January 31, 2020

Mr. Eric Oswald
Director, Drinking Water and Environmental Health Division
Michigan Department of Environment, Great Lakes, and Energy
Attention: Suzann Ruch
P.O. Box 30817
Lansing, Michigan 48909

RE: Supplying Water to the Public / Proposed Rule Set 2019-35 EG “PFAS”

Dear Mr. Oswald,

The Michigan Manufacturers Association (MMA) respectfully submits these comments on proposed rule set 2019-35 EG, otherwise known as “Supplying Water to the Public.”

MMA has served manufacturers and related industries for nearly 120 years. MMA’s membership represents approximately 1,700 manufacturers located in every corner of the state. These members include small, medium, and large manufacturers, with 85 percent employing 100 or fewer employees.

Manufacturing represents Michigan’s largest economic sector. It drives Michigan’s economy and provides livelihoods for more than 635,000 Michigan citizens and their families. Manufacturing generates nearly 20 percent of state GDP.

MMA has been actively engaged for more than two years in discussions on per- and poly-fluoroalkyl substances (PFAS) with state regulators, legislators, local communities, and our members. We all agree the safety of public drinking water supplies is paramount, as is public confidence in drinking water safety.

We believe the state can both protect the public health and its economic competitiveness; these are not mutually exclusive goals. As such, MMA welcomes being part of the solution to what clearly is a complex challenge.

To meaningfully contribute to the state’s rulemaking process, MMA commissioned an independent peer review by leading PFAS researchers of the draft ruleset. As directed by MMA, the purpose of the peer review is to provide technical comments on the Science Advisor Workgroup’s (SAW) recommendations to the Department of Environment, Great Lakes, and Energy (EGLE) that were used to establish the health-based drinking water values (HBVs) for PFAS.
MMA’s intent in providing this peer review is that it will aid in the rulemaking process by providing scientific, technical information for SAW, EGLE, and the Environmental Rules Review Committee (ERRC) to take into consideration before proceeding to promulgate rules.

**Professional Qualifications of Peer Review Scientists**

The technical review was completed by Dr. Michael L. Dourson, former U.S. Environmental Protection Agency (EPA) Advisor and current Director of Science for Toxicology Excellence for Risk Assessment (TERA); Dr. Edward J. Calabrese, professor at the University of Massachusetts-Amherst, and Mr. Richard J. Welsh, Director for ASTI Environmental, Inc.

**Dr. Michael L. Dourson of Toxicology Excellence for Risk Assessment (TERA)**

Michael Dourson has a PhD in toxicology from the University of Cincinnati, College of Medicine, and is a board-certified toxicologist (Diplomate of the American Board of Toxicology - DABT).

Dourson currently serves as the Director of Science at the 501c3 nonprofit organization TERA. Prior to this, he was Senior Advisor in the Office of the Administrator at the EPA. Before this, he was a Professor in the Risk Science Center at the University of Cincinnati, College of Medicine.

He was awarded the Arnold J. Lehman award from the Society of Toxicology, the International Achievement Award by the International Society of Regulatory Toxicology and Pharmacology, and four bronze medals by the EPA. He has been elected as a Fellow of the Academy of Toxicological Sciences and as a Fellow for the Society for Risk Analysis.

Dourson has co-published more than 150 papers on risk assessment methods or chemical-specific analyses, and co-authored well over 100 government risk assessment documents, many of them risk assessment guidance texts. He is a well-respected and frequently invited presenter within this specialization, chairing over 150 sessions at scientific meetings and independent peer reviews.

Dourson has been elected to multiple officer positions in the American Board of Toxicology (including its president), the Society of Toxicology (including the presidency of three specialty sections), the Society for Risk Analysis (including its secretary), and is currently president of the Toxicology Education Foundation, a nonprofit organization with a vision to assist public understanding of toxicology. In addition to numerous appointments on government panels, such as EPA’s Science Advisory Board, he is a current member on the editorial board of Regulatory Toxicology and Pharmacology and Human and Experimental Toxicology.

**Dr. Edward J. Calabrese of University of Massachusetts**

Edward J. Calabrese is a Professor of Toxicology at the University of Massachusetts, School of Public Health and Health Sciences, Amherst. Calabrese has extensively researched host factors affecting susceptibility to pollutants, and is the author of over 900 papers in scholarly journals, and more than 10 books, including Principles of Animal Extrapolation; Nutrition and Environmental Health, Vols. I and II; Ecogenetics; Multiple Chemical Interaction; Air Toxics and Risk Assessment; and Biological Effects of Low Level Exposures to Chemical and Radiation. Along with Mark Mattson (NIH) he is a co-
editor of the recently published book entitled Hormesis: A Revolution in Biology, Toxicology and Medicine.

Calabrese has been a member of the U.S. National Academy of Sciences and NATO Countries Safe Drinking Water committees, and on the Board of Scientific Counselors for the Agency for Toxic Substances and Disease Registry (ATSDR). He serves as chair of the Biological Effects of Low-Level Exposures (BELLE) and as director of the Northeast Regional Environmental Public Health Center at the University of Massachusetts.

Calabrese was awarded the 2009 Marie Curie Prize for his body of work on hormesis. He is the recipient of the International Society for Cell Communication and Signaling-Springer award for 2010. He was awarded an Honorary Doctor of Science Degree from McMaster University in 2013. In 2014 he was awarded the Peter Beckmann Award from Doctors for Disaster Preparedness.

Over the past 20 years, Professor Calabrese has redirected his research to understanding the nature of dose response in the low dose zone and underlying adaptive explanatory mechanisms. This research has led to important discoveries which indicate that the most fundamental dose response in toxicology and pharmacology is the hormetic-biphasic dose response relationship. These observations are leading to major transformations in improving drug discovery, development, and in the efficiency of the clinical trial, as well as the scientific foundations for risk assessment and environmental regulation for radiation and chemicals.

Mr. Richard J. Welsh of ASTI Environmental

Mr. Welsh is a board-certified toxicologist (DABT) and environmental chemist with over 30 years of environmental consulting and litigation support experience in disciplines including human health risk assessment, exposure assessment and ecological risk assessment. He holds a Master of Science degree in Pharmacology and Toxicology from the University of California, Davis. He is currently a director at ASTI Environmental, Inc.

Welsh has completed his career of work under the State Comprehensive Environmental Response, Compensation, & Liability Act, the Resource Conservation and Recovery Act, as well as a range of other state and international regulatory regimes. He has developed quantitative criteria and qualitative goals for soil, groundwater, sediments and air as well as supporting chemical fate and transport evaluations for a range of projects and environmental contaminants. Welsh has worked throughout the US, as well as in Western, Central & Eastern Europe, South America, the Middle East and Africa. His work includes contaminant groups PFAS, dioxins, PCBs, petroleum hydrocarbons (e.g., BTEX, PAHs & coal tar), metals (e.g., lead, chromium, mercury), industrial solvents (e.g., PCE), explosives, and agricultural chemicals.

Overview of Findings

In summary, the technical peer review identified the following:

- **Key studies were not referenced or discussed** by the Science Advisory Workgroup (SAW) in its risk assessment calculations;

- **Significant data gaps and scientific uncertainty are evident** in the SAW’s calculations;
• Curious conclusions and assumptions are evident in calculations for the Health-Based Values (HBVs); and

• SAW deviated from accepted standard practice when developing its Maximum Contaminant Levels (MCLs).

• There is an inadequate assessment of the compliance costs of the proposed rule that, ultimately, the public will bear. The absence of a robust assessment may weaken acceptance and support for the proposed criteria.

Recommendations
Based on the findings of the independent peer review, MMA encourages the following recommendations:

1. **Ensure public confidence in the process:** SAW should address and resolve any key scientific uncertainties and shortcomings that have been identified during the public comment period and subsequent to the development of proposed rules. MMA trusts that the peer review information provided here will assist in addressing some of the information gaps and questions that remain.

2. **Rely on settled science to develop MCLs:** Michigan should rely upon universally settled science when developing MCLs and ensure that Michigan is using a scientific community-consensus database. EGLE should refrain from developing MCLs on a class basis due the unique and varying effects of different PFAS constituents. As the body of scientific knowledge on exposure continues to grow, Michigan should reassess its previous determinations, consider adding other individual PFAS constituents, or modify the compliance requirements.

3. **Lead with regulation-ready rules:** Promulgate rules that are legally defensible and provide clarity, consistency, and certainty. The ruleset must also establish the proper mechanisms to ensure that EGLE, individuals, communities, and industry can understand, adapt to, and comply with the rules. *Regulation-ready* rules must include a screening and review process, as well as a site-specific plan approach for any testing site that registers a level that results in further action.

4. **Fully account for the cost:** Properly account for the costs to be incurred by employers, municipal water systems and their citizens by identifying the cost for retrofitting for existing municipal water supply systems of differing scale, costs as they relate to Industrial Pretreatment Programs, and for disposal cost elimination of PFAS material remaining after treatment. The Regulatory Impact Statement (RIS) also did not appropriately account for the ongoing operating costs, including a full assessment of the compliance monitoring costs, for municipal systems. Lastly, SAW should fully identify and consider costs when establishing HBVs, which does not appear to have been included in the overall assessment.

With EGLE’s implementation of these recommendations, Michigan can be a credible leader in PFAS-related safe drinking water standards, which the State has indicated as its goal.
Again, MMA appreciates the opportunity to provide formal comments on the proposed rules, and we trust the peer review will aid EGLE in using settled science as the foundation for setting standards, allowing the Department to establish regulation-ready standards to properly and confidently implement a credible, safe drinking water standard.

