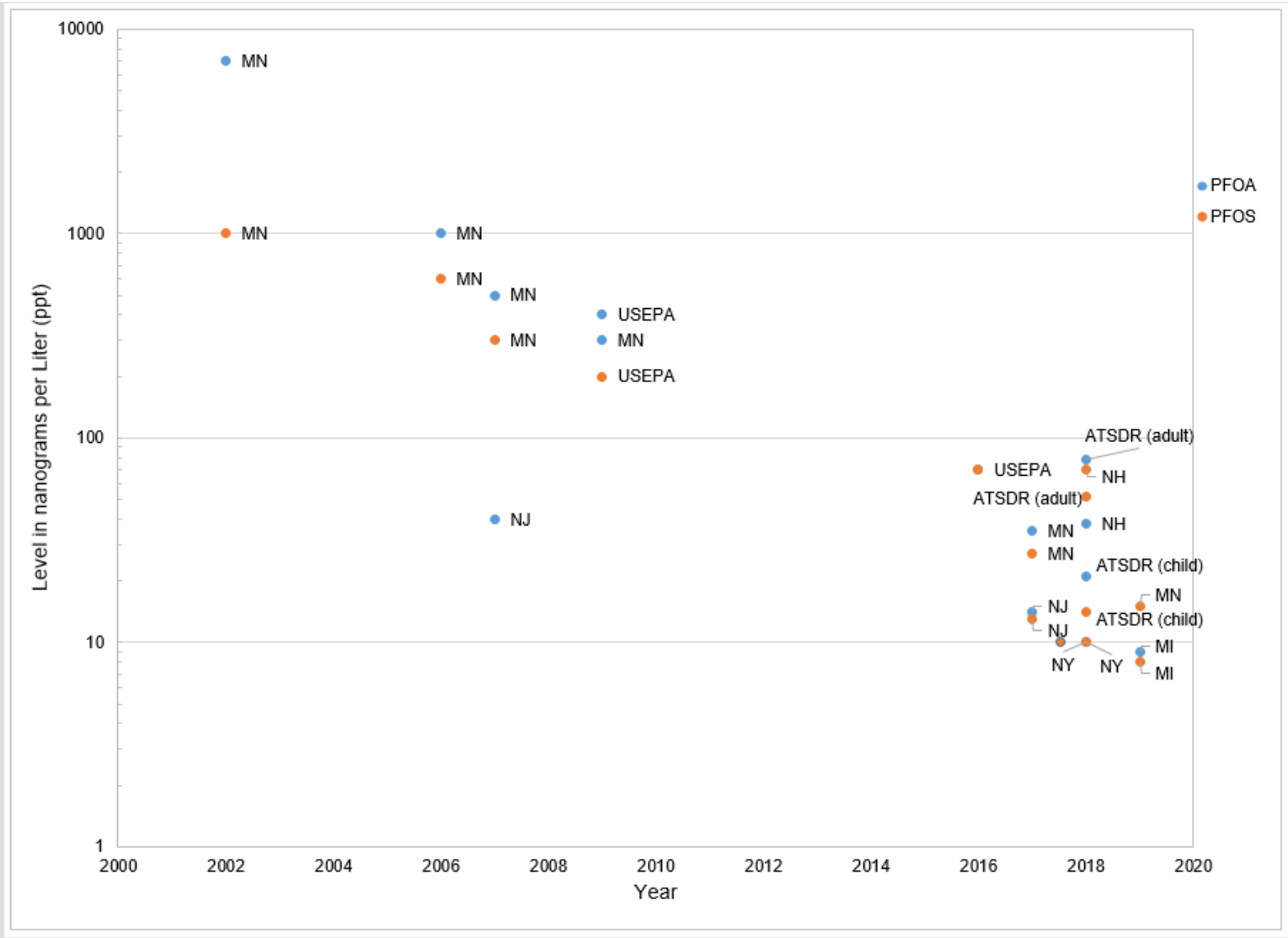


Figure 1: Screening Levels, Health-Based Values, and Regulatory Standards for PFOS and PFOA Over a 20-Year Timeframe.

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.

References

ATSDR. (2018). Agency for Toxic Substances and Disease Registry. Toxicological Profile for Perfluoroalkyls. Draft for Public Comment. June 2018.

