

March 2, 2018

Comments on the Systematic Review Protocol for the IRIS Chloroform Assessment (Inhalation)

Comments submitted online via *Regulations.gov* to docket EPA-HQ-ORD-2017-0497 (FRL-9973-15-ORD) and by email to Dr. James Avery, NCEA; telephone: 202-564-1494; email: avery.james@epa.gov.

These comments are submitted on behalf of the undersigned academics. We declare collectively that we have no direct or indirect financial or fiduciary interest in any chemical under consideration in these risk evaluations. The co-signers' institutional affiliations are included for identification purposes only and do not necessarily imply any institutional endorsement or support.

We appreciate the opportunity to provide written comments on the U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) program's Systematic Review Protocol for the IRIS Chloroform Assessment (Inhalation) [CASRN 67-66-3]. This is the first attempt from IRIS to conduct a formal systematic review in its chemical assessment process, including the pre-publication of a documented and publically available protocol that guides each step of the assessment. As recently discussed in the National Academies of Sciences (NAS) review of IRIS advancements, utilization of systematic review methods is essential to completing comprehensive, transparent and accurate chemical assessments. As such, we believe that this is a critical opportunity for scientists, researchers, and the community to participate in public comments that has the potential to guide future chemical assessments within the Agency.

Unfortunately, as it is currently written, this protocol is not a sound systematic review of the current scientific evidence on chloroform carcinogenicity. Our comments are highlighted below, followed by a more detailed discussion.

RECOMMENDATIONS

We recommend that EPA IRIS should:

- 1) Consider incorporating a longer review period for public comment;**
- 2) Conduct a rapid review or systematic review to update knowledge regarding the mode of action for chloroform carcinogenicity, which is by now 17 years outdated, clarify in the protocol that it is under evaluation, and delay finalization of the oral mode of action only once the systematic review of underlying science has been completed;**
- 3) Clearly outline the approach for searching, including, and evaluating scientific evidence from the non peer-reviewed literature;**
- 4) Develop metrics that reflect estimates of risk, as has been recommended by the NAS;**
- 5) Incorporate the financial conflict of interest of study authors as a consideration of potential bias for included studies; and**
- 6) Incorporate explicitly defined criteria for each risk of bias rating to transparently describe its corresponding level of evidence.**

DETAILED COMMENTS

1) EPA IRIS should consider incorporating a longer review period for public comment.

The systematic review document was posted on the Federal Register on January 31, 2018 and the public comment deadline ends March 2, 2018, a 30-day review period. Given the complexity of the document as well as its potential for setting precedence for the development of future protocols (particularly with the IRIS Handbook not being publically available yet) and conduct of future systematic reviews, we believe this may have warranted a longer public comment period. As such, with the 30-day review period in place, we offer our comments here by the deadline in brief, but we anticipate submitting further comments in the near future to EPA IRIS to append to these initial comments.

2) EPA IRIS should conduct a rapid review or systematic review to update knowledge regarding the mode of action for chloroform carcinogenicity, which is by now 17 years outdated, clarify in the protocol that it is under evaluation, and delay finalization of the oral mode of action only once the systematic review of underlying science has been completed.

This protocol outlines the proposed approach for the reassessment of the health effects of chloroform via the inhalation route of exposure. Given that the current IRIS inhalation unit risk (IUR) dates back to 1987, this is a much needed reassessment and we strongly support a re-evaluation of the science. However, as it is currently written, the protocol is not a true systematic review of the evidence on chloroform as the scope of the assessment is narrow and fundamentally flawed in its approach.

Within this document, IRIS states: “The chloroform inhalation assessment will be updated by deriving an RfC based on available inhalation data in human or animal studies, then evaluating this RfC considering the MOA analysis posted on the IRIS website in 2001. The results of this evaluation is anticipated to result in a new RfC that would replace the existing IUR from 1987.” (pg 6) This MOA analysis from 2001 concluded that for cancer, chloroform exhibits a “threshold” by all routes of exposure. This analysis is now 17 years out of date and some of the scientific peer reviewers raised significant concerns about the evaluation. The Scientific Advisory Board’s (SAB) review of the draft assessment noted that there could be competing modes of action, stating: “In considering this potential mode of action for chloroform-induced carcinogenicity, the Subcommittee expressed concern that a cytotoxicity/regenerative cell proliferation mode of action may not be the exclusive mode, and that alternative modes of action have not been rigorously studied.”¹ We anticipate that a systematic review of the original literature would provide a more clarifying evaluation of the science and more recent scientific literature likely will contribute additional knowledge to update this assumption.