Since this is the first time that Michigan has established an MCL without one first being established by EPA, MMA’s objective is to see that Michigan implements a sustainable and defensible regulation. While the work of SAW is considerable and significant, an obvious weakness is the absence of a robust peer review as part of the SAW rule development process. A robust, properly credentialed peer review protocol is required practice for the EPA when it establishes an MCL, and Michigan should follow this example in some credible manner.

As SAW did not include a proper peer review phase in its process, MMA believed it essential to engage an expert review so as to properly and credibly inform our organization and its members of proposed rulesets soundness, and also to provide SAW with a foundational peer review for ensuring the soundness of the final rules package. While SAW relied on studies employed by other states, the different selections of information and the unique amalgamated result was not peer reviewed by other scientists or technical experts.

Further, recognizing the state’s commitment to ensuring safe public drinking water supplies, and by doing so, looking to establish MCLs prior to any established by the EPA, EGLE must consider the following:

- SAW should expand the pool of experts used in developing the MCLs. SAW lacks the multidisciplinary pool to properly determine and establish MCLs and requires additional expert assistance for properly rooting the development of MCLs. For example, EPA used more than 30 different scientists from multiple disciplines to develop its health advisory standard — that is 10 times more than those used by SAW. Moreover, the budget and technical resources of EPA far exceed the ability of any individual state to set an MCL. (See, page 22; Section 3.25 of Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020).

- To properly establish an MCL and gain the public confidence that is necessary on this issue, SAW must expand its review and reevaluate the HBVs that it established. Alternatively, EGLE should proceed to regulate what is based on settled and established science and continue to consult and incorporate ongoing research conducted by the EPA and others to enable access to critical new findings as PFAS science evolves.

- SAW did not consider some of the newest science, nor did it consider human clinical studies that are available. SAW should further evaluate the more than 2,000-plus studies on PFOA and PFOS, as well as the 400 human epidemiological studies (or at a minimum discuss why it chose not to use the other available scientific studies.) (See, page 24; Section 3.26 of Independent Technical
Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020).

- Since the SAW report lacked a peer review process, it lacked the proper professional evaluation needed for establishing HBVs. With a proper scientific, technical peer review the SAW could have corrected scientifically curious assumptions and removed uncertainty from many aspects of the review used to establish HBVs. (See, page 20; Section 3.19 of Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020).

To expand on the scientifically unsettled assumptions and approach, SAW relied on scientific uncertainty by embedding uncertainty factors into many equations to establish HBVs rather than looking to settled and established science. By relying on the inclusion of subjective uncertainty factors to address scientific questions of toxicity and exposure rather than a settled-science based determination.

To emphasize: due to the multiple layers of uncertainty factors that were added, the proposed MCLs have a similar Point of Departure to many other chemicals with established MCLs, but those other chemicals have MCLs in the parts-per-million or parts-per-billion. Put another way, human exposure via drinking water of methyl mercury or perchlorate have radically higher safe dose levels even though it is well established that these chemicals have known adverse, toxic effects. (See, romanette page vii of Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020).

In addition, SAW also used uncertainty factors in place of available data for establishing dosage levels. At a minimum, SAW needs to further explain the reason for favoring scientifically curious data gaps rather than using well established and measured data. (see, page 9, 16, 22-23; Section 3.3, 3.12, 3.22 of Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020).

Of significant concern, SAW’s confidence statement failed to identify all the scientific uncertainty factors it used in lieu of established, settled science in its report establishing the HBVs. Moreover, SAW utilized uncertainty factors at a 10-fold multiple rather than filling in database deficiencies with settled science to establish its robust database. As such, SAW report omits appropriate criteria for assessing scientific uncertainty and ensuring a proper peer review and evaluation has been conducted. (See, pages 12, 15, 19, 20-21, 23; Sections 3.6, 3.7, 3.10, 3.15, 3.19-3.21, 3.23 of Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020). To alleviate the scientifically curious approach, SAW must at least modify its report to discuss why it chose not to use the other available scientific information available.
SAW did not properly match the exposure scenario needs to the exposure that caused the critical effect.

For example, SAW’s use of the breast-fed infant exposure as the target population in its review is incorrect. The critical effect occurs for in-utero exposure and not in the postnatal pups. Since SAW had this data gap, it added an uncertainty factor to try to address critical effect. SAW, however, added additional levels of uncertainty factors when proper data would have been available. SAW must address these issues to better understand the proper critical effect and how that determines appropriate HBVs. (See, page 15-16; Section 3.11 of Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020).

SAW did not follow EPA’s established, accepted standard practices when developing its MCLs.

For example, SAW deviated from standard EPA practice when it used a benchmark dose, lower confidence limit (BMDL) rather than a Benchmark Dose (BMD), No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) when estimating the Point of Departure. (See, romanette page vii of Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020).

SAW failed to use a Concentration maximum (CMax) for proper dose adjustment from mice to humans when calculating its HBVs.

More specifically, EPA guidelines highlight CMax as the standard, default dosimetric adjustment for critical effect when developing toxicity levels. (see, pages 6, 15, 19; Sections 3.1, 3.9, 3.17 of Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020).

SAW did not follow the EPA standard process as it relates to a cost analysis when generating proposed HBVs.

The Safe Drinking Water Act (SDWA) requires the EPA to prepare a health risk reduction and cost analysis in support of any National Primary Drinking Water Regulations. While EGLE did include some minimal estimate of the costs when preparing its Regulatory Impact Statement (RIS), SAW failed to provide a similar analysis.

As a result, SAW failed to analyze the quantifiable and non-quantifiable benefits that are likely to occur as a result of compliance with the proposed standards. (See, pages 12-14, 24; Sections 3.8, 3.26 of Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020).

For example, the prevalence of PFAS in consumer products combined with the exceedingly low proposed MCLs, as well as the still developing laboratory standards will establish higher
compliance costs and likely result in false positive results that will require water suppliers to commit technical and monetary resources on issues that may not actually exist.

The lack of a complete accounting for the cost of any proposed drinking water rules is of major concern for the public and the regulated community to assess the benefits of this proposal relative to the costs all will be asked to bear. It is also of concern for municipalities as represented by the Michigan Municipal League’s formal comments filed with the ERRC. In addition, the RIS excluded the costs filtration systems from municipal water systems in Ann Arbor and Plainfield Township; and according to news reports, the combined cost of for those systems exceed $3 million.

The State should not move forward without fully knowing and accounting for the financial impact on communities and their citizens on the cost of implementing safe drinking water standards. Nor should the state move forward without properly addressing and identifying the costs on industry for Industrial Pretreatment Plans and Part 201 cleanup criteria.

Peer reviewers also highlighted numerous areas where the scientific community remains without consensus on what is settled science. Unfortunately, this meant that SAW had to consistently use scientific uncertainty to fill in gaps in place of technical information and data.

As consensus and further understanding on the impacts of PFAS continues to evolve, the state should focus its regulatory efforts around what is already settled. To highlight the lack of scientific certainty and the gaps in data that remain, the independent review noted the following:

- Due to the lack of settled and certain science on PFAS, there is still considerable debate – among both scientists and governments – on safe dose exposure. To wit, there is a more than 500-fold difference in projected safe dose levels for PFOA by different governments, with Australia setting a safe dose level at 160 parts-per-trillion (ppt) and the UK setting a safe dose at 1,500 ppt. (See, romanette page v of Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020). Moreover, SAW had a more than 40,000-fold difference in safe doses based on the different PFAS constituents. (See, pages 2, 17, 19; Sections 3.13, 3.16 of Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020). Arguably, the safe dose levels vary so greatly due to data gaps and certainty, supporting the need for Michigan to remain credibly in step with leading knowledge as it continues to evolve.

- The scientific community continues to study and ascertain the amount of time certain PFAS compounds remain in and interact in humans. Specifically, scientific evaluation is still ongoing as it relates to prolonged exposure of PFAS compounds in human serum and how albumin protein impacts how long it takes for the exposure to be eliminated from the body. (See, page 11; Section 3.5 of Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020).
We must first understand the interactions of PFAS and the human body and only establish HBVs and MCLs on compounds where we have an established consensus based on settled science. MMA recommends that to best ensure public confidence and protect human health, the state consult and incorporate research conducted by the EPA and others to enable Michigan to access critical new findings as PFAS science evolves and not regulate in areas where the science is still unsettled.

Scientific studies, including one utilized by SAW, on dose levels use exceptionally high dosages, resulting in overtly toxic levels. While this has been a historically accepted practice, it is important to note that the high doses along with scientifically unusual assumptions and uncertainty factors are driving the HBVs for establishing MCLs, rather than settled science to properly determine proper, safe HBVs. (See, page 17-18; Section 3.14 of Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020).

- Recognizing that 8-carbon PFAS are no longer in production and the science on other short chain carbon continues to evolve, the scientific community continues to further evaluate the impacts of the different constituents. As a result, moving toward a class designation is premature and would likely generate rules that are not regulation ready. Michigan needs to include a screening and review process for exceedance findings. Due to the changing nature of the settled science, the database of established science will grow over time.

Having an additional level of review and evaluation embedded into the ruleset will allow for the state, as well as communities and industry to adjust and adapt as the body of settled science grows. (See, page 23; Section 3.24 of Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan, January 30, 2020).