Bartell SM, Calafat AM, Lyu C, et al. 2010. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ Health Perspect 118(2):222-228.

Beck, N.B., Becker, R.A., Erraguntla, N., Farland, W.H., Grant, Gray, G., Kirman, C., LaKind, J.S., Lewis, R.J., Nance, P., Pottenger, L.H., Santos, S.L., Shirley, S., Simon, T., and Dourson, M.L. (2016). Approaches for describing and communicating overall uncertainty in toxicity characterizations: U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS) as a case study. Environment International 89-90, 110-128.

Blystone, C. (2019). [Personal Communication. Use of NTP data tables and study protocol (January 2019 email exchange).]., cited in Minnesota Department of Health (2019). Toxicological Summary for Perfluorohexane sulfonate. Accessed online June 2019 at:

CDC. (2019). (Center for Disease Control) Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, January 2019, Volume One.

Chang, S., JL Butenhoff, GA Parker, PS Coder, JD Zitsow, RM Krisko, JA Bjork, KB Wallace, JG Seed. (2018). Reproductive and developmental toxicity of potassium perfluorohexanesulfonate in CD-1 mice. Reproductive Toxicology, 78, 150-168.

Das KP, Grey BE, Rosen MB, et al. 2015. Developmental toxicity of perfluorononanoic acid in mice. *Reproductive Toxicology* 51:133-144.

DeWitt and Belcher (2018) Memorandum from Jamie DeWitt and Scott Belcher to the members of the North Carolina Secretaries' Science Advisory Board. Accessed online June 2019.

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.

DuPont-18405-1037: E.I. du Pont de Nemours and Company (2010) An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice. USEPA OPPTS 870.3550; OECD Test Guideline 421. Study conducted by WIL Research Laboratories, LLC (Study Completion Date: December 29, 2010), Ashland, OH. (as cited in USEPA (2018)).

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.

Goeden HM, Greene CW, Jacobus, JA (2019) A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance. J. Exposure Sci. Env. Epidemiol. 29:183-195.

Goeden, HM., CW Greene, JA Jacobus. (2019). A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance. Journal of Exposure Science & Environmental Epidemiology.

Hall, AP, Elcombe, CR, Foster, JR, et al. (2012) Liver Hypertrophy: A Review of Adaptive (Adverse and Non-adverse) Changes—Conclusions from the 3rd International ESTP Expert Workshop. Toxicologic Pathol. 40: 971-94.

Klaunig, JE, Shinohara, M, Iwai, H, Chengelis, CP, Kirkpatrick, JB, Wang, Z, Bruner, RH (2015) Evaluation of the chronic toxicity and carcinogenicity of perfluorohexanoic acid (PFHxA) in Sprague-Dawley rats. Toxicol. Pathol. 43 (2), 209–220.

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.

Li, Y., T Fletcher, D Mucs, K Scott, CH Lindh, P Tallving, K Jakobsson. (2018). Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occupational and Environmental Medicine, 75, 46-51.

Loveless, S.E., Slezak, B., Serex, T., Lewis, J., Mukerji, P., O'Connor, J.C., Donner, E.M., Frame, S.R., Korzeniowski, S.H., Buck, R.C., 2009. Toxicological evaluation of sodium perfluorohexanoate. Toxicology 264 (1–2), 32–44.

Luz, AL, Anderson, JK, Goodrum, P, Durda, J. (2019) Perfluorohexanoic acid toxicity, part I: Development of chronic human health toxicity value for use in risk assessment. Reg. Toxicol. Pharmacol. 103: 41-55.

Minnesota Department of Health (2019). Toxicological Summary for Perfluorooctane sulfonate (PFOS). Accessed online June 2019.

Minnesota Department of Health (2017). Toxicological Summary for: Perfluorobutane Sulfonate (PFBS). Accessed online June 2019.

Minnesota Department of Health (2017). Background Document: Toxicokinetic Model for PFOS and PFOA and Its Use in the Derivation of Human Health-based Water Guidance Values.

Minnesota Department of Health (2019). HRA Toxicology Review Worksheet for PFHxS, last revised 3/8/2019.

North Carolina Department of Health and Human Services. Questions and Answers Regarding North Carolina Department of Health and Human Services Updated Risk Assessment for GenX (Perfluoro-2-propoxypropanoic acid). July 14, 2017. Accessed online May 2019.

