Comments of the Natural Resources Defense Council on the Michigan Department of Environment, Great Lakes, and Energy's Proposed PFAS MCLs Pending Rule Set: 2019-35-EG

January 31, 2020

On behalf of our more than 3 million members and online activists, including 69,000 members in Michigan, the Natural Resources Defense Council (NRDC) appreciates the opportunity to comment on the Michigan Department of Environment, Great Lakes, and Energy (EGLE) proposed Maximum Contaminant Levels (MCLs) for perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), perfluorobutane sulfonic acic (PFBS), perfluorohexane sulfonic acid (PFHxS), perfluorohexanoic acid (PFHxA), and hexafluoropropylene oxide dimer acid (GenX).

We laud the Whitmer Administration for its leadership in advancing drinking water standards to protect Michiganders instead of waiting for the U.S. Environmental Protection Agency (EPA) to take action. However, NRDC has serious concerns about the proposed MCLs, which we raised with the Michigan PFAS Action Response Team (MPART) after its Science Advisory Workgroup (SAW) released the Health-Based Values (HBVs) upon which Michigan's proposed MCL are based.

NRDC's comments focus on following two major shortcomings with the proposed rules:

1) Absence of class-based regulations; and
2) Inadequate consideration of science for individual PFAS MCLs, including new science and state action since the development of the HBVs.

Given what's at stake with PFAS in Michigan's drinking water and the resulting health risks posed to communities throughout the state, we believe the agency must be much more proactive in developing protections for this pathway of exposure.

I. ABSENCE OF CLASS-BASED REGULATION

The SAW recommended HBVs for seven individual PFAS chemicals, and a screening level for all other long-chain PFAS detected with Method 537.1, based on their strictest HBV of 6 ppt for

PFNA. As the SAW noted, "these compounds are expected to produce similar health effects." We agree with this approach for screening levels for poorly studied chemicals.

However, the HBVs and proposed MCLs for individual PFAS chemicals alone are not protective against the likelihood of additive or synergistic effects from exposure to multiple PFAS.

Michigan water testing confirms that when water is contaminated with PFAS, people are nearly always ingesting multiple chemicals. Furthermore, a recent Harvard Nurses Study publication that used a novel method known as extractable organofluorine (EOF) to measure total organic fluorine in drinking water in five Northeast cities.[1] The authors report that the total "unknown" fluorochemicals dwarfed the amount of identifiable per- and poly-fluorinated carboxylates and sulfonates in treated drinking water. The amount of total organic fluorine also increased dramatically in each of the water systems between 1990 and 2016.

Biomonitoring studies also demonstrate that Americans have chronic exposure to multiple PFAS chemicals throughout their lifetimes. CDC's national biomonitoring studies, NHANES, reveal that nearly every American has PFOS, PFOA, PFHxS and PFNA detected in their blood stream, including young children.[2] At least eight other PFAS are detected in blood serum by NHANES studies: MeFOSAA, PFDeA, PFUA, PFHpA, PFBS, FOSA, EtFOSAA, PFDoA, and PFHpA. Most other PFAS chemicals are not routinely included in biomonitoring studies. Similar to total organic fluorine measurements in drinking water, alternative methods for detecting PFAS in blood serum are showing an increasing trend of unidentified organofluorine in blood serum samples, which also suggest that people are being exposed to new and unidentified PFAS.[3,4]

The ATSDR toxicity profile on 14 PFAS[5] and the EPA's toxicity assessments of various PFAS suggest that PFAS chemicals, including newer generation PFAS, such as PFBS[6] and GenX,[7] share many of the same toxicity endpoints, including harm to the liver, thyroid, kidney, immune system, development and reproduction. In addition to shared toxicity endpoints, there are a few recent studies of the effects associated with exposure to mixtures of PFAS or mixtures of PFAS and other toxicants. For example, a study of PFOA, PFOS, and PFNA found that toxicity in a human macrophage cell line and acute toxicity in zebrafish were greater for mixtures than individual compounds.[8] An in vitro study of amphibian fibroblast cells showed that the cytotoxic effects of mixtures of PFAS were additive, except with PFOS and PFOA, which were slightly synergistic.[9] Zebrafish embryos exposed to either PFHxA and PCB126 or PFHxA, PFOS, and PCB126 showed lower oxidative stress response, an effect not seen for the individual chemicals or a mixture of PFOS and PCB126, which suggests PFHxA plays a synergistic role in inducing this effect.[10]

Not only do the proposed rules fail to address the risk of exposure to multiple known PFAS, they fall short of providing the co-benefits of a treatment-based water standard for public water systems with detectable PFAS. Although it was within MPART's authority to investigate the ability of different water treatment technologies to reduce concentrations of a range of PFAS chemicals in water, its SAW focused on quantitative limits for individual chemicals. A focus on treatments that are effective for broad numbers of PFAS chemicals will have significant co-benefits of reducing the bulk of unclassified PFAS chemicals, which include

perfluoroalkyl acids (PFAA) precursors which can transform over time into the very PFAS EGLE is proposing to regulate, and other water contaminants.

Other states, like Vermont and Massachusetts, have taken a more class-based approach to setting water standards for PFAS, setting a combined standard for 5 or 6 PFAS, respectively. Vermont updated its drinking water health advisory level, originally for PFOA and PFOS only, to include PFHxS, PFHpA, and PFNA based on class similarity.[11] Vermont also passed legislation last year directing the state to consider regulating PFAS as a class or subclasses.[12] Recent published research and various assessments by federal and state agencies led Massachusetts to announce, in January 2019, its initiation of the process of developing a combined MCL for 6 PFAS at 20 ppt: PFOA, PFOS, PFNA, PFHxS, PFHpA, and PFDA.[13] Similarly, Massachusetts stated that the "additional PFAS were included because they share very similar chemical structures and the available data indicates they are likely to exhibit similar toxicities." Even the EPA's health advisory is a combined level for PFOA and PFOS due to,

> "Adverse effects observed following exposures to PFOA and PFOS are the same or similar and include effects in humans on serum lipids, birth weight, and serum antibodies. Some of the animal studies show common effects on the liver, neonate development, and responses to immunological challenges. Both compounds were also associated with tumors in long-term animal studies. The RfDs for both PFOA and PFOS are based on similar developmental effects and are numerically identical; when these two chemicals co-occur at the same time and location in a drinking water source, a conservative and health-protective approach that EPA recommends would be to compare the sum of the concentrations ([PFOA] + [PFOS]) to the HA (0.07 μg/L)."[14]