**Regulatory Review comments**

As noted above, the EPA has historically developed MCLs because it is best equipped with the resources and expertise to provide the basis for addressing these complex public health questions. EPA has shown through its actions that it has been actively engaged in understanding and addressing PFAS public health concerns. To highlight this point, in 2016, EPA developed and released health advisories for PFOA and PFOS. (See, 81 Fed Reg. 101 (May 25, 2016). EPA has since issued its 2019 PFAS Action Plan, which includes EPA conducting an Integrated Risk Information System (IRIS) assessments of multiple PFAS constituents and developing MCLs for PFOA and PFOS under the SDWA. (See, U.S. EPA Per- and Polyfluoroalkyl Substances (PFAS) Action Plan (February 2019)). The agency has also recently issued interim recommendations for groundwater contamination due to PFOA and PFOS. (See, Interim Recommendations for Addressing Groundwater Contaminated with PFOA and PFOS (December 20, 2019)). EPA’s objective is to properly develop a unified regulatory mechanism for protecting the public health.
Moreover, while the **EPA is working through its long-established rulemaking process for MCLs**, Congress is also working diligently to ensure that EPA promulgates a national drinking water standard for PFAS constituents. (See, National Defense Authorization Act (NDAA) (P.L. 116-92) and (H.R. 535)). It is important that **Michigan continues to monitor the extensive research conducted by the EPA**, as well as the actions of Congress to enable Michigan to access and use critical new findings as PFAS science and regulations evolve.

Many states and the Federal government have recognized the importance of addressing this complex issue. It is imperative to **remember that the SDWA provides little direction other than the adoption of federal MCLs**, and that EGLE is authorized to promulgate rules that include drinking water standards and monitoring requirements, necessary to protect the public health. (See, MCL 325.1005(1)(b)).

Moreover, the law establishing the ERRC provides that draft rules are to be evaluated against certain criteria including that the rules do not exceed their statutory authorization; the rules reasonably implement and apply the relevant law; the rules are necessary and **suitable to achieve their purposes in proportion to their burdens on individuals and businesses**; and the rules are based on sound and **objective scientific reasoning**. (See, MCL 24.266(4)(a)-(e)).

Given the gaps in information described both above and in the attached technical review, it is not clear that the **proposed standards have ensured that SAW used settled science necessary to establish MCLs**. This is further highlighted by SAW’s own report, which stated in part that there “remains significant scientific uncertainty” relating to the values selected and that additional study was warranted. (See, page 9, Health-Based Drinking Water Value Recommendations for PFAS in Michigan, June 27, 2019).

Further, for reasons discussed above and below, there is a significant concern that **these rules do not take into account economic reasonableness and the necessity of these particular standards in proportion to the burdens on individuals, local communities, municipal water systems, and businesses** that would result from the adoption and imposition of these standards.

As previously noted, this is the first time that Michigan has developed its own MCLs. In fact, the SAW report specifically states that the most stringent HBV proposed – the 6 ppt level for PFNA – that was adopted into the rule should “be used as a screening level.” (See, page 25, Health-Based Drinking Water Value Recommendations for PFAS in Michigan, June 27, 2019).

Recognizing and understanding that the SAW had a more than 40,000-fold difference in safe doses based on the different PFAS constituents, **EGLE should not use SAW’s proposed levels as an automatic trigger as a point of violation as is proposed in draft ruleset**. Rather than adopting these levels as MCLs which could result in fines, penalties, and even the termination of water services pursuant to the SDWA, we urge **EGLE to entertain a slight revision to the proposed rules and use SAW’s report to set monitoring, attainment, and maintenance requirements through regular screening as empowered to do under the SDWA**. This would ensure continued sampling while also utilizing state and federal data and standards over time.
Due to the evolving and growing understanding of PFAS, the ruleset should not adopt MCLs, but instead, should provide for the proposed sampling as proposed and then provide for significant and robust evaluation and study of each specific situation before taking any enforcement actions regarding the detected results and a process whereby only drinking water systems with consistent detections of PFAS rather than intermittent detections would be required to provide a site-specific demonstration that the levels detected do not pose a human health risk with review by a review panel, or alternatively address EGLE’s concerns through a source or system modification.

Summary

MMA and its members universally agree that the safety of Michigan’s public drinking water supplies is the top priority. We also believe that the public’s confidence is achieved by ensuring the integrity and soundness of the process and information used as the solid foundation for setting safety standards. Anything less subjects regulators, drinking water systems and others to potential skepticism and lack of confidence in drinking water safety.

Michigan cannot and should not find itself in such position, especially in light of PFAS rule related litigation and implementation delays being experienced in other states that have failed to properly underpin standards and account for costs.

MMA believes the state has endeavored to establish appropriate standards, though our peer review identified some areas lacking in the kind of robust scientific and technical integrity to fully complete the effort. We believe the issues identified in the peer review report we are submitting, and associated recommendations, if implemented, should result in the state’s rule making initiative achieving the process and confidence milestones expected of state agencies.

MMA looks forward to working with EGLE to properly develop a ruleset that ensures the safety of public drinking water supplies and the public’s confidence in its drinking water. Doing so properly guarantees we protect the public health, while also ensuring Michigan’s continued economic vitality.

Respectfully,

Mike Johnston
Vice President, Government Affairs

Attachments: 1
Independent Technical Review of the Health-Based Drinking Water Value Recommendations for PFAS in Michigan

January 30, 2020

Report Prepared For:
Michigan Manufacturers Association
620 S. Capitol Ave.
Lansing, MI 48933

Report Prepared By:
Dr. Michael L. Dourson, TERA
Dr. Edward J. Calabrese, UMass
Mr. Richard J. Welsh, ASTI
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Table 1. The Primary Issue: Risks Among National Authorities Are Widely Disparate: “Safe” PFOA Doses

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Appendix B, Laboratory Animal Studies – Stress & Behavioral Effects
Executive Summary

An independent technical review was conducted for the primary studies used by Michigan per- and poly-fluoroalkyl substances (PFAS) Action Response Team (MPART), Science Advisory Workgroup (SAW) to calculate the MPART 2019 PFAS Health Based Values (HBVs), and in turn proposed Michigan Maximum Contaminant Levels (MCLs) for Seven PFAS (including the 8-Carbon Perfluorooctanoic acid (PFOA) and Perfluorooctanesulfonic acid (PFOS) as well as the primary studies used by the United States Environmental Protection Agency (USEPA) to calculate the 2016 USEPA Drinking Water Health Advisory for PFOA and PFOS. The review was completed by Dr. Michael L. Dourson of Toxicology Excellence for Risk Assessment (TERA), Dr. Edward J. Calabrese of University of Massachusetts, and Mr. Richard J. Welsh of ASTI Environmental. The review identified:

- Key studies not discussed by the MPART in their risk assessment calculations;
- Significant data gaps in the calculations; and
- Questionable conclusions and assumptions used by SAW in calculating the HBVs and the USEPA in the Drinking Water Health Advisory.

The range of PFAS drinking water values being generated in the USA as well as throughout the World shows there is considerable debate taking place within the scientific community and that the PFAS science is anything but settled (there is little scientific consensus). To get a sense of the breath of scientific uncertainty, refer to the 500-fold differences in the projected safe dose of PFOA by different national authorities shown in Table 1, or perhaps review the abstracts from a recent international conference on PFAS (SETAC, 2019, see: https://pfas.setac.org).
**Table 1. The Primary Issue: Risks Among National Authorities Are Widely Disparate: “Safe” PFOA Doses**

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Mouse fetal (Lau et al., 2006)</td>
<td>Perkins et al. (2004)</td>
<td>Mouse fetal (Lau et al., 2006)</td>
<td>Mouse fetal (Lau et al., 2006)</td>
<td>Mouse fetal (Koskela et al., 2016)</td>
</tr>
<tr>
<td>Critical Effect</td>
<td>Liver effects in pups &amp; adults</td>
<td>Rat liver hypertrophy</td>
<td>Reduced pup ossification, accelerated puberty</td>
<td>Fetal toxicity</td>
<td>Altered pup activity; skeletal alterations</td>
</tr>
<tr>
<td>Human Dose (mg/kg-day)</td>
<td>0.08 (MMDL of 0.3 ÷ 4)</td>
<td>0.00052</td>
<td>0.0053</td>
<td>0.0049</td>
<td>0.000821</td>
</tr>
<tr>
<td>Uncertainty Factor</td>
<td>50 (200 ÷ 4)</td>
<td>25</td>
<td>300</td>
<td>30</td>
<td>300</td>
</tr>
<tr>
<td>Safe Dose (ug/kg-day)</td>
<td>1.5</td>
<td>0.02</td>
<td>0.02</td>
<td>0.16</td>
<td>0.03</td>
</tr>
</tbody>
</table>

500- Fold Difference in Safe Dose

Another observation, the estimated safe dose for PFHxA is ~ 40,000-fold higher than other safe doses. A critical question is left unanswered here: Are the PFAS sufficiently different in toxicity among a 6 carbon PFAS, 8 carbon PFAS and 9 carbon PFAS to warrant such an extreme difference in HBVs? One conclusion is that the PFAS science is not yet settled, even basic information on the mechanisms of action are not known.
We looked at other MCLs generated by the USEPA and their Point of Departure (POD). It is curious from a "gut-check" perspective that the POD doses identified for PFAS are similar to many of the chemicals with existing MCLs, yet these other chemicals have much higher MCLs in the parts-per-million (ppm) or parts-per-billion range (ppb); versus parts-per-trillion (ppt) levels for the HBVs. From a scientific perspective, a ppt is an extremely low concentration (e.g., 1 second in 32,000 years, or traveling 6 inches out of a 93 million-mile journey toward the sun) and PFAS are very unlikely to be toxic in this range. Furthermore, this is not being communicated effectively to the public.