National Research Council (NRC). (2009). Science and Decisions: Advancing Risk Assessment. Washington D.C.: National Academies Press.

NTP. (2018). National Toxicology Program. TOX-96: Toxicity Report Tables and Curves for Short-term Studies: Perfluorinated Compounds: Sulfonates. Retrieved from https://tools.niehs.nih.gov/cebs3/views/?action=main.dataReview&bin_id=3874., cited

in Minnesota Department of Health (2019). Toxicological Summary for Perfluorohexane sulfonate. Accessed online June 2019 at: https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfhxs.pdf.

New Jersey DEP DWQI. (2018). Appendix A - Health-based Maximum Contaminant Level Support Document: Perfluorooctane sulfonate. Trenton, NJ: New Jersey Drinking Water Quality Institute.

New Jersey DEP DWQI. (2015). Maximum contaminant level recommendation for perfluorononanoic acid in drinking water. Trenton, NJ: New Jersey Drinking Water Quality Institute.

Ohmori K, Kudo N, Katayama K, et al. 2003. Comparison of the toxicokinetics between perfluorocarboxylic acids with different carbon chain length. Toxicology 184:135-140.

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.

Pachkowski B, Post GB, Stern AH. (2019) The derivation of a Reference Dose (RfD) for perfluorooctane sulfonate (PFOS) based on immune suppression. Environ Res. 2019 171:452-469.

Peden-Adams, MM, Keller, JM, EuDaly, JM, Berger, J, Gilkeson, GS, Keil, DE. (2008) Suppression of Humoral Immunity in Mice following Exposure to Perfluorooctane Sulfonate. Toxicol. Sci. 104(1): 144-154.

Russell, MH, Nilsson, H, Buck, RC (2013) Elimination kinetics of perfluorohexanoic acid in humans and comparison with mouse, rat and monkey. Chemosphere. 93: 2419-2425.

Sundstrom, M., SC Chang, PE Noker, GS Gorman, JA Hart, DJ Ehresman, A Bergman, JL Butenhoff. (2012). Comparative pharmacokinetics of perfluorohexanesulfonate (PFHxS) in rats, mice, and monkeys. Reproductive Toxicology, 33, 441-451.

Thompson, J., M. Lorber, L.-M.L. Toms, K. Kato, A.M. Calafat, and J.F. Mueller. 2010. Use of simple pharmacokinetic modeling to characterize exposure of Australians to perfluorooctanoic acid and perfluorooctane sulfonic acid. Environment International 36:390–397.

United States Environmental Protection Agency (2000). Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health. EPA-822-B-00-004. USEPA Office of Water, Washington, DC. Accessed online June 2019.

United States Environmental Protection Agency. (2002). A Review of the Reference Dose and Reference Concentration Processes. Risk Assessment Forum. EPA/630/P-02/002F, December 2002.

United States Environmental Protection Agency. (2011) Exposure Factor Handbook: 2011 Edition. EPA/600/R-09/052F. USEPA, National Center for Environmental Assessment, Office of Research and Development, Washington, DC. Accessed online June 2019.

United States Environmental Protection Agency (2011a). Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose. EPA/100/R11/0001. USEPA, Office of the Science Advisor, Risk Assessment Forum, Washington, DC. Accessed online May 2018.

United States Environmental Protection Agency (2011b). Exposure Factors Handbook 2011 Edition. EPA/600/R-09/052F. USEPA, National Center for Environmental Assessment, Office of Research and Development, Washington, DC. Accessed online May 2019.

United States Environmental Protection Agency (2018). Human Health Toxicity Values for Perfluorobutane Sulfonic Acid (CASRN 375-73-5) and Related Compound Potassium Perfluorobutane Sulfonate (CASRN 29420-49-3). Public Comment Draft. EPA-823-R-18-307. USEPA, Office of Research and Development, Washington, DC. Accessed online June 1, 2019.

United States Environmental Protection Agency (2018). Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3), Also Known as "GenX Chemicals". Public Comment Draft. EPA-823-P-18-001. USEPA Office of Water, Washington, DC. Accessed online May 2019.

