STATE OF MICHIGAN
DEPARTMENT OF HEALTH AND HUMAN SERVICES
LANSING

RICK SNYDER
GOVERNOR

NICK LYON
DIRECTOR

Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry
1600 Clifton Rd. NE
MS F-57
Atlanta, GA 30329
Attn: Docket No. ATSDR-2015-0004

August 17, 2018

The Michigan PFAS Action Response Team (MPART), a multi-agency action team that is responsible for guiding the state's response to the public health and environmental concerns with PFAS, appreciates the comprehensive and thorough analysis put forth by the Agency for Toxic Substances and Disease Registry (ATSDR) within their draft *Toxicological Profile for Perfluoroalkyls*. In response to a request for public comment in the Federal Register, established in June 2018 as Docket # ATSDR-2015-0004, MPART, as a key recipient of this information, provides the following feedback.

The Perfluoroalkyl Toxicological Profile appears to have captured all relevant peer-reviewed literature available at the time of document development regarding the identified subset of PFAS and their potential environmental and health effects. It is understood that the PFAS family of emerging chemical contaminants of public health concern have not been fully studied. However, ATSDR has presented a comprehensive peer review that, to date, supports the strengthening of evidence regarding human health impacts, primarily upon reproductive health, immunologic, and endocrine impacts, in addition to other associations observed during population studies such as the C8 Study. The document also provides a description of the integration of the epidemiological and toxicological studies. This description includes a weight-of-evidence approach for the evaluated adverse health effects based on the epidemiological studies and the limitations of the epidemiological data.

The draft Toxicological Profile also identified several data needs. In particular, MPART reiterates the need for additional toxicology studies that would provide necessary information to adequately evaluate immunological and developmental endpoints after acute, intermediate, and chronic exposure. MPART is also supportive of laboratory animal studies examining mixtures of PFAS, to assist with interpretation of the real-world PFAS exposure occurring in human populations identified in the epidemiological studies. Given the evolving knowledge on PFAS, MPART suggests that ATSDR conduct a focused literature review in case studies, which are newly available, that address these data gaps before finalization of the Toxicological Profile.

Of note, in addition to providing revised intermediate oral Minimum Risk Levels (MRLs) for PFOS and PFOA, new intermediate oral MRLs have been provided for PFHxS and PFNA. For Michigan, which is now addressing over 34 sites of PFAS contamination, these additional MRLs will assist the state in responding to these environmental contaminants, particularly as PFHxS and PFNA have also been found along with PFOS and PFOA during our investigations. The MRL development is generally well described in Appendix A, with the last step to apply appropriate uncertainty factors informed by comparison of the point-of-departure to serum PFAS levels reported in epidemiology studies.

This approach is a reasonable way to use the epidemiological information given the limitations of those studies. However, MPART requests that additional detail be added to clarify what serum levels were considered from what epidemiological studies, and what uncertainty factors were applied due to information from epidemiological studies. Because of the very high level of interest and concern about the MRLs, it is important that their derivation be completely transparent – the data that were used, the assumptions made, and the calculations. In addition, it would be helpful to note how these may be updated as the toxicology and epidemiology research on PFAS continues.

Additional points suggesting clarification discussion for the MRL development are presented below.

1) The ATSDR has applied a modifying factor to the development of the provisional intermediate oral MRLs for PFHxS and PFNA. The justification provided for using this modifying factor is database limitations; specifically, to account for the small number of studies examining the toxicity of these substances following intermediate-duration exposure and the limited scope of these studies examining immunotoxicity. ATSDR also supports this justification by generically stating that immunotoxicity is a “sensitive endpoint for other perfluoroalkyl compounds”. However, the provisional intermediate oral MRLs for PFOS and PFOA are derived using developmental, not immunotoxicity, endpoints as the most sensitive effect. MPART asks that ATSDR provide a more robust discussion in support of this recommendation as it appears inconsistent with actions taken by the ATSDR for PFOA, where application of a modifying factor to address uncertain immunotoxicity effects has not been similarly applied. The rationale underlying the assignment of uncertainty factors is not clear yet has a substantial impact on the derivation of MRLs.