Finally, in December 2019, the European Commission proposed setting a drinking water standard for the entire class.[15] In addition, Sweden, the Netherlands, Germany, and Denmark have proposed a plan to the European Commission to phase out most uses of PFAS compounds by 2030.[16]

Michigan has led the nation on PFAS action so far. However, not considering the structural similarities of PFAS and the potential harm the entire class poses does not follow this trend. It puts Michiganders at increased, unnecessary risk. We recommend the following (please see attached NRDC report for further details):

1) **Set a Maximum Contaminant Level Goal (MCLG) of Zero for Total PFAS**

   PFAS share similar structure and properties, including extreme persistence and high mobility in the environment. Many PFAS are also associated with similar health endpoints, some at extremely low levels of exposure. There is additionally potential for additive or synergistic toxicity among PFAS. Given the similarity among chemicals of the PFAS class and the known risk of the well-studied PFAS, there is reason to believe that other members of the PFAS class pose similar risk. Therefore, health-protective standards for PFAS should be based on the known adverse effects of the well-studied members of the PFAS class.

   First, there is sufficient evidence to classify PFOA as a known or probable carcinogen.

Therefore, a MCLG of zero should be promulgated for PFOA, consistent with EPA's approach to regulating known or probable carcinogens. Both IARC's and EPA's findings on PFOA's carcinogenic potential are based heavily on the C8 study, whose Science Panel determined that PFOA is a probable carcinogen. There is also significant additional animal and human evidence for an association between PFOA exposure and cancer, particularly kidney and testicular cancer, and more recently for pancreatic cancer.

In addition to being a carcinogen, PFOA causes adverse non-cancer health effects at exceedingly low doses. A MCLG based on altered mammary gland development would be well below 1 ppt for PFOA, further supporting our recommendation of zero for a MCLG. Although the evidence of carcinogenic potential for other PFAS is not as well established as PFOA, given the similarities in structure and toxicity to PFOA, their potential for carcinogenicity cannot be ruled out. We therefore recommend a MCLG of zero for other PFAS as well.

In support, other shared health effects amongst PFAS occur at extremely low levels, such as immunotoxicity, developmental harm, and liver damage. For example, evidence indicates that PFOS causes adverse cancer and non-cancer health effects at exceedingly low doses. A MCLG based on immunotoxicity or pancreatic cancer (see Section II.3 below) would be well below 1 ppt for PFOS, further supporting our recommendation of zero for a MCLG. A MCLG for PFNA based on developmental toxicity is below 1 ppt, approximately 2 ppt for PFHxS based on thyroid toxicity, and below 1 ppt for GenX based on liver toxicity (see attached NRDC report for calculations); and as low as the single digit to teens ppt for PFBS and PFHxA (see Section II.6 and II.7 below). The health harms associated with these PFAS, combined with their co-occurrence in our environment, must be considered in setting a health protective MCLG for these PFAS.

The structure of the fluorine-carbon bond and the impacts documented on the studied PFAS already available support concern over the health impacts of the entire class. This is supported by the constant exposure to short-chain chemicals, even if they have a relatively short presence in the body, as well as the fact that in many cases the use of these chemicals may be much higher than their long-chain cousins. Furthermore, many PFAS can convert into PFAAs (a PFAS subgroup, which includes PFOA and PFOS, that is linked to many adverse health effects) or PFAAs are used in their manufacture and can be contaminants in their final product.

Setting a MCLG of zero for the class is needed to provide an adequate margin of safety to protect public health from a class of chemicals that is characterized by extreme persistence, high mobility, and is associated with a multitude of different types of toxicity at very low levels of exposure.

2) Set a Combined Standard for the PFAS Michigan is Proposing to Regulate

As discussed in the previous section and in the attached report, NRDC's review of the toxicity data on PFAS finds evidence that they are linked to cancer and other serious adverse health effects. Following conventional risk assessment protocols, we determine that the goal for PFAS should be zero exposure to these chemicals in drinking water.

As technologies for detection and water treatment do not currently allow for the complete removal of PFAS from drinking water, a MCL for any PFAS should be based on the best detection and treatment technologies available. **Our review of current technology suggests a combined MCL of 2 ppt is feasible for PFOA, PFOS, PFNA, PFHxS, PFHxA, and PFBS, with a separate MCL of 5 ppt for GenX.**

Laboratory methods support a reporting limit of 2 ppt with EPA Method 537.1 (5 ppt for GenX), and therefore all water testing should be required to achieve this limit for the PFAS chemicals detectable with this method. Further, the removal of all of these PFAS has been demonstrated to be effective with technologies such as GAC and RO to below detection levels, supporting our determination that the MCL meets technological feasibility.

3) Develop a Treatment Standard for Total PFAS within Two Years

In the absence of a reliable method that is economically and technically feasible to measure a contaminant at concentrations to indicate there is not a public health concern, the state should establish a treatment technique. **A treatment technique is a minimum treatment requirement or a necessary methodology or technology that a public water supply must follow to ensure control of a contaminant.**

At present, there is no single methodology for isolating, identifying, and quantifying all PFAS in drinking water. We recommend that Michian explore an analytical method, or combination of methods, that can be used as a surrogate for total PFAS. In particular, we recommend that Michigan evaluate alternative detection methodologies, such as the total oxidizable precursor or extractable organofluorine assays, to measure the concentration of non-discrete and difficult to measure PFAS compounds that are not determined by conventional analytical methods.