United States Environmental Protection Agency (2019) Exposure Factors Handbook Chapter 3 (Update): Ingestion of Water and Other Select Liquids. EPA/600/R-18/259F. USEPA Office of Research and Development, Washington, DC. Accessed online June 2019.

Wambaugh JF, Setzer RW, Pitruzzello AM, et al. 2013. Dosimetric anchoring of in vivo and in vitro studies for perfluorooctanoate and perfluorooctanesulfonate. Toxicol Sci 136(2):308-327.

Zhang Y, Beesoon S, Zhu L, et al. 2013. Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life. Environ Sci Technol 47(18):10619-10627.

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

Appendix B: MPART Motion for Creation of Science Advisory Workgroup, April 4, 2019

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.

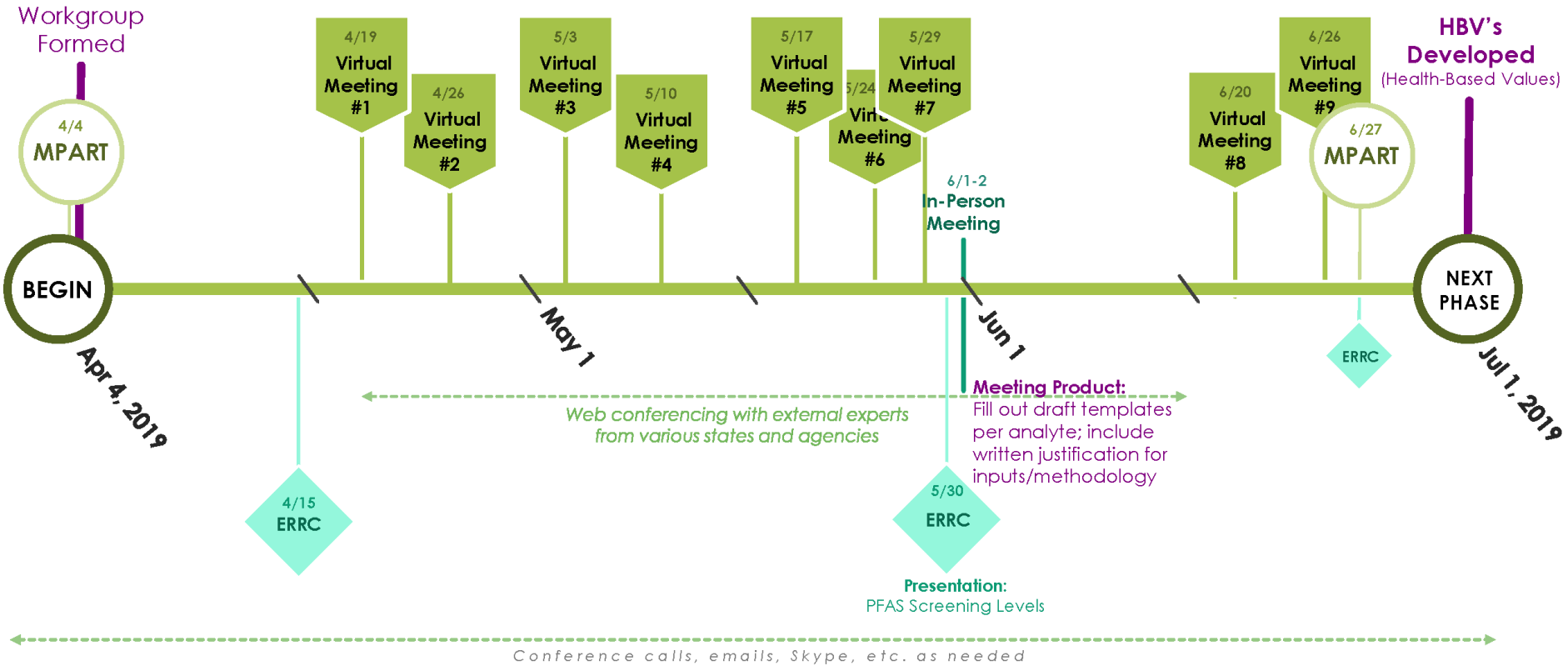
End

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



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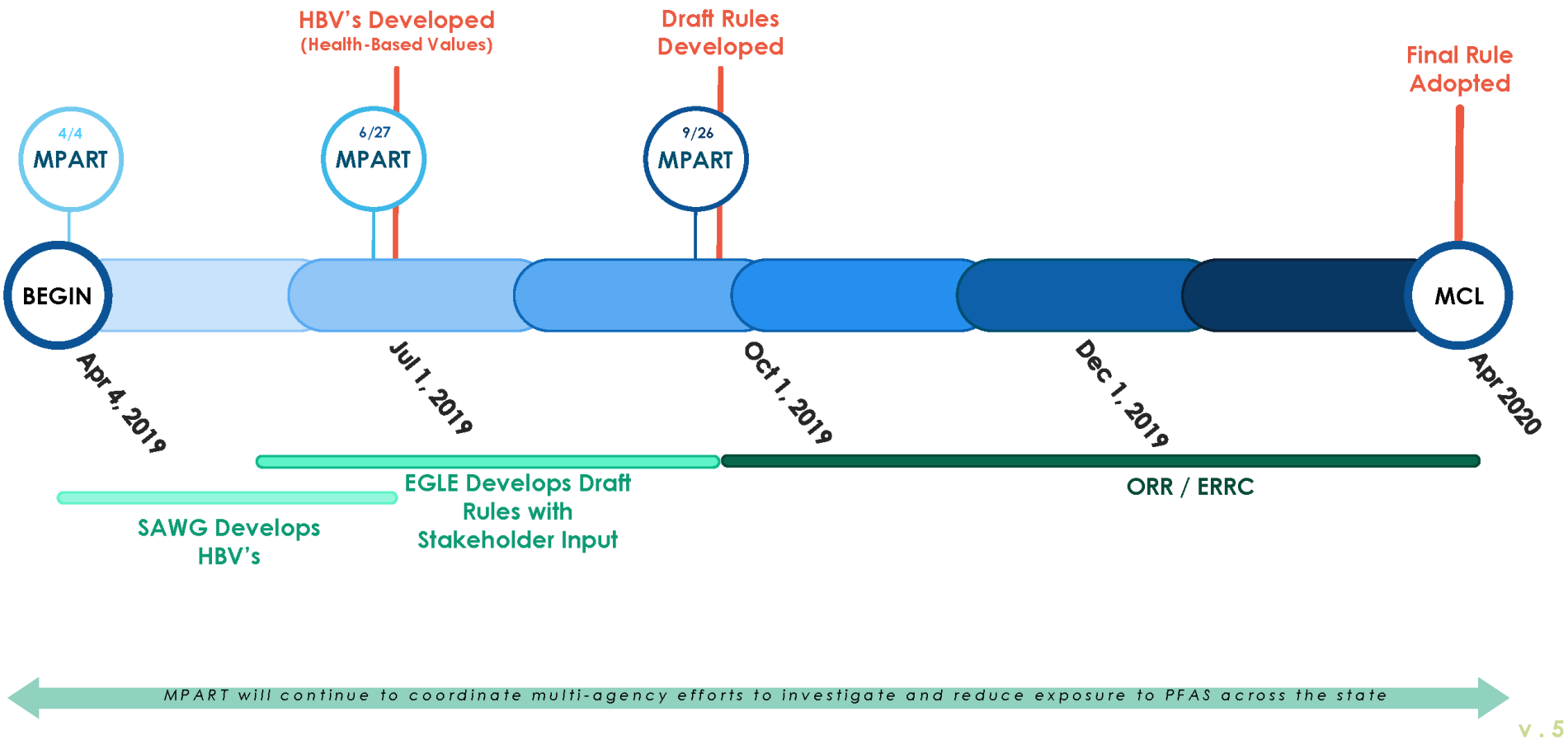
ERRC = Environmental Rules Review Committee

Appendix E: Timeline of the Maximum Contaminant Level Development Process



Advancing the ball: Using guinea pigs to study perfluorinated alkyl substances (PFAS)

Laura C. Green, Ph.D., D.A.B.T. and Edmund A.C. Crouch, Ph.D.

January 5, 2019

Hundreds of studies, and dozens of agencies, have attempted to estimate risks to human health posed by perfluorinated alkyl substances (PFAS). Essentially none of these studies, guidelines, or regulations has been based on evidence of health effects in humans exposed to PFAS (as all of us are, to greater or lesser extents).