For comparison purposes, consider perchlorate. Although starting with a lower, more toxic, point of departure, perchlorate has a radically higher drinking water health advisory versus PFAS drinking water health advisory (Figure 1).

*Figure 1, USEPA Health Advisory Level for Perchlorate*
It is understood that SAW proposed select changes to the traditional risk assessment approach (e.g., drinking water intake values for assessing development effects), however, such a radical departure from other past Health Advisory or MCL calculations (especially for chemicals arguably much more toxic than PFAS) needs further evaluation by the scientific community. To illustrate this point, consider methyl mercury. Methyl mercury is known to damage the developing brains of human fetuses and, in human children, result in deficits in attention, behavior, cognition and motor skills. Yet, the HBV for methyl mercury, the USEPA reference dose, is much higher, indicating that methyl mercury is less toxic, than all the PFAS toxicity factors, less one.

As an example of studies not discussed by SAW in the HBVs, there is a human clinical cancer treatment dosing study for PFOA (Elcombe et al., 2013), and published in part by Convertino et al. (2018). Dourson et al. (2019) also conducted a review of this clinical study, and recently received an award for best paper of the year from the Society of Toxicology’s Regulatory and Safety Evaluation Specialty Section. The study provides data on PFOA blood serum levels at various dose levels given to cancer patients. This study also provides badly needed data on how long it takes for humans to clear PFAS from their bodies (called the “half-life” in humans).

Thus, using actual human clinical data (instead of the calculations and assumptions) and a Benchmark Dose approach for PFOA (two reasonable changes), the USEPA Drinking Water Health Advisory would be recalculated to be 8,800 ppt instead of 70 ppt (See Figure 2 below). As elaborated further in this review, the benchmark dose, lower confidence limit (BMDL) rather than a no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect-level (LOAEL) is generally preferred by the USEPA for estimating the Point of Departure (POD).
As discussed, this report goes on to identify other significant data gaps in the calculations as well as other questionable conclusions and assumptions used by SAW in calculating the HBVs and the Drinking Water Health Advisory. Addressing these issues will further raise the calculated acceptable drinking water levels. For example, we provided examples (there are many more) of reduced toxic responses of PFAS at low dose levels (called hormesis). In other words, what is happening at the high dose levels in laboratory animal studies does not predict whether a chemical is toxic at low (ppt) dose levels. This needs to be further debated by the scientific community and then addressed in the HBVs.

Also consider that the USEPA PFAS Drinking Water Health Advisory, by definition, does not include a cost-benefit analysis, but the MCL process does. This analysis appears to be missing from the current HBV discussions. Note that California recently had its hexavalent
chromium MCL rescinded, and now New Hampshire has had its PFAS MCL blocked by State Courts, due to inadequate assessment of the cost for compliance.

Lastly, we compared the risk assessment process for generating the HBVs (and thus the upcoming State of Michigan MCL) to the typical process used by the USEPA in generating their MCLs. Simply put, there is and will be a large difference in level of effort and budget for the upcoming comprehensive USEPA MCL process. This level of effort, once completed, is anticipated to produce significantly higher USEPA MCL values than the SAW HBVs. It also needs to be determined whether multiple MCLs be developed for the higher 8-carbon PFAS versus the replacement lower carbon PFAS based on differences with both their toxicities, toxicokinetics and chemistries.

The independent technical review does not provide recommended MCLs, but instead highlights areas where the SAW had data gaps and indefensible or questionable conclusions and assumptions. The take-away from this review is that it is the scientifically unusual assumptions and uncertainty factors used in the SAW calculations that are driving the HBVs into the parts-per-trillion range, not the underlying science.
1.0 INTRODUCTION

At the direction of the Michigan per- and poly-fluoroalkyl substances (PFAS) Action Response Team (MPART), the document entitled “Health-based drinking water value recommendations for PFAS in Michigan” dated June 27, 2019 was prepared by Michigan Science Advisory Workgroup (SAW). The SAW Approach (MPART 2019) included that:

- 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.

- 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:
  
  o The critical study or studies, point of departure from each study, and conversion to a human equivalent dose;
  o Uncertainty factors and a calculated toxicity value;
  o Exposure parameters, and methodology for calculation of a drinking water health-based value.

The 2019 SAW report provides Health Based Values (HBVs) recommendations for seven PFAS compounds as shown in Table 2:
Table 2. SAW Health Based Values (HBVs)

<table>
<thead>
<tr>
<th>Specific PFAS</th>
<th>SAW Drinking Water Health Based Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFNA – Perfluorononanoic acid</td>
<td>6 ng/L (ppt)</td>
</tr>
<tr>
<td>PFOA – Perfluorooctanoic acid</td>
<td>8 ng/L (ppt)</td>
</tr>
<tr>
<td>PFHxA – Perfluorohexanoic acid</td>
<td>400,000 ng/L (ppt)</td>
</tr>
<tr>
<td>PFOS – Perfluorooctanesulfonic acid</td>
<td>16 ng/L (ppt)</td>
</tr>
<tr>
<td>PFHxS – Perfluorohexanesulfonic acid</td>
<td>51 ng/L (ppt)</td>
</tr>
<tr>
<td>PFBS – Perfluorobutanesulfonic acid</td>
<td>420 ng/L (ppt)</td>
</tr>
<tr>
<td>GenX (HFPO-DA) – Hexafluoropropylene oxide dimer acid</td>
<td>370 ng/L (ppt)</td>
</tr>
</tbody>
</table>

ng/L – nanograms per liter
ppt – parts-per-trillion

The objectives of this Independent PFAS Review Report are to provide:

- A technical review of the “PFAS Chemical Summary Sheets” generated by SAW and the associated key study (or studies) used by SAW to develop the seven individual PFAS HBVs as well as the USEPA May 2016 Drinking Water Health Advisory for PFOS and PFOA (with emphasis on the toxic endpoints, point of departure, human equivalent dose calculations, exposure parameters, uncertainty factors, etc.).
- A technical review of additional key studies (not address in the 2019 SAW Report) to provide further information and clarifications to the HBV calculations.
- An assessment of the HBVs relative to the typical drinking water maximum contaminant level (MCL) process used by the United States Environmental Protection Agency (USEPA) including cost of implementation.

The results of the independent technical review are presented below after a brief overview of the team Biographies.
2.0 TEAM BIOGRAPHIES

The independent technical review was completed by Dr. Michael L. Dourson of Toxicology Excellence for Risk Assessment (TERA), Dr. Edward J. Calabrese of University of Massachusetts, and Mr. Richard J. Welsh of ASTI Environmental.

Dr. Michael L. Dourson of Toxicology Excellence for Risk Assessment (TERA)

Michael Dourson has a PhD in toxicology from the University of Cincinnati, College of Medicine, and is a board-certified toxicologist (i.e., Diplomate of the American Board of Toxicology - DABT) serving as the Director of Science at the 501c3 nonprofit organization Toxicology Excellence for Risk Assessment (TERA). Prior to this, he was Senior Advisor in the Office of the Administrator at the USEPA. Before this, he was a Professor in the Risk Science Center at the University of Cincinnati, College of Medicine and also worked at TERA and USEPA.

He has been awarded the Arnold J. Lehman award from the Society of Toxicology, the International Achievement Award by the International Society of Regulatory Toxicology and Pharmacology, and 4 bronze medals from the USEPA. He has been elected as a Fellow of the Academy of Toxicological Sciences (i.e., FATS) and as a Fellow for the Society for Risk Analysis (i.e., FSRA).

He has co-published more than 150 papers on risk assessment methods or chemical-specific analyses, and co-authored well over 100 government risk assessment documents, many of them risk assessment guidance texts. He has made over 150 invited presentations to a variety of organizations and has chaired over 150 sessions at scientific meetings and independent peer reviews. He has been elected to multiple officer positions in the American Board of Toxicology (including its President), the Society of Toxicology (including the presidency of 3 specialty sections), the Society for Risk Analysis (including its Secretary), and is currently the President of the Toxicology Education Foundation, a nonprofit organization with a vision to help our public understand the essentials of toxicology. In addition to numerous appointments
on government panels, such as USEPA’s Science Advisory Board, he is a current member on the editorial board of Regulatory Toxicology and Pharmacology and Human and Experimental Toxicology.