Furthermore, we recommend reverse osmosis, or other treatment method that has been demonstrated to be at least as effective as reverse osmosis for removing all identified PFAS chemicals, as the treatment technique for public water supplies. Reverse osmosis is currently the preferred treatment technology for the following reasons:

- Reverse osmosis has been demonstrated to effectively remove a broad range of PFAS compounds.**Error! Bookmark not defined.**
- Reverse osmosis is the most robust technology for protecting against unidentified contaminants.**Error! Bookmark not defined.**
- Reverse osmosis would likely result in lower finished water concentrations of GenX and other PFAS compounds such as PFMOAA and PFO2HxA.**Error! Bookmark not defined.**
- Reverse osmosis does not require frequent change out of treatment media and does not release elevated concentrations after granular activated carbon bed life is spent or ion exchange feed concentration drops.**Error! Bookmark not defined.**

Reverse osmosis requires considerations for the safe disposal of high-strength waste streams and spent/used membranes. **We also recommend Michigan evaluate the safest disposal method for contaminated waste, and that disposal require full destruction of PFAS compounds before entering the environment.**

II. INADEQUATE CONSIDERATION OF SCIENCE FOR INDIVIDUAL PFAS MCLS

In order to fully protect public health, the MCLs adopted by EGLE should rely on current science, properly account for scientific uncertainties, and strive to be protective of the likely additive effects of exposure to multiple PFAS chemicals over a lifetime of exposure. NRDC's comments underscore multiple opportunities for EGLE to strengthen the protection of human health, especially for those most vulnerable to PFAS exposure, developing fetuses, infants, and children.

1. **Protecting fetuses, infants and children.**

   We support the SAW's use of the Minnesota transgenerational toxicokinetic model[17] to estimate drinking water exposures over a person's lifetime (and the use of infant exposure assumptions when there was not enough data to use the model) for PFOA, PFOS, PFNA, PFHxS, and PFBS. **We take exception to the SAW's decisions for GenX and PFHxA, where adult exposure assumptions were used.**

   Fetuses and infants have greater exposure to PFAS than adults, and are also more sensitive to the effects of these contaminants.[18] Almost all fetuses and infants will have some degree of exposure, including exposure as fetuses during pregnancy through placental transfer.[19] For infants, exposure may be further elevated due to ingestion of contaminated breastmilk (a result of the mothers' ingestion of contaminated water and other sources) or infant formula prepared with contaminated drinking water.[20] Levels of PFOA and other PFAS in breastmilk are much higher than what is typically found in drinking water, as PFOA and other PFAS bioaccumulate in the body and are then transferred into the breastmilk.[21] Moreover, since infants consume approximately five times more water per body weight than adults,[22] their exposure is likely higher than adults regardless of whether they are breastfeed or are fed infant formula prepared with PFAS-contaminated drinking water. Infant blood serum levels of PFAS are often the highest of any age group in studies that compare people in multiple stages of life.[23] Compounding the issue of increased exposure, fetuses, infants, and children are also more vulnerable to exposure-related health effects than adults. The young may be more sensitive to the effects of PFAS due to their immature, developing biological systems (such as the immune system), and rapid body growth during development.[24] For example, exposure to PFAS before birth and/or in early childhood may result in decreased birthweight, decreased immune responses, and hormonal effects later in life.[25]

Decisions made when developing a health benchmark, such as evaluation of data gaps, the selection of uncertainty factors, and choice of exposure parameters to use, should be made to be protective of the most vulnerable populations, particularly developing fetuses, infants, and children. In fact, **the National Academy of Sciences (NAS) has recommended the use of an additional uncertainty factor of 10 to ensure protection of fetuses, infants and children who often are not sufficiently protected from toxic chemicals such as pesticides by the traditional intraspecies (human variability) uncertainty factor**.[26] Congress adopted this requirement in the Food Quality Protection Act for pesticides in foods.[27] Considering the many health effects linked to PFAS that affect this vulnerable population and the substantial data gaps on exposure and toxicity of these compounds in complex mixtures, **we recommend the use of this uncertainty factor when deriving health-protective benchmarks for PFAS.**

2. **The HBV for GenX does not fully acknowledge the uncertainty in the risk assessment process and is not protective of fetuses, infants and children, the most vulnerable populations to PFAS exposure.**

    a. Derivation of human equivalent oral exposures.

Like the EPA, the SAW used the Body Weight$^{3/4}$ allometric scaling approach to calculate a human equivalent dose from an animal-based point of departure. The Body Weight$^{3/4}$ allometric scaling approach is based on body surface area and basal metabolic rate in adults.[28] While the liver effects in the critical study for GenX occurred in adult mice, developmental effects also occur at low doses, and infants and children may be a more vulnerable population. The EPA states that this approach is not suitable for estimating an equivalent dose in infants and children. Therefore, it is unclear how the human equivalent dose based on liver effects in adults would compare to the human equivalent dose based on developmental effects in infants and children. **This uncertainty should be acknowledged in an additional uncertainty factor to protect fetuses, infants and children.**[29]

Furthermore, this approach does not account for differences in toxicokinetics between animals and humans, which for PFAS are often vastly different.[30] Even within animal models, data suggest a potentially complex toxicokinetic profile for GenX when dosing occurs over multiple days.[31] When male mice received doses of 1, 10 and 100 mg/kg/day for 28 days, their serum levels did not reach a steady state. This indicates possible changes in toxicokinetics after repeated dosing, which is relevant when considering safety levels in a public drinking water supply.

Depending on the specific PFAS, human clearance time can be an order of magnitude, or more, higher than in animal models. Therefore, the Netherland's National Institute for Public Health and the Environment (RIVM) determined that although the elimination rates for GenX are faster than PFOA in animal models, without data in humans, it is not possible to make assumptions on the human toxicokinetics of GenX chemicals.[32] Due to the uncertainty from lack of human toxicokinetic data on GenX chemicals, RIVM calculated and applied an additional uncertainty factor to account for the potential kinetic

difference between animals and humans. RIVM postulated that the vast differences in clearance rates between animals and humans may be due to species differences between organic anion transporters (OATs). Differences in OATs could result in stronger reabsorption of anions, like the anion forms of PFOA and HFPO dimer acid (GenX), from the lumen of the kidney back into the blood in humans.[33]

It is possible that the shorter half-live of GenX in animal models is due to little to no reabsorption by OATs in these species. However, RIVM reasoned that it could not be assumed this would be the same for humans, due to the genetic differences of the OATs between animal models and humans.[34] RIVM states, "contrary to other perfluorinated compounds, no data are available for FRD-902 [GenX chemical] to confirm whether the fast elimination and absence of accumulation as seen in several animal species also applies to humans. In view of the above, an additional toxicokinetic assessment factor is applied to take into account the uncertainty in the human elimination rate of FRD-902." This additional toxicokinetic factor used by RIVM is based on the difference in half-lives between cynomolgus monkeys and humans for PFOA. A half-life ratio was calculated using a half-life of 1378 days in humans[35] and of 20.9 days in male cynomolgus monkeys[36] resulting in an additional toxicokinetic factor of 66 (1378 / 20.9). **This additional uncertainty factor to account for the potential kinetic difference between animals and humans is an example of an alternative approach to extrapolating animal doses to human doses for PFAS that do not yet have human toxicokinetic data. At the very least an uncertainty factor of 10, not 3, should be used for animal to human differences.**

b. Database uncertainty.