At the same time, guidelines for allowable levels of PFAS in drinking water and other media are exceptionally stringent — making perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), for example, appear to be much riskier to human health than arsenic, mercury, benzene, and countless other, better characterized chemicals.

As a scientific matter, such stringency seems unjustified. Part of the problem is that, to date, PFAS have been studied almost exclusively in laboratory rats and mice; and these rodent-species, unfortunately, are quite poor models for humans — at least when it comes to this class of compounds.

To rectify this situation, we propose a simple solution: Bring back the guinea pig as the laboratory model of choice.

Our reasoning is as follows.

PFAS are "peroxisome proliferators", working through peroxisome proliferator-activated receptors (PPARs) to cause biological effects that may vary according to animal-species. As noted by Bell and colleagues (1998), "The guinea pig models the human response to peroxisome proliferators, where other rodents differ fundamentally in their regulation of hepatic lipid metabolism." Because of these differences, guinea pigs are employed preferentially in research focused on developing drugs, such as fibrates, used to treat people who have abnormally high levels of lipids in their blood (that is, hyperlipidemia) in order to prevent atherosclerosis and other diseases (Vázquez et al., 1995; West and Fernandez, 2004; Fernandez and Volek, 2006).

With regard to the potentially toxic effects of fibrates, PFAS, and other chemicals that activate PPAR, Dr. Chris Corton and his colleagues (2018) also note that "guinea pigs and non-human primates are better human surrogates than mice and rats because of differences in PPAR expression and activity." More generally, Corton et al. (2018) analyze the "striking differences in species responses" with regard to how different animal-species react to the clinical and toxic effects of various activators of PPAR-alpha

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activators.

As to the liver tumors and other adverse hepatic effects caused by peroxisome proliferators, Corton and co-investigators (2000, 2014 & 2018) argue convincingly that both qualitative and quantitative risk assessment should be based not on results from studies in rats and mice, but instead on results from studies in animal-species such as the guinea pig (and, when available, primates, including of course humans).

In many other, potentially relevant respects, guinea pigs are known to be better biological models for humans than are other rodents, such as rats and mice.

For example, as noted by Burns (1957), "Man, other primates and guinea pig are the only mammals that are known to be unable to synthesize L-ascorbic acid ; thus they require vitamin C in their diet to prevent scurvy."[1] Humans, monkeys, and guinea pigs are therefore susceptible to adverse health-conditions caused or exacerbated by deficiencies of vitamin C, while rats and mice are not.

Vitamin C is an antioxidant, acting *in vivo* to counter the potentially toxic effects of oxidation by hydroxyl and peroxyl radicals formed from the metabolism of dietary fats and other chemicals (Padayatty et al., 2003). Humans and guinea pigs with low (but still "adequate") levels of vitamin C are thus susceptible to the adverse effects of "oxidative stress," believed to be a major risk factor for the development of cardiovascular disease, cancer, immune system dysfunction, and other diseases linked to chronic inflammation (Ross, 1993; Santilli et al., 2015; Siti et al., 2015; Carr & Maggini, 2017; Shenoy et al., 2018; Ang et al., 2018).

In rats, mice, and most other mammals (but, again, not in humans nor in guinea pigs), vitamin C is biosynthesized (from glucose) in animals' livers: the enzyme required for the last synthetic step is missing from the liver of humans and of guinea pigs (Loewus et al., 1960; Nishikimi et al. 1992, 1994).

The livers of guinea pigs and human livers are alike in still other respects. In particular, the human metabolism of lipids, cholesterol, and many other important molecules are well modeled by guinea pigs, and poorly modeled by rats and mice.

More generally, as summarized by Podell et al. (2017) in their paper describing a guinea pig model of human type 2 diabetes that more closely mimics various aspects of the human syndrome than available rat and mouse models:

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[1] That was the state of knowledge as of 1957. More recently, a few other mammalian species, including the capybara and various species of bats, have also been found to be unable to biosynthesize Vitamin C (Birney et al., 1976; Cui et al., 2011; Padayatty & Levine, 2016).