Dr. Edward J. Calabrese of University of Massachusetts

Edward J. Calabrese is a Professor of Toxicology at the University of Massachusetts, School of Public Health and Health Sciences, Amherst. Dr. Calabrese has researched extensively in the area of host factors affecting susceptibility to pollutants, and is the author of over 900 papers in scholarly journals, as well as more than 10 books, including Principles of Animal Extrapolation; Nutrition and Environmental Health, Vols. I and II; Ecogenetics; Multiple Chemical Interaction; Air Toxics and Risk Assessment; and Biological Effects of Low Level Exposures to Chemical and Radiation. Along with Mark Mattson (NIH) he is a co-editor of the recently published book entitled Hormesis: A Revolution in Biology, Toxicology and Medicine. He has been a member of the U.S. National Academy of Sciences and NATO Countries Safe Drinking Water committees, and on the Board of Scientific Counselors for the Agency for Toxic Substances and Disease Registry (ATSDR). Dr. Calabrese also serves as Chairman of the Biological Effects of Low Level Exposures (BELLE) and as Director of the Northeast Regional Environmental Public Health Center at the University of Massachusetts. Dr. Calabrese was awarded the 2009 Marie Curie Prize for his body of work on hormesis. He is the recipient of the International Society for Cell Communication and Signaling-Springer award for 2010. He was awarded an Honorary Doctor of Science Degree from McMaster University in 2013. In 2014 he was awarded the Peter Beckmann Award from Doctors for Disaster Preparedness. Over the past 20 years Professor Calabrese has redirected his research to understanding the nature of the dose response in the low dose zone and underlying adaptive explanatory mechanisms. Of particular note is that this research has led to important discoveries which indicate that the most fundamental dose response in toxicology and pharmacology is the hormetic-biphasic dose response relationship. These observations are leading to a major transformation in improving drug discovery, development, and in the efficiency of the clinical trial, as well as the scientific foundations for risk assessment and environmental regulation for radiation and chemicals.
Mr. Richard J. Welsh of ASTI Environmental

Mr. Welsh is a board-certified toxicologist (i.e., Diplomate of the American Board of Toxicology - DABT) and Environmental Chemist with over 30 years toxicology and environmental consulting support experience in a range of disciplines including human health risk assessment, exposure assessment and ecological risk assessment. He has a Master of Science (MSc) degree in Pharmacology and Toxicology from the University of California, Davis. He is currently a Director at ASTI Environmental, Inc. Mr. Welsh has conducted much of his work under the State Comprehensive Environmental Response, Compensation, & Liability Act, the Resource Conservation and Recovery Act, as well as a range of other State and Worldwide regulatory regimes. He has developed quantitative criteria and qualitative goals for soil, groundwater, sediments and air as well as supporting chemical fate and transport evaluations for a range of projects and environmental contaminants. Geographically, he has worked throughout the USA as well as in Western, Central & Eastern Europe, South America, the Middle East and Africa. The contaminant groups he has worked with include PFAS, dioxins, PCBs, petroleum hydrocarbons (e.g., BTEX, PAHs & coal tar), metals (e.g., lead, chromium, mercury), industrial solvents (e.g., PCE), explosives, and agricultural chemicals.
3.0 SPECIFIC COMMENTS ON 2019 SAW HBVs

Provided below are comments to the SAW report and the individual HBVs.

3.1 Actual Human Data versus Estimated Human Equivalent Dose (HED): Pages 10, 12, 16, & 18

Key Finding: A clinical human cancer treatment study by Elcombe et al. (2013) provides actual human PFOA dosing and Cmax blood serum concentrations. These measured data should be used instead of the Human Equivalent Dose (HED) calculated estimates by SAW. We recommend that SAW review this information and update the HBVs accordingly.

A key paper, Elcombe et al. (2013), and published in part by Convertino et al. (2018), appears to have not been reviewed in the analysis described in the 2019 SAW report.

Elcombe et al. (2013) is a phase one, human clinical study where PFOA was used as a cancer chemotherapeutic agent. While the 40+ patients were in various stages of cancer, acceptance into the study necessitated good liver and kidney function, and kinetics were carefully monitored. The data are described in a “Patent Application” are complex.

Note, the human PFOA clinical trial data reported in Elcombe et al. (2013) and in Appendix A of the report hint at a much lower human elimination half-life (i.e., 70 to 136 days) for PFOA than previous studies (e.g., 2 to 3 years), and the half-life data from the Elcombe study would support a higher HBV for PFOA. However, this was a phase one clinical trial of often very sick patients, some of whom did not survive for the duration of the trial. Consequently, it is possible that other factors influenced PFOA elimination and thus the derived half-lives. Regardless, these data warrant careful consideration since they show good kinetic data in humans over 6 weeks of exposure and sometimes beyond. Moreover, entry into the study necessitated good liver and kidney functions.
Dourson et al. (2019) provides an analysis of the Elcombe human clinical data with the intent to compare them with relevant kinetic data in mice. This comparison can then be used to consider whether Cmax (maximum plasma concentration) is the relevant dosimeter, rather than area under the curve or AUC (useful for calculating the average plasma concentration over time) as per USEPA (1991) developmental toxicity guidelines. This paper by Dourson et al. (2019) will receive the award for best paper of the year from the Society of Toxicology’s Society of Toxicology’s Regulatory and Safety Evaluation Specialty Section in March of 2020.

As illustrated in Figure 2 below, using actual human clinical data (instead of the calculations and assumptions) and a Benchmark Dose for PFOA (two reasonable changes), the USEPA Drinking Water Health Advisory would be recalculated to be 8,800 ppt instead of 70 ppt:

*Figure 2. Example Calculations for Alternate Health Advisory Level for PFOA*
These human dosing data can also be used to develop some initial quantitative findings of PFOA half-life in humans, which appears to be under one-year (see Appendix A), and which is consistent with initial work done by Dr. Harvey Clewell [Harvey Clewell, personal communication, Alliance for Risk Assessment-Beyond Science and Decisions Workshop, TCEQ, February (ARA, 2019)].

This is all in contrast to using observational human studies by SAW to estimate half-life and thus Human Equivalent Dose (HED). Pages 10, 12, 16, & 18 from the 2019 SAW Report converted the blood serum concentrations in laboratory animals to the serum concentrations in Humans based on the following calculation (instead of the actual human data):

\[
\text{NOAEL (or LOAEL)} = \text{TWA Serum Concentration} \times \text{Ke} \times \text{Vd}
\]

Where:
- TWA = Time Weighted Average Serum Concentrations
- Ke = Human Elimination Rate Constant
- Vd = Human Volume of Distribution

This methodology breaks down (compared to the actual human data) in that observational data (a human blood ½ life of 2.3 years) was used to estimate the Ke. The SAW report uses scientific uncertainty in place of technical information resulting in unjustified lower HBV.

Note also that while the previous observational human studies are useful to get a sense of PFAS half-lives in humans, it appears several of them may not have addressed other exposure pathways to PFAS in items such as house-hold dust and commercial products. If so, then estimates of half-lives from such observational studies would be longer, and perhaps significantly longer, than the actual human dosing / half-life data.

Note, many PFAS half-life studies in humans do not appear to address other sources of exposure (i.e., food or house dust) beyond drinking water, and by not accounting for these additional exposure routes, the derived serum elimination half-lives are biased high. For example, the PFOS half-life derived by Li et al. (2018) and used in the SAW PFOA assessment appears not to have been corrected for general background exposure, meaning that the estimated PFOS half-life is likely an overestimate. However, it may be that additional background sources are sufficiently low as to not be biasing the
half-lives to a large extent. For example, serum half-lives are often derived from occupationally exposed cohorts or from populations exposed to elevated PFAS due to contaminated drinking water. In these cohorts the occupational exposure or drinking water exposure might account for most of the PFAS exposure, and other sources contributing to general exposure (i.e., dust or food) might be relatively minor. Regardless, it makes sense to carefully check these human observational studies in light of the clinical findings of Elcombe et al. (2013) and Convertino et al. (2018).

3.2 PFNA POD and $C_{\text{max}}$, Page 10

**Key Finding:** SAW did not use the appropriate dose adjustment from mice to humans based on USEPA (1991) guidelines. Refer to Section 2.2 below for recalculated HBV.

According to USEPA (1991) the default dosimetric adjustment for critical effects that are developmental toxicity is $C_{\text{max}}$ (“$C$oncentration $\text{max}imum$” or peak PFAS blood serum concentration). Here the critical effects appear to be related to in-utero exposures, with possible exposure postnatally via suckling. Choices other than this default dosimeter, such as area under the curve represented by half-life, need to be based on data specific for the critical effect. The resulting safe dose for PFNA would be much different with the choice of $C_{\text{max}}$ as the dosimeter. See Section 3.3 below, a recent publication on this very topic by Dourson et al. (2019) where PFOA is used as a case study.

3.3 PFOA Use of Benchmark Dose instead of LOAEL: Page 12

**Key Finding:** USEPA’s 2009 draft of its PFOA Health Advisory used a Benchmark Dose (BMD) as its point of departure, based in part on finding from authors of the critical study. This changed in its USEPA’s 2016 final document due to the review of other developmental toxicity effects in this critical study. The use of the low dose of the critical study as a LOAEL, rather than a BMD from the authors of the critical study lowered the health advisory by 10-fold regardless of other changes.
3.4 PFAS Exposure Prenatal / Breast Feeding, Bottom Paragraph, Page 8

Key Finding: "These traditional equations do not consider the PFAS body-burden at birth or any transfer of maternal PFAS through breastmilk “ (SAW 2019 page 8). Yes, breast feeding would result in greater exposure to the young infant. But it would not pertain later in life for a mother’s exposure during pregnancy, and it is during pregnancy when the critical effect occurs. Thus, this calculation is flawed. When evaluating development effects to the fetus, it is only the exposure to the pregnant mother that is significant. Indeed, this is the only exposure to the fetus.

This statement, while true, is not accurate in that it does not consider if the critical effect is found to be from a certain type/route of exposure (e.g., developmental toxicity from exposure to pregnant animals). If studies are available that evaluate effects from other exposures (e.g., 2-gen reproductive study that monitors suckling pups), then the appropriate exposure for developing an HBV is the one associated with the critical effect; that is, the pregnant animal. In this case, studies for developmental toxicity from exposure to pregnant animals as well as a 2-generation reproductive study that monitored for postnatal effects (i.e., suckling pups) are available and the developmental endpoints should be considered. The SAW report deviated from appropriate scientific process.

Therefore, the use of the Goeden et al. (2019) model would be inappropriate when developmental toxicity is the critical effect and effects from breast-feeding are already monitored (as generally in a 2-gen study), because it is the exposure to the dam that evoked the critical effect in the pups. If the 2-gen study is missing, then an uncertainty factor for an incomplete database is often used based in part of the work of Dourson et al. (1992). Either way, the exposure scenario is still based on that of the critical effect, in this case maternal exposure causing the fetal effect.
3.5 Serum Half-Life and Interspecies Differences

Key Finding: The Elcombe et al., (2013) human PFAS study cited above provides unique empirical information on serum half-life. However, one of the key concerns has been how to relate serum half-life for PFAS in animal models to humans. While there are multiple factors that may contribute to the occurrence of the differences in human versus mouse half-lives, one may be the difference in serum albumin half-life.

PFAS compounds are principally bound to serum proteins, such as serum albumin being about 97-99% bound. Of particular interest is that the albumin half-life in the adult mouse has been estimated to be 0.87 days as compared to the 21-day estimate for human adults. In addition, the quantity of serum in neonatal mice is in a hypo-condition for most serum proteins, including albumin, which displays about 50% of adult values by the end of the first week of postnatal life, reaching adult values by about one month (Zaias et al., 2009). While there are multiple factors that may contribute to the occurrence of the differences in human versus mouse half-lives one may be the difference in serum albumin half-life. Since the human adult displays about a 20-25 fold greater serum albumin half-life than the adult mouse this may account for a large proportion of the difference in half-life.

The difference becomes even greater when the human adult half-life is compared to the neonatal mouse. Since the PFAS are so tightly bound to serum proteins these agents are prevented from entering into cells during this binding period (e.g., no accumulation in red blood cells). The approximately 20 fold difference in serum albumin levels would reasonably well correspond to the difference in lifespan between mice and humans, and would correspond roughly with a 14-fold factor developed by Dourson et al. (2019) for extrapolating the findings of developmental toxicity in mice to pregnant humans. Thus, while there has been considerable concern raised about the prolonged human serum half-life for the PFAS class of compounds relative to the mouse, a consideration of the role of serum proteins seems to allometrically integrate the animal and human findings, enhancing toxicological interpretations.
3.6 **Confidence Statement, 1st paragraph, Page 9**

**Key Finding:** Not all of the scientific uncertainties have been listed.

Absent from the list of general uncertainties in the SAW report are those associated with assumptions of kinetic parameters among species. For specific thoughts on these uncertainties, please see below in Section 3.7.

3.7 **Confidence Statement, 2nd paragraph, Page 9**

**Key Finding:** Not all of the scientific uncertainties have been listed. Important ones described below are missing. SAW report omits appropriate criteria for assessing scientific uncertainty.

Absent from this list of specific scientific uncertainties are those associated with:

- The assumption of experimental animal parameters in lieu of human information on kinetics when compared with the kinetics of experimental animals; differences among species are large; and existing information on humans is sparse. This is a large uncertainty that needs to be highlighted;
- Uncertainties in the estimation of human half-life of certain PFAS chemicals based on human observational studies that may not have accounted for all sources of PFAS; and
- The use of LOAELs instead of benchmark doses in the development of HBVs (e.g., for USEPA's PFOA).

3.8 **PFNA & PFOS, Dose Response Issues, Pages 10 & 16**

**Key Finding:** Key studies used by SAW to develop the HBVs did not discuss observations of reduced response and toxicity at low dose levels (known as Hormesis) including Dong et al. (2009) and Das et al. (2015). The implications of this are profound
as this would radically change the HBV calculations, since existing safe doses appear to be well below the hormetic dose range (i.e., the range of enhanced performance).

The report of Dong et al. (2009) provided evidence of a possible hormetic dose response with respect to NK cells (thus lower toxicity / response at low doses). The hormetic response occurred at the same dosage as the changes in plaque forming cell response and increased liver mass. However, the hormetic response was still observed at 0.5 mg/kg, the dosage selected for the NOAEL. Thus, the issue of whether a potential beneficial response may have been occurring was not addressed in the assessment of the SAW.

A second hormetic dose response was also discussed above with respect to the eye opening endpoint (Abbott et al., 2007). In the case of the NK endpoint, the authors of the study did not discuss these findings (Figure 3). The authors appear to have focused on apparent adverse effects at higher doses.

*Figure 3. Effect of Pfluorooctanesulfonate (PFOS) on Splenic Natural Killer (NK) Activity in Adult C57Bl/6 mice following oral exposure for 60 days (based on Dong et al., 2009)*

In the report of Das et al. (2015) a key endpoint to be assessed was the occurrence of both eyes opening. It is a measure of developmental performance and maturity. The PFAS treatment at high doses delayed the eye opening. However, in another study (Abbott et al.,
2007) with PFOA, one not cited as a key study - using a broader range of exposures, reported that eye opening in the low dose groups occurred earlier than in the control group (Figure 4). This indicated not only a threshold response but also a potentially enhanced performance at doses below the threshold. For example, this may be similar to when a child starts to walk at 10 months of age rather than at 12 months.

The intention of this discussion is, in part, to illustrate the importance of assessing a broad dose response spectrum. Failure to do so can led to the exclusion of hormetic responses regardless of whether they show a harmful or beneficial response. The hormetic findings for eyelid opening with PFOA suggest the need for PFNA to have been tested over a lower dosage range.

Figure 4. Effect of perfluorooctanoic acid (PFOA) on both eyes full open in Wiltype and PPAR KO mice on Days 13 and 14 (based on Abbott et al., 2007)
3.9 PFNA Human Equivalent Dose (HED), Page 10

Key Finding: As discussed in Sections 3.1, 3.2 & 3.3. SAW failed to discuss the use of the appropriate dose adjustment from mice to humans based on USEPA (1991) guidelines.

These estimations of half-life will not be needed if the appropriate dosimetric adjustment is Cmax, as stated above. Otherwise, the work group needs to carefully consider whether all sources of PFNA were addressed in the Zhang et al. (2013) paper. At a recent Society of Environmental Toxicology and Chemistry (SETAC) meeting, it was demonstrated that unexpected sources of PFAS were potentially house-hold dust and commercial products. Consideration of household dust and commercial products, if not already included, would result in shorter and more appropriate half-lives than suggested by Zhang et al. or other human observational studies. Shorter half-lives would result in the use of smaller uncertainty factors and higher safe doses.

3.10 PFNA Toxicity Value, Page 11

Key Finding: Using uncertainty factors on internal doses needs justification.

This division assumes that the kinetics are linear from the extrapolated serum Point of Departure or POD to the serum level associated with the HBV. Are they? If so, then this division is appropriate. If not, then the appropriate adjustment might be either greater or smaller. Irrespective of the outcome, the SAW needs to address and justify the approach to allow others to determine if the uncertainty was appropriate.

3.11 PFNA Exposure Parameters, Page 11

Key Finding: The exposure scenario needs to match the exposure that caused the critical effect.

The choice of a breast-fed infant exposure as the target subpopulation is not correct. The critical effect occurs in the fetus on an in-utero exposure and not in pups from postnatal
exposure via breast-milk. In fact, exposures to breast feeding infants were not investigated, making adverse effects to this target subpopulation speculation. However, this lack of data appears to be one reason for the 10-fold uncertainty factor for incomplete database, and therefore, reliance on a breast-milk exposure is again not needed since this data gap is addressed in the use of this uncertainty factor. In other words, the SAW appears to have added additional levels uncertainty factors when it was unnecessary.

3.12 PFOA Use of One Dose, Page 12

Key Finding: ATSDR’s choice of study is not supportable due to small n, only one dose, and likely pup-based statistics.

The use of a single dose Koskela et al. (2016) is particularly of concern in a study that employed a very modest sample size, that is, only 8-10 mice/treatment per comparison and when there was no information provided concerning historical control group responses for the endpoints studied. Furthermore, this is the only key study used by SAW in which the animals received the dosing more normally via food rather than via a gavage like process. These two reasons raised substantial concerns over the use by SAW of such a limited study for generation of the HBVs. Furthermore, the decreased time spent in the darkened area by the PFOS males as reported in this study does not have to be interpreted as a negative or adverse effect. The response of these males could be interpreted as displaying heighten caution, rather than the opposite of enhanced exploratory behavior had they exceeded the response of the control. A cautionary response may be an adaptive response in specific biological contexts.

In contrast, the study used by USEPA, Lau et al. (2006), is recommended because of more animals, more doses and a more standard design. However, consider developing a benchmark dose, lower confidence limit (BMDL) rather than a LOAEL from the Lau et al. (2006) study as the point of departure.
3.13 PFHxA, Page 14

**Key Finding:** This is a simple general observation: How can the HBV developed for this chemical be 40,000-fold different than its closely related analogs?

The toxicology database for PFHxA is robust and consists of multiple acute toxicity studies, three subchronic studies (one 28-day and two 90-day studies all conducted in rats), two developmental/reproductive toxicity studies (one in mice and one in rats), one two-year carcinogenicity study (in rats), and multiple toxicokinetics studies [see Luz et al. (2019) for a review of the PFHxA toxicology database], however, as SAW incorrectly states “no additional developmental data in a second species, as part of their rationale for applying a database uncertainty factor of 10.

Iwai and Hoberman (2014) conducted a combined reproductive and developmental toxicity study in mice, while Loveless et al. (2009) conducted reproductive and developmental toxicity studies in rats. A database uncertainty factor of 3-fold would be a better judgment.

In addition, SAW leaves a critical question unanswered: Are the chemistries sufficiently different in toxicity among a 6 carbon PFAS, 8 carbon PFAS and 9 carbon PFAS to warrant such an extreme difference in HBVs? The estimated safe dose for this PFHxA is ~ 40,000-fold higher than others. Differences in toxicity due to small changes in closely related structures are not uncommon (e.g., ethanol versus methanol). However, the proposed magnitude difference needs to be carefully investigated, since it implies that one or more of these proposed safe doses are not done correctly. Note: the toxicity value should be 0.083 mg/kg-day.

3.14 PFOS, High Dose Levels, Page 16

**Key Finding:** The comments below are simply a general observation, likely not known to the public.

The dose range used in the key studies by SAW for the generation of the HBVs ranged from 0.5 to 500 mg/kg.
Example studies include:

- Dong et al., (2009) administered PFOS to mice daily for 60 days at doses of 0, 0.5, 5, 25, 50, and 125 mg/kg. The laboratory animals at 25, 50, and 125 mg/kg dose levels showed significant weight loss, thus stress (acute toxicity).

- Lau et al., (2005) administered PFOS to mice from gestational day 1 to 17 at doses of 1, 3, 5, 10, 20, and 40 mg/kg. The laboratory animals at 10, 20 and 40mg/kg dose levels showed significant weight loss, thus stress (acute toxicity to the mothers).

A dose of 40 mg/kg for a human weighing 80 kg (175 pounds) is relative equivalent to a human consuming 2400 mg of PFAS per day or about a teaspoon of PFAS per day. Doses of approximately 10 to 20 mg/kg were generally associated with significant weight loss by these laboratory animals. In other words, these animals were significantly stressed.

Dose levels approximately one order of magnitude below these overtly toxic levels are then generally used to identify potential toxicity endpoints in the laboratory animals. It is understood that this is accepted standard of practice in toxicology.

The observation is whether the public is aware of the relatively high doses of PFAS being fed to laboratory animals to elicit toxic effects. Then, is the public really aware of the layers of calculations and uncertainty factors that are applied to that dose level (e.g., equivalent to eating a teaspoon of PFAS per day in humans) to calculate in a HBV of a part-per-trillion.

The answer is likely no. Again, the take-away from this independent technical review is that it is the scientifically unusual assumptions and uncertainty factors used in the SAW calculations that are driving the HBVs into the parts-per-trillion range, not the underlying science.

In conclusion, it is reasonable to assume that the normal defense mechanisms (e.g., repair mechanisms, metabolism, immune responses, etc.) are being overwhelmed at these high doses being fed to laboratory animals (i.e., a human consuming close to a teaspoon of PFAS per day).
3.15 **PFOS Toxicity Value and Exposure Parameters, Page 17**

**Key Finding:** Same comments as for PFNA (i.e. 3.10 above).

For the toxicity value section, an assumption is being made that the kinetics are linear from the extrapolated serum Point of Departure or POD to the serum level associated with the HBV. Are they? Otherwise, the uncertainty factors used may not be appropriate. For the exposure parameters section, if the critical effect is in adults and an uncertainty factor for database factor is not being used, why is the breast-fed infant exposure being used? The appropriate exposure scenario is the adult.

3.16 **PFHxS, Page 18**

**Key Finding:** How can the health value developed for this chemical be ~8,000-fold lower than its acid analog? This does not appear to make biological sense.

How is it possible that the acid, PFHxA, is so much less toxic than the associated sulfate as shown here? This difference is ~8,000-fold. The SAW needs to address this difference. Otherwise, it gives the impression that it was missed. If missed, then the SAW should consider whether such a large difference makes biological sense.

3.17 **PFHxS Human Equivalent Dose (HED), Page 18**

**Key Finding:** SAW needs to confirm that AUC and not Cmax is the appropriate dosimeter.

SAW determined that the critical effect, decreased serum free thyroxin (T4) levels, is associated with AUC as the dosimeter, and not Cmax. Is that correct? Has the gavage nature of the exposure been considered? Furthermore, the recent Society of Environmental Toxicology and Chemistry (SETAC) meeting describe PFAS exposures is pervasive. Did the human observational study of Sundstrom et al. (2012) account for all exposures? If not, then the stated half-life might be too long because the population might be receiving a continuous source of PFAS. A more scientifically appropriate half-life might result in a higher safe dose.
3.18 PFHxS Uncertainty Factors, Page 19

**Key Finding:** Rats are more sensitive to thyroid hormone changes than humans. This uncertainty factor is not appropriate.

The choice of a toxicodynamic factor of 3 is not consistent with the underlying biological differences between rat and human for thyroid hormone disturbance. Because rats are more sensitive than humans to thyroid effects, rats need 10 times the replacement T4 than humans, due to human binding of T4 in the serum (Casarett and Doull 2018). This 3-fold factor could be proposed as 0.1, as it was in many independent peer reviews during USEPA’s RfD development for perchlorate.

USEPA actually used a value of 1.0. Thus, the safe dose would be 3-fold higher with USEPA’s choice or 30-fold higher with the recommendation from the peer review.

3.19 PFHxS Toxicity Value and Exposure Parameters, Page 19

**Key Finding:** Same comments as for PFNA (i.e. 3.10 above).

For the toxicity value section, an assumption is being made that the kinetics are linear from the extrapolated serum Point of Departure or POD to the serum level associated with the health based value. Are they? Otherwise, the uncertainty factors used may not be appropriate. For the exposure parameters section, if the critical effect is in adults and an uncertainty factor for database factor is not being used, why is the breast fed infant exposure being used? The appropriate exposure scenario is the adult.
3.20 PFBS Human Equivalent Dose (HED), Toxicity Value, Exposure Parameters, Page 21

Key Finding: Same comments as for PFNA (i.e. 3.10 above).

For the human equivalent dose section, SAW used a dosimetric adjustment factor of 316 (i.e., the ratio of the human half-life to the mouse half-life) to derive the Human Equivalent Dose (HED). This approach may not be warranted based on USEPA who has derived toxicity values for PFBS on two separate occasions. In 2014, USEPA derived a Provisional Peer-Reviewed Toxicity Value for PFBS, and in 2018 USEPA released their draft toxicity assessment for PFBS. For both assessments, USEPA determined that allometric body-weight scaling to the 3/4 power was the most appropriate method to derive the HED, which resulted in use of a factor of approximately 4. Allometric body-weight scaling appears to be the most appropriate method for deriving an HED for PFBS, and use of an allometric body-weight scaling factor would increase the PFBS toxicity value and subsequent HBV by approximately a factor of 75. At a minimum, the SAW must explain why it departed from USEPA practice.

For the toxicity value section, an assumption is being made that the kinetics are linear from the extrapolated serum Point of Departure or POD to the serum level associated with the health based value. Are they? Otherwise, the uncertainty factors used may not be appropriate. For the exposure parameters section, if the critical effect is in newborns after day 1, then the effect is most likely from in utero exposure and the exposure scenario to the pregnant dam should be used, not breast-fed infants.

3.21 GenX Uncertainty Factors, Page 23

Key Finding: SAW needs to confirm its understanding of uncertainty factor justification.

The lack of epidemiological information is not a basis for this use of a database uncertainty factor. That said, the other stated gaps are sufficient to suggest the use of 3-fold (thus, no difference to the HBV).
3.22 Laboratory Animal Studies – Stress & Behavioral Effects

**Key Finding:** Standard operating procedures were not provided to address the potential for stress and behavioral effects in the laboratory animals. These study design limitations can have profound effects on the results of the toxicological studies.

Use of Controls, Animal Husbandry, Animal Stress

The key studies used by SAW to develop the HBVs did not provide standard operating procedures to address the potential for induced stress and potential for exacerbated toxicological effects. This includes the studies by Das et al., (2015); Dong et al., (2009); Feng et al., (2017); and Klaunig et al., (2015). The implications of this study design limitation would create the possibility that these study protocols may have exacerbated the chemical toxicity by an undetermined amount and done so in a differential manner across control and treatment groups affecting study validity thereby compromising the use of these experiments for regulatory applications. Refer to Appendix B for further discussion.

Reporting and Controlling for Aggressive Behavior in Laboratory Animals

The key studies used by SAW to develop the HBVs, including Klaunig et al., (2015), did not provide standard operating procedures for reporting and controlling for aggressive behavior in laboratory animals. Of importance is that these actions can lead to profound changes in stress physiology, immune responses following wounding and other altered physiological processes. Thus, there is the possibility that these study protocols may have exacerbated the chemical toxicity by an undetermined amount and done so in a differential manner across control and treatment groups affecting study validity thereby compromising the use of these experiments for regulatory applications. Refer to Appendix B for further discussion.

Technician Variability

The key studies used by SAW to develop the HBVs did not provide standard operating procedures for addressing technician variability. These procedures affect laboratory animal behavior and thus numerous biological processes. Thus, there is the possibility that these
study protocols may have exacerbated the chemical toxicity by an undetermined amount and
done so in a differential manner across control and treatment groups affecting study validity
thereby compromising the use of these experiments for regulatory applications. Refer to
Appendix B for further discussion.