There are significant database limitations for GenX. **A factor of 3 is insufficient to cover this level of uncertainty in the database.** In contrast, the Agency for Toxic Substance and Disease Registry (ATSDR) used a database uncertainty factor of 10 for PFNA and PFHxS (two PFAS with far more data than GenX) due to lack of, or limited testing of developmental and immunological effects, which ATSDR identified as two of the most sensitive PFAS endpoints.[37] Uncertainties in the database on GenX include:

- No human data.

  Human data has significantly improved our understanding of the toxicological profile of many PFAS.[38] Human data is especially important considering the difference in elimination rates for PFAS between animal models and humans. A lack of human data to complement and compare to animal toxicological data is a critical data gap.

- No chronic studies in mice.

  The single chronic study was performed in rats, which are less sensitive than mice to GenX chemicals. An additional limitation of this study is that there were higher than normal early deaths across all study groups.[39]

- Limited data on developmental toxicity and immunotoxicity.

Developmental toxicity and immunotoxicity are common health effects associated with PFAS exposure, both of which can occur at extremely low levels of exposure.[40] Two developmental toxicity studies, only one of which was in mice, and a single study that specifically assesses immune effects is a serious database limitation. One critical data gap is the lack of a full 2-generation toxicity study evaluating exposures during early organogenesis. Additionally, there are many developmental and immune effects that have yet to be assessed, including reproductive system development (i.e. mammary gland development and function), neurodevelopment, autoimmunity, infectious disease resistance, and immune hypersensitivity (i.e. asthma and allergies).

- Limited peer-reviewed, independently funded studies for GenX.

Of the studies that assess health effects of GenX, only three were peer-reviewed. Of these three, one was independently funded,[41] one was funded by DuPont,[42] and one was independently funded but excluded from the EPA assessment,[43] on which the SAW's assessment is based.

- Lack of toxicity data from inhalation and dermal exposure routes.

GenX can be transported through air.[44] Inhalation could be a significant exposure route, especially in areas where GenX processing or use occurs. In 2017 the North Carolina Division of Air Quality estimated that despite some cutback in emissions, the Chemours Fayetteville Works plant emitted approximately 2,700 pounds of GenX chemicals per year[45] and GenX chemicals have been found in rainwater up to 7 miles from the Chemours Fayetteville Works plant.[46] Minimal dermal absorption of GenX has also been demonstrated,[47] however, there is a lack of information on the dermal absorption potential or toxicity of GenX.

- New toxicity data on GenX chemicals not considered

SAW relied on EPA's draft toxicity assessment of GenX, released in November of 2018. New toxicity data on GenX chemicals has been published since this time.[48] At the time of EPA's assessment, very few peer-reviewed studies were available, as noted above. Therefore, it is especially important for Michigan to consider any new peer-reviewed studies on GenX toxicity.

c. Overall uncertainty not addressed.

The total uncertainty factor used by North Carolina's Department of Environmental Quality was 1000.[49] The total uncertainty factor used by the RIVM was 1088. Both North Carolina and RIVM concluded that the current overall uncertainty in assessing the toxicity of GenX is at least three times greater than what the SAW is acknowledging through its application of a total uncertainty factor of 300.

d. Use of adult drinking water exposure assumptions

The SAW applied drinking water exposure parameters for adults, which does not account for the most vulnerable populations to PFAS exposure in drinking water. Sensitive members of the population, such as fetuses, infants, children, pregnant women, nursing mothers, and those with certain pre-existing conditions, face particular risk from chemicals of such persistence, and which demonstrate clear adverse effects at very low levels of exposure. Michigan should develop a health benchmark protective of the of the most vulnerable populations, particularly developing fetuses, infants, and children, by accounting for these sensitive subgroups in the choice of exposure parameters to use.[50] The SAW states that it used adult drinking water exposure assumptions because the critical effect (liver damage) they selected occurred in adults and at a lower dose than the developmental effects seen. However, as discussed in Section III.2.b, there is limited data on developmental toxicity for GenX. There is not enough data to confidently determine how fetuses, infants and children are affected by GenX, in their livers and in general. Until there is more confidence that development is not being affected at lower levels than liver effects in adults, infant exposure assumptions should be applied. As explained above in Section III.1, infants are more likely to have higher exposure than adults to these contaminants because they ingest more water per kilogram of body weight than adults. **Accounting for the unique exposure situation of infants would significantly reduce the health-based value for GenX to approximately 109 ppt. The health-based value would be lowered to approximately 11 ppt if full uncertainty factors for database limitations and animal to human differences, discussed above, were applied, and to 1 ppt with an additional uncertainty factor to ensure adequate protection of fetuses, infants and children,** as recommended by the National Academy of Sciences and as required in the Food Quality Protection Act.[51]

3. The HBV for PFOA does not incorporate the most recent science on PFOA associated health effects and therefore is not protective of cancer or altered mammary gland development, the most sensitive health endpoints associated with PFOA exposure.

The SAW did not select the most sensitive health effects associated with PFOA exposure, cancer and altered mammary gland development. For the later, it states, "mammary gland effects may represent a delay that may not be considered adverse."

However, in a 2009 a workshop of experts in mammary gland biology and risk assessment came to the consensus that changes in mammary gland growth and differentiation, including changes in developmental timing, are a health concern.[52] Altered mammary gland development may lead to difficulty in breastfeeding and/or an increase in susceptibility to breast cancer later in life.[53]

Only one animal study has assessed the effects of PFOA exposure on mammary gland growth and differentiation for multiple generations.[54] The authors saw striking morphological abnormalities in the lactating glands of dams (mothers) chronically

exposed to environmentally relevant levels of PFOA; however, no effects on body weight of their pups were seen. It is possible that compensatory behavior, such as increased number of nursing events per day or longer nursing duration per event masked a decreased potential in milk production by the dams, however the authors did not evaluate these endpoints in the study. It is also possible that PFOA exposure could increase time to peak milk output through the reduction in number and density of alveoli available to produce milk.