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"In addition to inflammatory changes induced by high-fat and high-sugar diets (Fernandez and Volek, 2006; Ye et al., 2013), the guinea pig is widely regarded for research in specific diseases, including cardiovascular disease, atherosclerosis and arthritis, as well as a number of infectious diseases that have been linked as comorbidities with diabetes (West and Fernandez, 2004; Madsen et al., 2008; Padilla-Carlin et al., 2008). The guinea pig is crucial for development of new vaccines, particularly because of its immunological and pathological similarities in response to a number of infectious diseases of humans (Hickey, 2011). Additionally, the guinea pig, more so than any other rodent, shares commonalities with human lipid metabolism, including cholesterol metabolism and transport, with a greater proportion of cholesterol carried in association with low-density lipoproteins (Ensign et al., 2002; Fernandez et al., 1999; Ye et al., 2013)."

And an earlier review (West and Fernandez, 2004) noted:

". . . cholesterol and lipoprotein metabolism in guinea pigs has remarkable similarities to that of human metabolism (28). These analogies include: 1) high LDL-to-HDL ratios (25); 2) higher concentrations of free compared to esterified cholesterol in the liver (2); 3) similar intravascular processing of plasma lipoproteins (20,30,62); 4) comparable rates of hepatic cholesterol synthesis (66), esterification (26) and catabolism (67); 5) higher HDL concentrations in females compared to males (69); 6) similar plasma lipid profiles in ovariectomized guinea pigs compared to postmenopausal women (69); and 7) decreases in triacylglycerol (TG) concentrations and increases in plasma HDL cholesterol (HDL-C) with prolonged exercise (22). Due to these similarities and others, it is easy to understand why guinea pig responses to drug treatment have been shown to mimic human alterations in cholesterol and lipoprotein metabolism."

Guinea pigs are also used by researchers studying the causes of, and treatments for, diseases such as non-alcoholic fatty liver disease (NAFLD — a major cause of liver disease worldwide; Younossi et al., 2016; Perumpail et al., 2017; Ipsen et al., 2018). "Unlike mice and rats," note Ipsen and colleagues (2018), "guinea pigs naturally resemble the human lipoprotein profile and develop human-like NASH [non-alcoholic steatohepatitis] histopathology, dyslipidemia, and hepatic oxidative stress when fed a Western diet . . . ."

As our last example, in a study comparing the toxicity and the efficacy of a drug used for metal chelation (1,2-diethyl-3-hydroxypyridin-4-one; "CP94") in rats and in guinea pigs, Porter and colleagues (1993) reported that "CP94 was highly effective at mobilizing liver iron in rats but showed toxicity at higher doses, whereas in the guinea-pig the compound lacked toxicity but was ineffective at mobilizing liver iron." They added "[t]he lack of both efficacy and toxicity in the guinea-pig may therefore be explained by the rapid inactivation of CP94 by glucuronidation. This metabolism of CP94 in the guinea-pig is closer to humans than the rat, suggesting that both the efficacy and

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toxicity of this compound in humans may also be limited by glucuronidation."

* * * * *

Overall, then, we would urge the health risk-assessment community to generate and/or rely upon the best toxicity data it can, employing test-species thought to be most like humans in relevant biological respects.

* * * * *

References

Ang A, Pullar JM, Currie MJ, Vissers MCM. Vitamin C and immune cell function in inflammation and cancer. Biochem Soc Trans. 2018 Oct 19;46(5):1147–1159.

Bell AR, Savory R, Horley NJ, Choudhury AI, Dickins M, Tim JB, Salter AM, Bell DR. Molecular basis of non-responsiveness to peroxisome proliferators: the guinea-pig PPARα is functional and mediates peroxisome proliferator-induced hypolipidaemia. Biochemical Journal. 1998 Jun 15;332(3):689–693.

Birney EC, Jenness R, Ayaz KM. Inability of bats to synthesise L-ascorbic acid. Nature. 1976 Apr 15;260(5552):626–628.

Burns JJ. Missing step in man, monkey and guinea pig required for the biosynthesis of L-ascorbic acid. Nature. 1957 Sep;180(4585):553.

Carr A, Maggini S. Vitamin C and immune function. Nutrients. 2017;9(11):1211.

Corton JC, Anderson SP, Stauber A. Central role of peroxisome proliferator–activated receptors in the actions of peroxisome proliferators. Annual Review of Pharmacology and Toxicology. 2000 Apr;40(1):491–518.