3.23 Uncertainty Factors for Database Deficiencies

**Key Finding:** Uncertainty factors for database deficiencies of up to 10x are used by
SAW for many of the HBVs. This reduction in the HBV (or future MCL) by 10-fold can
be obviated by the generation of a robust database. Studies that could be helpful
included developmental toxicity studies in two species, a two-generation reproductive
study and standard toxicity studies in different species.

3.24 Relative Source Contribution

**Key Finding:** Given the 8-carbon PFAS are no longer in production, and thus no longer
in commercial products used by the public, when will a higher RSCs of 0.8 or 1.0 be
used in the future HBV or MCL calculations? Based on this consideration, should
separate HBVs (and thus MCLs) be produced for the 8-carbon PFAS versus the smaller
replacement PFAS?

3.25 USEPA MCL Process

**Key Finding:** The risk assessment process for generating the HBVs (and thus
upcoming State of Michigan MCL) was compared to the typical process used by the
USEPA in generating their MCLs. Simply put, there is and will be a significant difference
level of effort and budget for the upcoming USEPA MCL process. This level of effort,
once completed, is anticipated to produce significantly higher MCL value(s) than the
SAW HBVs.

Noteworthy is the approximately 30 scientists and toxicologists employed to generate the
USEPA Drinking Water Health Advisory. The USEPA effort will be expected to increase
significantly during development of their upcoming PFAS MCL(s). Tens of scientists and peer
review candidates are usually deployed for the effort. Considerable budgets will also be set aside, budgets that are typically not available within individual U.S. States. There are over 2000 studies alone on PFOA and PFOS as well as over 400 human epidemiology studies. The pool of multidisciplinary scientists and toxicologists needed to review the PFAS literature will undoubtably also include several of the known, for lack of better words, premier toxicologists. As with other professions such as medicine and engineering, there are also a range of different toxicologist specialties that will need to be consulted as a part of this effort. As the science of PFAS is highly unsettled, it will take this level of effort and budget to resolve many of the key technical issues identified in the HBV calculations. Part of this effort will also be in completing the ongoing studies being conducted, or proposed, by the USEPA and the world scientific community to fill identified data gaps in the PFAS literature. Using scientifically unusual calculations and assumptions as well as questionable uncertainty factors is not the interim answer.

3.26 MCL Process, Cost Analysis

**Key Finding:** A cost analysis consistent with the USEPA MCL process does not appear to have been addressed by SAW in generating the proposed HBVs (and thus future MCL).

The Safe Drinking Water Act (SDWA) requires USEPA to prepare a health risk reduction and cost analysis (HRRCA) in support of any National Primary Drinking Water Regulations (NPDWR). Under the SDWA, the USEPA must analyze the quantifiable and non-quantifiable benefits that are likely to occur as the result of compliance with the proposed standard. The USEPA must also analyze certain increased costs that will result from the proposed drinking water standard.
REFERENCES


APPENDICES
Appendix A
Human Clinical Dosing Study, Elcombe et al. (2013)

Forty-three patients in the Elcombe et al. (2013) study received PFOA once a week by capsule for 6 weeks at different doses. Nine of them continued after 6 weeks and an apparent plateau was reach as shown in the figure below. Tentative conclusion from this figure is that the apparent half-life of PFOA is 5 weeks (~1/5th the plateau time).

Elcombe et al. (2013) weekly doses in excess of 6 weeks, shown as Figure 78 of their text.

Conclusion: ½ life is 5 weeks
Forty-three patients in the Elcombe et al. (2013) study received PFOA once a week by capsule for 6 weeks at different doses. The figure below shows the average decrease in PFOA in each dose group over the first week, that is from the first dose to the time just before the second dose. The apparent half-life is 11 days, very different from the previous figure. Why the difference?
Three patients in the Elcombe et al. (2013) study received only one dose of PFOA at 50 mg and were followed for 6 weeks. The average decline in serum concentration is shown below. The tentative conclusion from this figure is that the apparent half-life of PFOA is biphasic, which helps explain why the estimated half-lives from the first two figures were different.

**Figure 14**

Elcombe et al. (2013)

Average concentrations of Ammonium Perfluorooctanoate, up to day 37, measured in patients dosed with 50mg capsules once.

Conclusion: Elimination is biphasic
A tentative analysis of kinetic information from the three patients of the previous figure is possible. The half-life of the initial phase appears to be 6 hours. The half-life of the second phase appears to be 70 to 140 days.

**All Times:** Patients 1, 2, and 3 given 50 mg of PFOA once (Elcombe et al., 2013)

**1st Phase Elimination:** Patients 1, 2, and 3 given 50 mg of PFOA

**2nd Phase Elimination:** Patients 1, 2, and 3 given 50 mg of PFOA

**2nd Phase Elimination (alternate):** Patients 1, 2, and 3

Half life: 70 days

Half life: 6 hours;

Half life: 136 days
Appendix B

Laboratory Animal Studies – Stress & Behavioral Effects

Use of Controls, Animal Husbandry, Animal Stress

The process of picking up and handing the animal induces stress. The fact that one employs a vehicle control that is gavaged does not have the potential to detect if there is an interaction between the chemical treatment and the induced stress. The control group addresses the issue of the stress, but not for potential stress-chemical interaction. That handling stress could interact with chemical induced toxicity enhancing toxicity beyond that of the chemical treatment alone was reported by Calabrese (2001). This study reported that prior handling of rats before carbon tetrachloride exposure enhanced liver toxicity by 3-fold. In that study, the handling process was dissected into multiple components to determine which part of the handling process may have affected the increase in toxicity. In the study, all that was required to enhance toxicity was the act of briefly picking up the rat for several days prior to treatment. The toxicity was not further enhanced by additional handling, placing the rat in a restraining plexiglass frame, modestly warming the tail, taking blood from the tail vein and other procedures.

Reporting and Controlling for Aggressive Behavior in Laboratory Animals

According to Deacon (2006), male mice housed in groups often display aggressive behaviors, as well as fighting, biting and wounding. The biting/wounding typically would occur on the back, tail and genitals. Substantial literature indicates that many factors can contribute to such aggressive behaviors and fighting/wounding, including strain specific genetic factors, gender, age, cage size, animal density in the cages, presence or absence of environmental enrichment and other factors. Of importance is that these actions can lead to profound changes in stress physiology, immune responses following wounding and other altered physiological processes. Some of the key studies provided a focus on immune parameters. There was no information provided concerning how the key studies reported any information on these behavior parameters. Furthermore, several of the studies included periodic random selection/removal of animals for testing. However, each mouse caging condition is expected
to have a unique social hierarchy. In the selection of random animals from each cage, it is unlikely that the selected animals would have the same social status as in other cages. These conditions reintroduce a new round of aggressive behaviors, including fighting, biting and wounding. This would have the potential to create another new variable between the various treatment groups and the control group. Some of the key studies in fact employed well-recognized aggressive mouse strains such as the CD-1 strain.

Hierarchy in the mouse cage can affect both behavior and gene expression for hypothalamus corticotropin releasing hormone (CRH) and hippocampal serotonin receptor subtypes in the male C57/BL/6 mouse model used in several of the key studies (Horii et al., 2017). CRH can suppress appetite, increase anxiety and enhance inflammation amongst many physiological changes that could impact the reported study endpoints. CRH is also synthesized in T-lymphocytes, a cell of particular relevance to immune endpoints. The increased synthesis of hypothalamus serotonin has the capacity to affect dietary behavior, inflammatory responses and broad spectrum of behavioral responses.

In the Klaunig et al. 2015 rat study the animals were in single cages (i.e., one rat/cage). Rats are highly social and single rat housing, especially for a prolonged time as in this study, leads to considerable stress in the animals. In such cases, the adrenals enlarge, corticosterone rises, and the rats become physiologically somewhat abnormal (Deacon, 2006).

**Technician Variabilities that Go Unreported**

The technician/animal handler and others in the room with the animals can have a major impact on the outcome of an experiment. Rodents can be very sensitive to many features of people that are underappreciated. For example, their sense of smell is approximately 100,000 times more sensitive than that of humans (Deacon, 2006). Thus, rodents can perceive and be affected by various perfumes of differing strengths and deodorants. This is also the case for creating noise of considerably different types and intensities (Deacon, 2006). In no case did the published papers indicate any information about whether the technicians were instructed not to use perfumes, deodorants other detectable materials. There is no information on whether the same technician handled all the treatment groups as well as the
control groups. There was no information provided concerning how the animals were picked up. It is well known that mice are calmer when picked up by hand and cupped rather than by the tail (Charles River, 2012; Hurst and West, 2010). There was no information provided concerning how they were picked up and any variation between animals, cages, treatments and technicians. There is no information concerning how many different technicians were used and when during these key studies. There was also no information concerning the possibility of fire alarms occurring (i.e., due to maintenance accidental occurrences and other circumstances) during the studies. If these occurred then it would be important to know when, how often, the decibel level and the duration of the exposures.

The key studies used by SAW in generating the HBVs did not provide (with one exception) information on bedding and how often it was changed. This was also the case for cage cleaning. Yet, studies indicate that these findings can markedly affect aggressive behaviors in mice (Lidster et al., 2019). For example, cage cleaning alters scent marks, which can disrupt social hierarchy and decrease social stability, leading to more fighting. As for bedding, there is much variation in how it may be handled. Some studies throw out soiled bedding, others transfer it, amongst other practices. All of these options affect behavior and numerous biological processes. The SAW report did not document the practices and to assess how it may be affected the outcome of the study.