What makes the current protocol confusing is that IRIS also states: “Therefore, only new cancer MOA evidence will be screened to confirm those conclusions are still valid. In the absence of

¹ Chloroform Risk Assessment Review Subcommittee (CRARS) of the US EPA Science Advisory Board (SAB). 2000. Review of the Draft Chloroform Risk Assessment.

new information that may impact the 2001 conclusions, the current assessment will rely on other published authoritative sources like public health agency reports and expert review articles to summarize mechanistic information for chloroform.” (pg. 40) Therefore, it appears that EPA IRIS does indeed plan to review this assumption and update it based on newer scientific information, but as it is currently written the protocol is clearly biased towards assuming that the threshold assumption still holds true. This is not appropriate, and we strongly encourage EPA IRIS to re-write the protocol to clearly state that the update will review the scientific evidence and determine the validity of the 2001 MOA analysis.

Furthermore, the proposed approach to identify relevant mechanistic information as it is presented in the protocol is limited and biased, as EPA IRIS will only consider mechanistic information that is retrieved incidentally from its search for relevant animal/human studies—“Mechanistic studies that were tagged preliminarily during title/abstract screening as ‘Supplemental material’ will be sorted according to hazard categories or types of mechanistic outcomes/pathways.” (page 13) Although EPA IRIS is seeking newer scientific information regarding the carcinogenic MOA for chloroform, it is not explicitly seeking all relevant literature related to this topic. Therefore, this approach is unnecessarily limited, biased, and will not reflect the true knowledge contained in the scientific literature. As such, we strongly encourage EPA IRIS to incorporate a formal review of the mechanistic information to update this assumption based on newer scientific information. This can be accomplished by undertaking either a systematic review or, in the event that time or resource constraints are of concern, a rapid review of the evidence, which can be completed in a matter of weeks, as IRIS has accomplished for other assessments.²

We commend EPA IRIS for its commitment to reviewing newer scientific information to update the cancer MOA for chloroform. The intent of this review is to reassess the health effects of chloroform through a systematic review approach, and relying on an outdated assumption regarding chloroform MOA would implicitly bias the results. Therefore, we strongly encourage EPA IRIS to reflect this by performing a formal review of the mechanistic information on chloroform carcinogenicity MOA (through a rapid or systematic review) and re-writing the protocol to clearly reflect that EPA IRIS will perform a robust systematic review of all relevant scientific evidence. Furthermore, the oral mode of action should not be considered finalized until the completion of such a review and evaluating the support from relevant scientific information.

3) EPA IRIS should clearly outline the approach for searching, including, and evaluating scientific evidence from the non peer-reviewed literature;

In Section 4.3 (Unpublished Data, page 11) of the protocol, stating that “...it is possible that unpublished data directly relevant to the PECO may be identified during assessment development. In this case, if these data would likely make a substantial impact on assessment decisions or conclusions, EPA can conduct an external peer review of this information if the owners of the data are willing to have the study details and results made publically available.” However, in Section 4.4 (Literature Screening Process, page 12), the following exclusion criteria are listed:

² U.S. EPA. Systematic Review of Chloroprene. U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-09/010F, 2018.

- Records that did not contain original data, such as reviews, editorials, or commentaries; and
- Study materials that have not been peer reviewed (e.g., conference abstracts, theses/dissertations, working papers from research groups of committees, and white papers)

It is unclear where and how often in the screening process the authors of these “grey literature”-type records are contacted to determine whether data may be shared, peer-reviewed, and made publically available. As it appears from Section 4.3 that EPA IRIS is open to considering non peer-reviewed literature as the basis for its assessments if certain criteria are met, the protocol should better reflect the process by which these types of studies will be sought for inclusion in the assessment to ensure an approach that minimizes bias with respect to the types of non peer-reviewed studies that are ultimately considered in the assessment.

4) EPA IRIS should develop metrics that reflect estimates of risk, as has been recommended by the National Academy of Sciences (NAS).