Corton JC, Cunningham ML, Hummer BT, Lau C, Meek B, Peters JM, Popp JA, Rhomberg L, Seed J, Klaunig JE. Mode of action framework analysis for receptor-mediated toxicity: The peroxisome proliferator-activated receptor alpha (PPAR α) as a case study. Critical Reviews in Toxicology. 2014 Jan 1;44(1):1–49.

Corton JC, Peters JM, Klaunig JE. The PPARα-dependent rodent liver tumor response is not relevant to humans: addressing misconceptions. Archives of Toxicology. 2018 Jan 1;92(1):83–119.

Cui J, Yuan X, Wang L, Jones G, Zhang S. Recent loss of vitamin C biosynthesis ability in bats. PLoS One. 2011;6(11):e27114.

Fernandez ML, Volek JS. Guinea pigs: a suitable animal model to study lipoprotein metabolism, atherosclerosis and inflammation. Nutrition & Metabolism. 2006 Dec;3(1):17.

Ipsen DH, Lykkesfeldt J, Tveden-Nyborg P. Molecular mechanisms of hepatic lipid accumulation in non-alcoholic fatty liver disease. Cellular and Molecular Life Sciences. 2018 Sep 1:75(18)3313–3327.

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Loewus FA, Kelly S, Hiatt HH. Ascorbic acid synthesis from D-glucose-2-C14 in the liver of the intact rat. The Journal of Biological Chemistry. 1960 Apr 1;236(4):937–939.

Nishikimi M, Fukuyama R, Minoshima S, Shimizu N, Yagi K. Cloning and chromosomal mapping of the human nonfunctional gene for L-gulono-gamma-lactone oxidase, the enzyme for L-ascorbic acid biosynthesis missing in man. Journal of Biological Chemistry. 1994 May 6;269(18):13685–13688.

Nishikimi M, Kawai T, Yagi K. Guinea pigs possess a highly mutated gene for L-gulono-gamma-lactone oxidase, the key enzyme for L-ascorbic acid biosynthesis missing in this species. Journal of Biological Chemistry. 1992 Oct 25;267(30):21967–21972.

Padayatty SJ, Katz A, Wang Y, Eck P, Kwon O, Lee JH, Chen S, Corpe C, Dutta A, Dutta SK, Levine M. Vitamin C as an antioxidant: evaluation of its role in disease prevention. Journal of the American College of Nutrition. 2003 Feb 1;22(1):18–35.

Padayatty SJ, Levine M. Vitamin C: the known and the unknown and Goldilocks. Oral Dis. 2016 Sep;22(6):463–493.

Perumpail BJ, Khan MA, Yoo ER, Cholankeril G, Kim D, Ahmed A. Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. World J Gastroenterol. 2017 Dec 21;23(47):8263–8276.

Porter JB, Abeysinghe RD, Hoyes KP, Barra C, Huehns ER, Brooks PN, Blackwell MP, Araneta M, Brittenham G, Singh S, Dobbin P. Contrasting interspecies efficacy and toxicology of 1,2-diethy-3-hydroxypyridin-4-one, CP94, relates to differing metabolism of the iron chelating site. British Journal of Haematology. 1993 Sep;85(1):159–168.

Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993;362:801–809.

Santilli F, D'Ardes D, Davì G. Oxidative stress in chronic vascular disease: From prediction to prevention. Vascul Pharmacol. 2015 Nov;74:23–37.

Shenoy N, Creagan E, Witzig T, Levine M. Ascorbic Acid in Cancer Treatment: Let the Phoenix Fly. Cancer Cell. 2018 Nov 12;34(5):700–706.

Siti HN, Kamisah Y, Kamsiah J. The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). Vascul Pharmacol. 2015 Aug;71:40–56.

Vázquez M, Alegret M, López M, Rodríguez C, Adzet T, Merlos M, Laguna JC. Different effects of fibrates on the microsomal fatty acid chain elongation and the acyl composition of phospholipids in guinea-pigs. British Journal of Pharmacology. 1995 Dec 1;116(8):3337–3343.

West KL, Fernandez ML. Guinea pigs as models to study the hypocholesterolemic effects of drugs. Cardiovascular Drug Reviews. 2004 Mar;22(1):55–70.

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Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease — meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016 Jul 1;64(1):73‐84.

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