2) The ATSDR has proposed applying a modifying factor to the development of the provisional intermediate oral MRL for PFOS based on the “…concern that immunotoxicity may be a more sensitive endpoint of PFOS toxicity than developmental toxicity”. While PFOS immunotoxicity animal studies were identified by the ATSDR, they were not pursued as candidates for the principal study because pharmacokinetic model parameters were unavailable for the specific animal strains used in these studies. MPART suggests that ATSDR evaluate these immunotoxicity studies using pharmacokinetic model parameters from appropriate surrogate rodent strains, and include a discussion in Appendix A. This would better inform the uncertainty of the decision making as to whether immunotoxicity truly represents a more sensitive effect than the developmental effects and if the immunotoxicity

study itself should be used to develop the MRL. At a minimum a more informed decision could be made as to whether a modifying factor is necessary, and if so, whether the full 10-fold value or a partial value is warranted to ensure adequate human health protection. Where there is not a clear-cut "most sensitive" endpoint based on existing literature, derivation of MRLs for more than one endpoint would help in the interpretation of the evidence.

3) The ATSDR has developed provisional intermediate oral MRLs for PFOS, PFOA, PFHxS, and PFNA. The agency indicates that chronic toxicity studies are available for PFOA, PFOS, and PFHxA, but that they were not considered suitable for derivation of provisional chronic oral MRLs because they (i.e., the chronic studies) did not evaluate immunotoxicity. MPART suggests that the ASTDR should provide additional discussion on this issue as limitations associated with immunotoxicity studies did not prevent the development of provisional intermediate oral MRLs for PFOS, PFHxS, or PFNA. The dividing line between "adequate" and "inadequate" for deriving MRLs is not clearly stated.

MPART fully supports the mission of the ATSDR in forwarding scientific findings towards mitigating harms to public health across the United States and supports the rationale for the provision of revised and new MRLs for PFOS, PFOA, PFHxS and PFNA. What is of concern to MPART, however, is that the application, or operationalization, of the new MRL's, albeit not an objective of a Toxicological Profile, has not been addressed by the Centers for Disease Control and Prevention (CDC), or by the Environmental Protection Agency (EPA). While the EPA has used a Lifetime Health Advisory of 70 ppt for PFOA + PFAS, it is unclear how a state should operationalize the current findings by ATSDR for a public health or environmental regulatory response. While this is beyond the content of a Toxicological Profiles, additional guidance from the ATSDR would be beneficial on use of the MRLs and resulting drinking water comparison values, especially with the context of other federal agency values. Perhaps a companion statement could be provided to offer considerations in the translation of the new MRLs into policy, acknowledging the pressing need for a clear, practical approach to addressing the rapidly growing number of PFAS-contaminated sites. Several issues arise that will need to be addressed at a national level:

- Is there additional guidance the ATSDR can provide on whether the summative amount of the four PFAS (PFOS, PFOA, PFHxS and PFNA) be utilized at a site, similar to how EPA provides a PFOS + PFOA limit of 70 ppt; or, should the presence of just one of the four PFAS above the intermediate MRL trigger environmental or public health agency responses?
- How will the MRLs be utilized by ATSDR during future site assessments, such as the upcoming PFAS Exposure Health Assessments being conducted around Department of Defense sites? Perhaps that could serve as a guide for states as they proceed with implementation of ATSDR's *PFAS Exposure Assessment Technical Toolkit (PEATT)* at their respective PFAS sites.

Thank you for the opportunity to comment. Please contact me if you have any questions or would like additional information.

Sincerely,

Eden Wells, MD, MPH, FACPM
Chief Medical Executive
Member, Michigan PFAS Action Response Team