Updates of the IRIS process to chemicals assessment, for instance through the incorporation of novel methods in the field of environmental health such as systematic review, provide an opportunity for EPA to update their chemical assessment methods and approaches to incorporate modern scientific knowledge gained in the past several decades. Modern methods and approaches are recommended and discussed in detail by the NAS in several landmark publications, *Science and Decisions*, *Phthalates and Cumulative Risk*, and *Review of EPA’s Integrated Risk Information System (IRIS) Process*.^{3,4,5} The RfD/RfC is not an actual estimate of risk, nor does it provide information about the potential risk at various exposure estimates. EPA IRIS acknowledge this in the chloroform protocol, stating: “Reference values are not predictive risk values; that is, they provide no information about risks at higher or lower exposure levels.” (page 54) This raises serious concerns regarding the utility of this assessment; for instance, the EPA cannot conduct a benefits analysis using solely the RfD/RfC because there is no accompanying dose-response information.

We strongly encourage EPA to incorporate the recommendations of recent NAS reports³ and utilize alternative available analytical methods to develop quantified estimates of risk that can be of use to both risk managers and decision-makers.

5) EPA IRIS should incorporate the financial conflict of interest of study authors as a consideration of potential bias for included studies.

In Appendix B (Typical Data Extraction Fields, page 67), EPA IRIS includes “Funding” as one data extraction field, which contains the elements “Funding source(s)” and “Reporting of conflict

³ National Research Council, *Science and Decisions: Advancing Risk Assessment*, ed. Committee on Improving Risk Analysis Approaches Used by the U.S. EPA, Board on Environmental Studies and Toxicology, and Division on Earth and Life Studies. 2009, Washington, D.C.: National Academies Press.

⁴ National Research Council, *Phthalates and cumulative risk assessment: the task ahead*. 2008, Washington, D.C.: National Academies Press.

⁵ National Research Council, *Review of EPA’s Integrated Risk Information System (IRIS) Process*. 2014, National Academies Press: Washington, DC.

of interest (COI) by authors.” However, the protocol does not discuss how these particular data extraction fields are incorporated into the assessment.

We also recommend that conflict of interest (in particular, financial conflicts of interest) be incorporated as part of the evidence evaluation. This domain has been identified by the Cochrane Collaboration and GRADE as an important risk of bias,⁶ based on empirical data from studies of the health effects of tobacco,^{7,8} the safety and efficacy of pharmaceuticals,^{9,10,11} and medical procedures,^{12,13} which have all shown that, on average, source of funding influences study outcome. We have also demonstrated its use in our case studies of applying the Navigation Guide Systematic Review method.^{14,15,16,17,18,19,20,21} Since EPA IRIS is extracting this information as a component of its data extraction process, the Agency should clarify how it intends to utilize this information, and we strongly recommend that it be incorporated as a separate domain for risk of bias, as has been done in other approaches.^{14,15,16,17,18,19,20,21}

6) EPA IRIS should incorporate explicitly defined criteria for each risk of bias rating to transparently describe its corresponding level of evidence.

In Section 6.2 (Epidemiology Study Evaluation, page 19), Table 5 (Questions to guide the development of criteria for each domain in epidemiology studies, Page 21) EPA IRIS outlines Core Questions, Prompting Questions, and Follow-up Questions for each risk of bias domain for

⁶ Bero, L.A., 2013. Why the Cochrane risk of bias tool should include funding source as a standard item. *Cochrane Database Syst Rev*, 12:ED000075

⁷ Barnes, D.E. and Bero, L.A., 1997. Scientific quality of original research articles on environmental tobacco smoke. *Tobacco Control*, 6(1), pp.19-26.

⁸ Barnes, D.E. and Bero, L.A., 1998. Why review articles on the health effects of passive smoking reach different conclusions. *Jama*, 279(19), pp.1566-1570.

⁹ Bero, L., Oostvogel, F., Bacchetti, P. and Lee, K., 2007. Factors associated with findings of published trials of drug–drug comparisons: why some statins appear more efficacious than others. *PLoS Medicine*, 4(6), p.e184.

¹⁰ Lexchin, J., Bero, L.A., Djulbegovic, B. and Clark, O., 2003. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *Bmj*, 326(7400), pp.1167-1170.

¹¹ Lundh, A., Sisonondo, S., Lexchin, J., Busuioic, O.A. and Bero, L., 2012. Industry sponsorship and research outcome. *Cochrane Database Syst Rev*, 12(12).

¹² Popelut, A., Valet, F., Fromentin, O., Thomas, A. and Bouchard, P., 2010. Relationship between sponsorship and failure rate of dental implants: a systematic approach. *PLoS one*, 5(4), p.e10274.

¹³ Shah, R.V., Albert, T.J., Bruegel-Sanchez, V., Vaccaro, A.R., Hilibrand, A.S. and Grauer, J.N., 2005. Industry support and correlation to study outcome for papers published in *Spine*. *Spine*, 30(9), pp.1099-1104.