For human mothers, low-level functional effects on lactation that cause even a short delay in substantial milk output might result in cessation in breastfeeding before the recommended time-frame. This is supported by three human studies which have reported that maternal PFOA exposure is associated with decreased duration of breastfeeding.[55]

Early life exposures to factors that disrupt development may influence susceptibility to carcinogens later in life. For example, hormone disruption is an important determinant of breast cancer susceptibility in humans and rodents.[56] Proliferating and undifferentiated structures, such as terminal end buds, display elevated DNA synthesis compared to other mammary gland structures; which is why terminal end buds are considered the most vulnerable mammary gland target structure of carcinogen exposure.[57] Delays in mammary gland development would result in a prolonged window of increased vulnerability to carcinogens. In humans, perturbations to the timing of menarche is linked to breast cancer.[58] This further raises the concern that changes in patterns of breast development in U.S. girls could be contributing to an increased risk of breast cancer or other adult diseases later in life.[59] However, an increase in susceptibility to breast cancer later in life was not explored in the multigeneration mammary gland development study.

In general, as the 2018 Michigan Science Advisory Panel states, "developmental delay can reflect an overall detrimental effect of chemical exposure that lead to growth and developmental deficit in the offspring."[60]

While the SAW applied an extra uncertainty factor of 3 to protect against the possibility of endocrine effects (related to mammary gland development) occurring at lower levels than the health effect they chose, this is not sufficient to protect against mammary gland effects. **Indeed, New Jersey has calculated a reference dose for mammary gland development, and if this had been used, the HBV for PFOA would be less than 1 ppt.[61]**

Furthermore, in August of 2019, California's Office of Environmental Health Hazard Assessment developed reference levels PFOA and PFOS in drinking water for both cancer and non-cancer effects.[62] The cancer effect reference level is based on the concentration of the chemical in drinking water that would not pose more than a one in one million cancer risk over a lifetime. **For PFOA, OEHHA derived a reference level of <u>0.1 ppt</u> based on pancreatic and liver tumors found in male rats in a new National Toxicology Program study.[63] We urge Michigan to examine OEHHA's risk assessment on PFOA as it is significantly stricter than what was proposed by SAW, which developed its HBV recommendations before August 2019.**

4. **The HBV for PFOS does not incorporate the most recent science on PFOS associated health effects.**

   As explained above, OEHHA recently developed reference levels PFOA and PFOS in drinking water for both cancer and non-cancer effects.[64] **For PFOS, OEHHA derived a reference level of <u>0.4 ppt</u> based on liver tumors in male rats and the structural and biological similarity of PFOS to PFOA. Again, we urge Michigan to examine OEHHA's risk assessment on PFOS as it is significantly stricter than what was proposed by SAW.**

5. **The HBV for PFHxS does not incorporate the most recent science on PFHxS associated health effects.**

   As noted by the SAW's use of an uncertainty factor of 10 for database deficiencies (lack of a two-generational study and limited understanding of immunotoxicity and early life sensitivity), the science on possible health effects associated with exposure to PFHxS is still developing. In fact, **a new derivation of a chronic reference dose for PFHxS based on a different study (Chang et al., 2018[65]) and health endpoint (impaired reproduction – reduced litter size) was just published**.[66] This approach was originally **used by New Hampshire to set a MCL of 18 ppt for PFHxS** in July 2019, and then published in September 2019. Considering the significantly stricter level that results from use of this new information it is imperative that Michigan consider this recent publication to ensure it sets a health-protective MCL for PFHxS.

   In short, the new study reviewed available toxicity studies using a weight-of-evidence approach, which led them to choose a 42-day reproductive study in mice (Chang, 2018). They performed benchmark dose modeling to derive a point of departure (13,000 ng/ml PFHxS in serum) for reduced litter size. The authors then used a similar dosimetric adjustment factor and the same total uncertainty factor as SAW to arrive at a chronic reference dose of 4 ng/kg/day, approximately 2.5 times lower than SAW's reference dose. Like SAW, New Hampshire used the Minnesota transgenerational toxicokinetic model to generate a drinking water limit from its reference dose.

   The SAW does state that its point of departure was comparable to the NOAEL of the Chang, 2018 study, however it also states that in general a benchmark dose modeling-based point of departure is preferred to a NOAEL. A benchmark dose level (BMDL) for the Chang, 2018 study was not available to the SAW at the time to compare its point of departure to (based on thyroid effects). However, now that New Hampshire has derived a BMDL-based point of departure for the Chang, 2018 study, we can see that the two points of departure are not comparable and that the point of departure for the Chang, 2018 study is significantly lower.

   The SAW stated that the health outcome (reduced litter size) in Chang, 2018 was a marginal effect. However, it was statistically significant and more than a 10% decrease in

litter size in the study. **Given the enormous personal and societal impact of infertility and pregnancy complications in a human population, the SAW should not dismiss these important indicators of harm in animal models.**

6. **The HBV for PFHxA does not fully acknowledge the uncertainty in the risk assessment process and is not protective of fetuses, infants and children, the most vulnerable populations to PFAS exposure.**

    a. Derivation of human equivalent oral exposures.

Due to limited data on PFHxA, the SAW used the Body Weight$^{3/4}$ allometric scaling approach to calculate a human equivalent dose from an animal-based point of departure. The Body Weight$^{3/4}$ allometric scaling approach is based on body surface area and basal metabolic rate in adults.[67] This approach resulted in a dose adjustment factor of approximately 3. The EPA states that this approach is not suitable for estimating an equivalent dose in infants and children. Therefore, it is unclear how the human equivalent dose based on kidney effects in adults would compare to the human equivalent dose based on developmental effects in infants and children. **This uncertainty should be acknowledged in an additional uncertainty factor to protect fetuses, infants and children.[68] And, due to the limited data on how humans process PFHxA, an uncertainty factor of 10, not 3, should be used to account for animal to human differences.**

Furthermore, this approach does not account for differences in toxicokinetics between animals and humans, which for PFAS are often vastly different.[69] Depending on the specific PFAS, human clearance time can be an order of magnitude, or more, higher than in animal models. PFBS is also a short-chain PFAS, with shorter half-life than long-chain PFAS, such as PFOA and PFAS. However, the dose adjustment factor the SAW used for PFBS was based on the ratio of human to animal half-lives for PFBS, not the Body Weight$^{3/4}$ allometric scaling approach. The SAW states,

> "As that [half-life-based dose adjustment factor] allowed conversion of the point of departure to a human equivalent dose using chemical-specific information, the SAW selected this approach over the allometric scaling used in the draft USEPA (2018) PFBS toxicity assessment."

Although the half-life of PFBS and PFHxA is significantly shorter than long-chain PFAS (665 hours vs. 1241 days for PFOS), the half-life in humans is still much longer than in animals (665 hours in humans vs 2.1 hours mice) for PFBS. The dose adjustment factor for PFBS was 316.

This is similar to PFHxA, the human half-life for PFHxA is estimated to be 32 days, or 768 hours (geomean), 1 hour for mice, between 0.4 and 9.8 hours for rats, and from 2 to 5 hours for monkeys, resulting in dose adjustment factors ranging from 78 to 1920, depending on the mammalian species used.[70] As the critical study occurred in rats, the dose adjustment factor for calculating a human equivalent dose from the rat dose would

be based on the human to rat half-life ratio. The most health-protective choice would be to use the half-life estimate of 0.4 hours for rats, resulting in a dose adjustment factor of 1920. In comparison, the dose adjustment factor based on Body Weight$^{3/4}$ allometric scaling is 3.65 for PFHxA, suggesting that the Body Weight$^{3/4}$ allometric scaling approach for PFAS, even short-chain PFAS, is not an appropriate approach to convert animal dose to human equivalent doses and that the human equivalent dose (and thus the health-based value) for PFHxA could be off by at least a couple orders of magnitude. Although the same level of information is available for PFBS and PFHxA, the SAW does not clearly explain why it chooses a different approach for the two chemicals. The PFBS approach to extrapolating from animal to human doses is more relevant to the unique properties of PFAS and would result in a point of departure for PFHxA ranging from 0.0471 to 1.15 mg/kg/day, depending on the dose adjustment factor used. **Application of full uncertainty factors for human variation, animal to human differences, database deficiencies, and to protect fetuses, infants and children would then result in a toxicity value ranging between 4.7 to 115 ng/kg/day.**

b. Use of adult drinking water exposure assumptions

The SAW states that it used adult drinking water exposure assumptions because the critical effect (kidney effects) they selected occurred in adults. However, there is limited data on developmental toxicity for PFHxA. There is not enough data to confidently determine how fetuses, infants and children are affected by PFHxA, in their kidneys and in general. Until there is more confidence that development is not being affected at lower levels than kidney effects in adults, infant exposure assumptions should be applied. As explained above in Section III.1, infants are more likely to have higher exposure than adults to these contaminants because they ingest more water per kilogram of body weight than adults. **The health-based value would be between 7 to 162 ppt if the SAW's infant exposure assumptions (0.142 L/kg/day, 20% relative source contribution) were applied to the toxicity values listed above.**

7. PFBS and PFNA

We support the SAW's use of a half-life-based dose adjustment factor over the BodyWeight ¾ allometric scaling method for generating a human equivalent dose from an animal point of departure for PFBS. We also support the use of drinking water exposure assumptions based on infants, in order to better protect this vulnerable population. However, we suggest Michigan consider applying a full uncertainty factor for animal to human variability, as there is a lack of toxicological information on PFBS, and the SAW's preferred models were not able to be used for deriving the HBV.

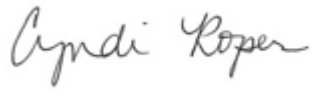
We also generally support the SAW's choices in developing a HBV PFNA, however, would **urge Michigan to consider (for all the PFAS analyzed) NAS' recommendation to apply an additional uncertainty factor of 10 to ensure protection of fetuses, infants and children** who often are not sufficiently protected from toxic chemicals by the traditional human variability uncertainty factor.

CONCLUSION

The Whitmer Administration has moved quickly to address the dangers posed by PFAS in Michigan's drinking water. MPART's SAW was charged with reviewing PFAS scientific data, and their recommendations became the basis for EGLE's proposed enforceable drinking water protections. However, more studies and analysis have been performed since SAW's review and our scientific review identified significant shortcomings in the recommendations adopted by MPART in June. As tends to be the trend with PFAS, further study of the health harms associated with PFAS exposure suggest the need for stricter health protections from this very concerning class of chemicals. We urge EGLE to adopt the recommendations laid out in these comments that reflect the current state of science and actions needed to protect public health.

Respectfully submitted,

Anna Reade, PhD
Staff Scientist
Healthy People & Thriving Communities Program
Natural Resources Defense Council



Cyndi Roper
Michigan Senior Policy Advocate
Safe Water Initiative – Healthy People & Thriving Communities Program
Natural Resources Defense Council
croper@nrdc.org

[1] Xindi C. Hu, et al., 2019. Tap Water Contributions to Plasma Concentrations of Poly- and Perfluoroalkyl Substances (PFAS) in a Nationwide Prospective Cohort of U.S. Women. *Environ Health Perspect*, 127: 6.

[2] Centers for Disease Control and Prevention, 2018. Fourth National Report on Human Exposure to Environmental Chemicals. Department of Health and Human Services. Updated Tables, March 2018. https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Mar2018.pdf

[3] Yeung LWY, et al., 2008. Perfluorinated compounds and total and extractable organic fluorine in human blood samples from China. Environ. Sci. Technol 42(21): 8140-8145.

[4] Yeung LW and Mabury SA, 2016. Are humans exposed to increasing amounts of unidentified organofluorine. *Environ. Chem*, *13*(1), 102-110.

[5] Agency for Toxic Substances and Disease Registry (ATSDR), 2018. Toxicological Profile for Perfluoroalkyls: Draft for Public Comment (June 2018). https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf

[6] U.S. Environmental Protection Agency, 2018. Toxicity Assessment: Human Health Toxicity Values for Perfluorobutane Sulfonic Acid (CASRN 375-73-5) and Related Compound Potassium Perfluorobutane Sulfonate (CASRN 29420-49-3). November 2018. EPA 823-R-18-0307. U.S. Environmental Protection Agency, Office of Water. Washington, DC.

[7] U.S. Environmental Protection Agency, 2018. Toxicity Assessment: Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3). November 2018. EPA 823-P-18-001. U.S. Environmental Protection Agency, Office of Water. Washington, DC.

[8] Rainieri S, et al., 2017. Toxic effects of perfluorinated compounds at human cellular level and on a model vertebrate. *Food and Chemical Toxicology* 104:14–25.

[9] Hoover G, et al., 2019. In vitro and in silico modeling of perfluoroalkyl substances mixture toxicity in an amphibian fibroblast cell line. *Chemosphere* 233:25–33.

[10] Blanc M, et al., 2017. Mixture-specific gene expression in zebrafish (Danio rerio) embryos exposed to perfluorooctane sulfonic acid (PFOS), perfluorohexanoic acid (PFHxA) and 3,3′,4,4′,5-pentachlorobiphenyl (PCB126). *Science of The Total Environment* 590–591:249–257.

[11] Vermont Department of Health, 2018. Drinking Water Health Advisory for Five PFAS (per- and polyfluorinated alkyl substances). Memo dated July 10, 2018

[12] Vermont. Senate Bill 49. 2019 Regular Session. Accessed at: https://legislature.vermont.gov/Documents/2020/Docs/ACTS/ACT021/ACT021%20As%20Enacted.pdf.

[13] Mass.gov. Development of a PFAS Drinking Water Standard (MCL). Accessed at: https://www.mass.gov/lists/development-of-a-pfas-drinking-water-standard-mcl#stakeholders-meeting-#2---june-20,-2019-

[14] U.S. Environmental Protection Agency, 2016a. Drinking Water Health Advisory for perfluorooctanoic acid (PFOA). May 2016. EPA 822-R-16-005. U.S. Environmental Protection Agency, Office of Water. Washington, DC.

[15] The Greens/EFA in the European Parliament. Media Briefing, December 19, 2019. Accessed at: https://sven-giegold.de/wp-content/uploads/2019/12/Media-briefing-Drinking-water-19.12.2019.pdf.

[16] European Commission. Elements for a EU-strategy for PFAS. December 2019. Accessed at: https://www.documentcloud.org/documents/6586418-EU-Strategy-for-PFASs-FINAL-VERSION-December-19.html.

[17] Goeden HM, et al., 2019. A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance. *J Expo Sci & Environ Epi* 29:1833-195

[18] Reade A, et al., 2019. NRDC Report: Scientific and Policy Assessment for Addressing Per- and Polyfluoroalkyl Substances (PFAS) in Drinking Water. https://bit.ly/2LN1T4f

Agency for Toxic Substances and Disease Registry (ATSDR), 2018. Toxicological Profile for Perfluoroalkyls: Draft for Public Comment (June 2018). https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf

[19] Manzano-Salgado CB, et al., 2015. Transfer of perfluoroalkyl substances from mother to fetus in a Spanish birth cohort. *Environ Res* 142:471-478. 10.1016/j.envres.2015.07.020

Liu J, et al., 2011. Comparison on gestation and lactation exposure of perfluorinated compounds for newborns. *Environ Int* 37(7):1206-1212.

[20] Gyllenhammar K, et al., 2018. Perfluoroalkyl Acids (PFAAs) in serum from 2-4-month-old infants: Influence of maternal serum concentration, gestational age, breast-feeding, and contaminated drinking water. *Environ Sci Technol* 52:7101-7110

Llorca M, et al., 2010. Infant exposure of perfluorinated compounds: levels in breast milk and commercial baby food. *Environ Int* 36(6): 584-592

[21] Mondal D, et al., 2014. Breastfeeding: a potential excretion route for mothers and implications for infant exposure to perfluoroalkyl acids. *Environ Health Perspect* 122(2):187-192

Kim SK, et al., 2011. Distribution of perfluorochemicals between sera and milk from the same mothers and implications for prenatal and postnatal exposures. *Environ Pollut* 159(1):169-174.

[22] United States Environmental Protection Agency (EPA), 2011a. Exposure Factors Handbook, 2011 Edition (Final Report). https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252.

[23] Goeden HM, et al., 2019.

[24] Landrigan P and Goldman L, 2011. Children's Vulnerability to Toxic Chemicals: A Challenge and Opportunity to Strengthen Health and Environmental Policy. *Health Affairs* 30(5):842-850

[25] Kristen M. Rappazzo et al., 2017. Exposure to Perfluorinated Alkyl Substances and Health Outcomes in Children: A Systematic Review of the Epidemiologic Literature, *Int J Envrion Res Public Health* 14(7): 691

[26] National Academy of Sciences (NAS), 1993. Pesticides in the Diets of Infants and Children, National Research Council. https://www.nap.edu/catalog/2126/pesticides-in-the-diets-of-infants-and-children.

[27] Food Quality Protection Act for pesticides in foods. 21 U.S.C. § 346a(b)(2)(C)(ii)(II).

[28] United States Environmental Protection Agency (EPA), 2011b. Recommended Use of Body Weight3/4 as the Default Method in Derivation of the Oral Reference Dose. EPA/100/R11/0001. https://www.epa.gov/sites/production/files/2013-09/documents/recommended-use-of-bw34.pdf

[29] NAS, 1993

21 U.S.C. § 346a(b)(2)(C)(ii)(II).

[30] ATSDR, 2018.

[31] Rushing BR, et al. 2017. Evaluation of the immunomodulatory effects of 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate in c57bl/6 mice. *Toxicol Sci*

[32] RIVM, 2016. Evaluation of substances used in the Genx technology by Chemours, Dordrecht. RIVM Letter report 2016-0174. The Netherlands: National Institute for Public Health and the Environment. https://www.rivm.nl/bibliotheek/rapporten/2016-0174.pdf

[33] Yang CH, Glover KP, Han X. 2010. Characterization of cellular uptake of perfluorooctanoate via organic anion transporting polypeptide 1a2, organic anion transporter 4, and urate transporter 1 for their potential roles in mediating human renal reabsorption of perfluorocarboxylates. *Toxicol Sci,* 117:294-302.

[34] Yang et al. 2010.

[35] Olsen GW, et al., 2007. Half-life of serum elimination of perfluorooctane sulfonate, perfluorohexane sulfonate, and perfluorooctanoate in retired fluorochemical production workers. *Environ Health Perspect* 115:1298-1305.

[36] Buttenhoff JL, et al., 2004. Pharmacokinetics of perfluorooctanoate in cynomolgus monkeys. *Toxicol Sci*, 82:394-406.

[37] ATSDR, 2018

[38] ATSDR, 2018.

[39] Dupont Chem C., 2010. Dupont-18405-1238: H-28548: Combined chronic toxicity/oncogenicity study 2-year oral gavage study in rats. Mattawan, Michigan.

[40] ATSDR, 2018

[41] Rushing et al. 2017.

[42] Caverly Rae JM, et al., 2015. Evaluation of chronic toxicity and carcinogenicity of ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate in sprague-dawley rats. *Toxicol Reports* 2:939-949.

[43] Wang J, et al. 2017. RNA-sequencing analysis reveals the hepatotoxic mechanism of perfluoroalkyl alternatives, hfpo2 and hfpo4, following exposure in mice. *J Applied Toxicol*, JAT 37:436-444.

[44] Dupont CCAS D., 2009. Sublimation of processing aids frd-903k and prd-902. Wilmington, DE:DuPont Corporate Center for Analytical Sciences.

[45] NC DEQ. 2018a. 60-day notice of intent to modify air quality permit no. 03735t43: The Chemours Company, Fayetteville works. North Carolina Department of Environmental Quality. https://files.nc.gov/ncdeq/GenX/2018_April6_Letter_to_Chemours_DAQ_FINAL_signed.pdf

[46] NC DEQ. 2018b. Groundwater and rainwater sample testing results. North Carolina Department of Environmental Quality.

[47] DuPont, 2008. Dupont-25292: Determination of a permeability coefficient (kp) for h-28308 using human and rat skin mounted in an in vitro static diffusion cell.

[48] Conley JM, et al. 2019. Adverse Maternal, Fetal, and Postnatal Effects of Hexafluoropropylene Oxide Dimer Acid (GenX) from Oral Gestational Exposure in Sprague-Dawley Rats. *Environ Health Perspect,* 127(3):37008.

[49] Questions and Answers Regarding North Carolina Department of Health and Human Services Updated Risk Assessment for GenX (Perfluoro-2-propoxypropanoic acid) https://ncdenr.s3.amazonaws.com/s3fs-public/GenX/NC%20DHHS%20Risk%20Assessment%20FAQ%20Final%20Clean%20071417%20PM.pdf

[50] Landrigan P and Goldman L, 2011.

[51] NAS, 1993.

21 U.S.C. § 346a(b)(2)(C)(ii)(II).

[52] Rudel RA, et al., 2011. Environmental exposures and mammary gland development: State of the science, public health implications, and research recommendations. *Environ Health Perspect* 119(8):1053-1061

[53] Macon MB and Fenton SE, 2013. Endocrine disruptors and the breast: Early life effects and later life disease. *J Mammary Gland Biol Neoplasia* 18(1):43-61.

[54] White SS, et al., 2011. Gestational and chronic low-dose PFOA exposures and mammary gland growth and differentiation in three generations of CD-1 mice. *Environ Health Perspect* 119(8):1070-1076

[55] Chunyuan F, et al., 2010. Maternal concentrations of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) and duration of breastfeeding. *Scand J Work Environ Health* 36: 413

Romano ME, et al., 2016. Maternal serum perfluoroalkyl substances during pregnancy and duration of breastfeeding, *Environ Res* 149: 239

Timmermann CA, et al., 2017. Shorter duration of breastfeeding at elevated exposures to perfluoroalkyl substances. *Reprod Toxicol* 68: 164

[56] Russo J and Russo IH, 2004. Molecular Basis of Breast Cancer: Prevention and Treatment. New York:Springer

[57] Medina D, 2007. Chemical carcinogenesis of rat and mouse mammary glands. *Breast Dis* 28:63-68

[58] Kelsey JL, et al., 1993. Reproductive factors and breast cancer. *Epidemiol Rev* 15(1):36-47

[59] Euling SY, et al., 2008. Role of environmental factors in the timing of puberty. *Pediatrics* 121(suppl 3):S167-S171

[60] Michigan PFAS Science Advisory Panel, 2018. Scientific Evidence and Recommendations for Managing PFAS Contamination in Michigan. December 7, 2018.

[61] Reade et al., 2019.

[62] Office of Environmental Health Hazard Assessment. Notification Level Recommendations. Perfluorooctanoic Acid and Perfluorooctane Sulfonate in Drinking Water. August 2019. Accessed at: https://oehha.ca.gov/media/downloads/water/chemicals/nl/final-pfoa-pfosnl082119.pdf

[63] National Toxicology Program. TR-598: Technical Report Pathology Tables and Curves - PFOA. 2018. Assessed at: https://tools.niehs.nih.gov/cebs3/views/?action=main.dataReview&bin_id=13658

[64] Office of Environmental Health Hazard Assessment. Notification Level Recommendations. Perfluorooctanoic Acid and Perfluorooctane Sulfonate in Drinking Water. August 2019. Accessed at: https://oehha.ca.gov/media/downloads/water/chemicals/nl/final-pfoa-pfosnl082119.pdf

[65] Chang S, et al. 2018. Reproductive and developmental toxicity of potassium perfluorohexanesulfonate in CD-1 mice. *Reprod Toxicol* 78: 150-168

[66] Ali JM, et al., 2019. Derivation of a chronic reference dose for perfluorohexane sulfonate (PFHxS) for reproductive toxicity in mice. Reg Toxicol Pharm 109: 104452

[67] EPA, 2011b.

[68] NAS, 1993.

21 U.S.C. § 346a(b)(2)(C)(ii)(II).

[69] ATSDR, 2018.

[70] Russell MH, et al., 2013. Elimiation kinetics of perfluorohexanoic acid in humans and comparison with mouse, rat and monkey. *Chemosphere* 93: 2419-2425