¹⁴ Lam, J., Koustas, E., Sutton, P., Johnson, P.I., Atchley, D.S., Sen, S., Robinson, K.A., Axelrad, D.A. and Woodruff, T.J., 2014. The Navigation Guide—evidence-based medicine meets environmental health: integration of animal and human evidence for PFOA effects on fetal growth. *Environmental health perspectives*, 122(10), p.1040.

¹⁵ Koustas, E., Lam, J., Sutton, P., Johnson, P.I., Atchley, D.S., Sen, S., Robinson, K.A., Axelrad, D.A. and Woodruff, T.J., 2014. The Navigation Guide—evidence-based medicine meets environmental health: systematic review of nonhuman evidence for PFOA effects on fetal growth. *Environmental health perspectives*, 122(10), p.1015.

¹⁶ Johnson, P.I., Sutton, P., Atchley, D.S., Koustas, E., Lam, J., Sen, S., Robinson, K.A., Axelrad, D.A. and Woodruff, T.J., 2014. The Navigation Guide—evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. *Environmental health perspectives*, 122(10), p.1028.

¹⁷ Woodruff, T.J. and Sutton, P., 2014. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. *Environmental health perspectives*, 122(10), p.1007.

¹⁸ Johnson, P.I., Koustas, E., Vesterinen, H.M., Sutton, P., Atchley, D.S., Kim, A.N., Campbell, M., Donald, J.M., Sen, S., Bero, L. and Zeise, L., 2016. Application of the Navigation Guide systematic review methodology to the evidence for developmental and reproductive toxicity of triclosan. *Environment international*, 92, pp.716-728.

¹⁹ Lam, J., Sutton, P., Kalkbrenner, A., Windham, G., Halladay, A., Koustas, E., Lawler, C., Davidson, L., Daniels, N., Newschaffer, C. and Woodruff, T., 2016. A systematic review and meta-analysis of multiple airborne pollutants and autism spectrum disorder. *PLoS One*, 11(9), p.e0161851.

²⁰ Vesterinen, H.M., Johnson, P.I., Atchley, D.S., Sutton, P., Lam, J., Zlatnik, M.G., Sen, S. and Woodruff, T.J., 2015. Fetal growth and maternal glomerular filtration rate: a systematic review. *The Journal of Maternal-Fetal & Neonatal Medicine*, 28(18), pp.2176-2181.

²¹ Lam, J., Lanphear, B.P., Bellinger, D., Axelrad, D.A., McPartland, J., Sutton, P., Davidson, L., Daniels, N., Sen, S. and Woodruff, T.J., 2017. Developmental PBDE Exposure and IQ/ADHD in Childhood: A Systematic Review and Meta-analysis. *Environmental health perspectives*, 125(8), pp.086001-1-20.

human studies. A similar table is presented for evaluating risk of bias for animal studies in Table 6 (page 25). However, there is no equivalent table for evaluating mechanistic information. As discussed above in Point #2, EPA IRIS intends to consider mechanistic information to evaluate the current scientific support for the chloroform carcinogenicity MOA analysis. Therefore, we encourage EPA IRIS to develop criteria for evaluating the internal validity of mechanistic studies to increase the transparency in how these types of studies will be evaluated and incorporated in their evaluation of data.

Along these same lines, we recommend that EPA IRIS increase the transparency of the risk of bias considerations for animal and human studies by defining the level of evidence associated with each risk of bias rating (i.e., “high” or “low” risk of bias). The explicit definition of these criteria up-front in the protocol helps to increase transparency, increase the consistency in rating among reviewers, and reduce the introduction of reviewer bias during the rating process. Other approaches have similarly incorporated this level of detail in their protocols—as an example, listing the important confounders that will be considered critical to include in an epidemiology study beforehand, in consultation with topic experts.^{14,15,16,17,18,19,20,21} We strongly encourage EPA to incorporate a greater level of detail within its protocol to achieve the overall protocol goal of reducing the introduction of bias and increasing transparency in the process.

We are appreciative of the opportunity to provide public input and we look forward to continuing to participate in such opportunities in the future. Please do not hesitate to contact us with any questions regarding these comments.

Sincerely,

Juleen Lam, PhD

Associate Research Scientist, Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Veena Singla, PhD

Associate Director, Science & Policy, Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Tracey Woodruff, PhD

Professor and Director, Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco