July 13, 2020

Comments on the Systematic Review Protocol for the Methylmercury IRIS Assessment

Submitted online via *Regulations.gov* to docket EPA-HQ-ORD-2018-0655

These comments are submitted on behalf of the undersigned scientists. We declare collectively that we have no direct or indirect financial or fiduciary interest in any chemical or product that is the subject of these comments. The co-signers' institutional affiliations are included for identification purposes only and do not imply institutional endorsement or support unless indicated otherwise.

We appreciate the opportunity to provide written comments on the Systematic Review Protocol for the Methylmercury IRIS Assessment (Preliminary Assessment Materials) [CASRN 22967-92-6] (which we will refer to as the Methylmercury Protocol).[1]

Over the last decade, the assessments produced by the Integrated Risk Information System (IRIS), U.S. Environmental Protection Agency (EPA), have undergone multiple reviews by the National Academies of Science (NAS). The NAS has also recommended changes to improve IRIS' approach to evaluating scientific evidence, including implementation of systematic review. In 2014 and 2018 the NAS released reports to determine whether the IRIS program had been responsive to its past recommendations.[2,3] Both review committees were impressed with IRIS' progress, including steps to develop and implement a systematic review methods and that there is "*a commitment to use systematic-review methods to conduct IRIS assessments.*"[4] We commend the EPA on the substantive changes it has made to the systematic review methods used in conducting the IRIS assessments. However, there are methodological flaws in the current Systematic Review Protocol for the Methylmercury IRIS Assessments; these flaws are not consistent with NAS recommendations or with the methods that EPA has stated to the NAS it is using in the IRIS program. For example, the risk of bias method presented in the Methylmercury protocol lacks validation and excludes studies based on one "critically deficient" domain, which could significantly reduce the available evidence to identify the harms caused by these substances.

We are therefore concerned that implementation of the current methods and processes outlined in the Methylmercury protocol can lead to biased assessments of the evidence. It is highly likely relevant studies will be excluded from the final evaluations, which would in turn underestimate the true harms of these chemicals.

Our comments address the following main issues:

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[1] US EPA (2020) Systematic Review Protocol for the Methylmercury IRIS Assessment (Preliminary Assessment Materials) [CASRN 22967-92-6], EPA/635/R-19/243. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345309

[2] National Research Council. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. https://doi.org/10.17226/18764.

[3] National Academies of Sciences, Engineering, and Medicine. 2018. Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press

[4] National Academies of Sciences, Engineering, and Medicine. 2018. Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Page 1. Washington, DC: The National Academies Press.

1. **EPA's IRIS systematic review method for the literature search is incomplete and does not follow established methods for systematic review that are based on the best available science**
2. **EPA fails to account for every reference identified in the literature search**
3. **The Methylmercury protocol epidemiology study evaluation is incompatible with validated best practice methods already being implemented in environmental health in fundamental ways:**
    a) **Use of an overall risk of bias rating is inappropriate, not recommended by the National Academies of Sciences and is not used by the National Toxicology Program's Office of Health Assessment and Translation or UCSF's Navigation Guide**
    b) **The Methylmercury protocol risk of bias method should not exclude research based on one "critically deficient" methodological limitation.**
4. **The Methylmercury protocol should consider financial conflicts of interest as a potential source of bias in research.**

We appreciate the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these comments.

Sincerely,

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DETAILED COMMENTS

1. **EPA's IRIS systematic review method for the literature search is incomplete and does not follow established methods for systematic review that are based on the best available science**

Overall, we commend the EPA for its efforts to incorporate many best practices for a comprehensive literature search in its systematic review framework described in section 4, "LITERATURE SEARCH AND SCREENING STRATEGIES." However, while we found EPA's framework to be consistent with the majority of the Institute of Medicine's (IOM's) best practices for the literature review step of a systematic review, [5] there are two key features of EPA's framework that are clearly inconsistent with IOM's best practices. EPA fails to:

1. Search grey-literature databases, clinical trial registries, and other sources of unpublished information about studies (IOM Standard 3.2.1)[6]
   Rationale: Negative or null results, or undesirable results, might be published in difficult to access sources.
2. Handsearch selected journals and conference abstracts (IOM Standard 3.2.4)[7]
   Rationale: Hand searching of sources most likely provides relevant up-to-date information and contributes to the likelihood of comprehensive identification of eligible studies.

Therefore, EPA should immediately update the Methylmercury Protocol by completing these steps and make its framework for conducting a literature review transparently congruent with these two additional practices to ensure that all relevant studies have been identified and included in its evaluation.

2. **EPA fails to account for every reference identified in the literature search**

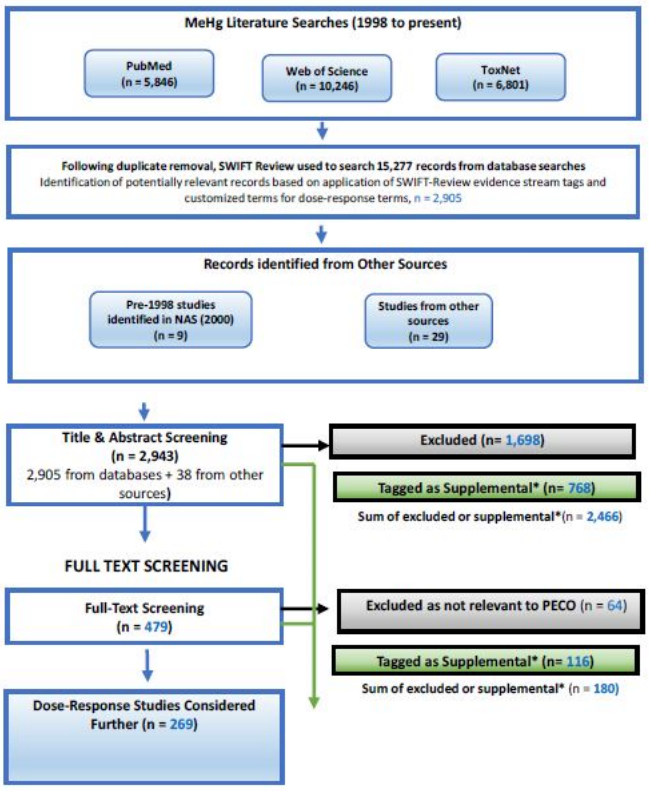
In section 4.1 "LITERATURE SEARCH STRATEGIES" EPA states that *"The four databases listed below were searched*:
• *PubMed (National Library of Medicine)*
• *Web of Science (Thomson Reuters)*
• *Toxline (National Library of Medicine)*
• *Science Direct (Elsevier)"* [8]

However, as shown below in Figure 3, "Literature search for MeHg DNT dose-response studies" EPA fails to include any studies from the Science Direct Database. In Appendix A, "ELECTRONIC DATABASE SEARCH STRATEGIES", Table A-1 "Overall database search strategy", for Science Direct, although between 1998–March 2017 there are 5,330 studies identified, EPA states, "HERO could not search Science Direct." [9] If EPA was unable to search the Science Direct database using HERO, it should have

[5] Institute of Medicine. (2011). Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academies Press
[6] Institute of Medicine. (2011). Finding What Works in Health Care: Standards for Systematic Reviews. Page 84. Washington, DC: The National Academies Press
[7] Institute of Medicine. (2011). Finding What Works in Health Care: Standards for Systematic Reviews. Page 84. Washington, DC: The National Academies Press
[8] US EPA (2020) Systematic Review Protocol for the Methylmercury IRIS Assessment (Preliminary Assessment Materials) [CASRN 22967-92-6], EPA/635/R-19/243. Page 13. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345309
[9] US EPA (2020) Systematic Review Protocol for the Methylmercury IRIS Assessment (Preliminary Assessment Materials)

found an alternate method to search the database and included the identified studies into the review process. Alternatively, EPA could have decided not to search this particular database. This should have been a decision made up-front in the protocol. As it stands, there are 5,330 studies that EPA has identified as possibly relevant to the Methylmercury systematic review that it has not included for screening. Such exclusions threaten the validity of the assessment and may bias the evaluation.

EPA has also failed to account for each study it has identified in the MeHg Literature Searches in Figure 3. "Literature search for MeHg DNT dose-response studies" below. In the Title and Abstract step there are **2943** studies, of which EPA excludes **2466**, therefore **477** studies should move to the Full Text Screening step, however EPA states it is **479** studies that move through to this step. EPA then excludes **180** studies from the Full Text Screening step, therefore **297** studies should move to the Dose Response step, however EPA states that there are only **269** studies that move through to this step. Therefore EPA has kept **2** additional studies and removed **28** studies from the Methylmercury systematic review without any explanation. Once again, this threatens the validity of the assessment and may bias the evaluation. This also limits transparency of the assessment and reduces the reproducibility of the approach, hindering the ability of a third party to evaluate this assessment or reproduce these results independently. EPA should immediately account for all of the missing studies from the literature search and update the protocol.



[CASRN 22967-92-6], EPA/635/R-19/243. Page 46. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345309

Figure 3. Literature search for MeHg DNT dose-response studies.[10]

3. **The Methylmercury protocol epidemiology study evaluation is incompatible with validated best practice methods already being implemented in environmental health in fundamental ways:**

    a) **Use of an overall risk of bias rating is inappropriate, not recommended by the National Academies of Sciences Engineering and Medicine and is not used by the National Toxicology Program's Office of Health Assessment and Translation or UCSFs Navigation Guide**

It is vital that the internal validity or risk of bias of the primary studies which underpin evidence-based decision making in environment health are assessed with transparent and accepted methods.[11] The approach to risk of bias in the Methylmercury protocol is inconsistent with two previously validated methods used to evaluate the risk of bias in human epidemiological studies recommended by the National Academies of Science (NAS), the Navigation Guide and the Office of Health Assessment and Translation (OHAT) Systematic Review Method.[12,13] The Methylmercury protocol's risk of bias evaluations of epidemiological evidence is based off of the principles of the Cochrane Risk of Bias in Nonrandomized Studies of Interventions [ROBINS-I] tool "*but modified to address environmental and occupational exposures*." [14] As shown in Figure 5 reproduced from the Methylmercury protocol below, **there are only six domains** for epidemiology studies and reviewers would need to assign a consensus judgment of *good*, *adequate*, *deficient*, or *critically deficient* for each domain.[15] However, it is concerning that **Figure 5 is not consistent with the domains EPA describes in the preceding page** it will use to assess risk of bias and study sensitivity of the included studies:

> "*Evaluation of epidemiology studies of health effects to assess risk of bias and study sensitivity will be conducted for the following domains: exposure measurement, outcome ascertainment, participant selection, potential confounding, analysis, study sensitivity, and* ***selective reporting***." [16]

[10] US EPA (2020) Systematic Review Protocol for the Methylmercury IRIS Assessment (Preliminary Assessment Materials) [CASRN 22967-92-6], EPA/635/R-19/243. Page 17. Available https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345309

[11] Rooney AA, Cooper GS, Jahnke GD, et al. How credible are the study results? Evaluating and applying internal validity tools to literature-based assessments of environmental health hazards Environ. Int., 92-93 (Supplement C) (2016), pp. 617-629

[12] Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect. 2014;122(10):1007-1014.

[13] National Toxicology Program (NTP). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Research Triangle Park, NC: National Toxicology Program; 2019.

[14] US EPA (2020) Systematic Review Protocol for the Methylmercury IRIS Assessment (Preliminary Assessment Materials) [CASRN 22967-92-6], EPA/635/R-19/243. Page 24. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345309

[15] US EPA (2020) Systematic Review Protocol for the Methylmercury IRIS Assessment (Preliminary Assessment Materials) [CASRN 22967-92-6], EPA/635/R-19/243. Page 21. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345309

[16] US EPA (2020) Systematic Review Protocol for the Methylmercury IRIS Assessment (Preliminary Assessment Materials) [CASRN 22967-92-6], EPA/635/R-19/243. Page 20. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345309

EPA should immediately correct its method and include the additional domain of selective reporting in Figure 5 or exclude it from the description on Page 20 of the Methylmercury protocol. We strongly recommend the former recommendation.

The domains assessed are similar to OHAT and Navigation Guide, with the important exception of not including financial conflict of interest, discussed more in point 2 below. The biggest difference comes in the next step, where reviewers then assign an overall study rating of *high*, *medium*, or *low* confidence, or *uninformative* for a specific health outcome.[17] This step is not part of the risk of bias evaluation in either Navigation Guide or OHAT method and has some fundamental scientific flaws described below.

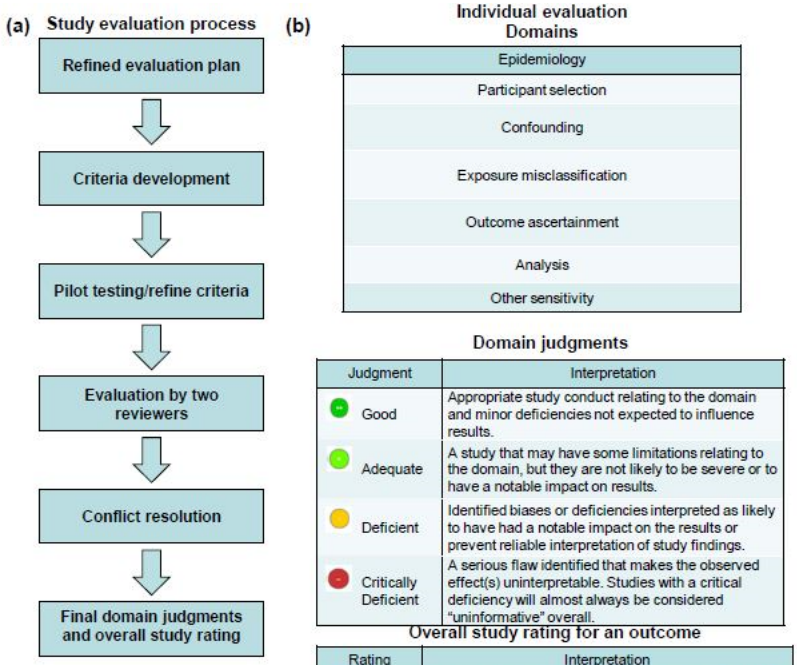


Figure 5. Overview of IRIS study evaluation process for epidemiology studies: (a) an overview of the evaluation process; (b) the evaluation domains and definitions for ratings (i.e., domain and overall judgments, performed on an outcome-specific basis).

[17] US EPA (2020) Systematic Review Protocol for the Methylmercury IRIS Assessment (Preliminary Assessment Materials) [CASRN 22967-92-6], EPA/635/R-19/243. Page 23. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345309

Figure 5. Overview of Integrated Risk Information System (IRIS) study evaluation process. (b) The evaluation domains and definitions for ratings (i.e., domain and overall judgments performed on an outcome-specific basis). [18]

The Methylmercury protocol provides guidance in addition to Figure 5 for rating the overall confidence, noting that studies rated as 'low confidence' "*have a deficient evaluation for one or more domains, although some medium-confidence studies may have a deficient rating in domain(s)considered to have less influence on the magnitude or direction of the of effect estimates.*" [19] While, "*Studies with critically deficient judgments in any evaluation domain are almost always classified as uninformative… Uninformative studies will not be considered further in the dose-response analysis*" [20]

The Methylmercury protocol's system for assigning an overall study rating is confusing, ambiguous and not empirically based. Firstly, the Methylmercury protocol states that studies rated as 'low confidence' "*have a deficient evaluation for one or more domains*" but at the same time it allows studies to be classified as 'medium-confidence' if they "*have a deficient rating in domain(s) considered to have less influence on the magnitude or direction of effect estimates.*" However, the protocol does not define what those domains are and provides no scientific evidence to support EPA's judgments of these domains as being more influential than other domains or on the magnitude or direction of the results. For example, there is empirical evidence that inadequate application of randomization and blinding results in overestimation of efficacy estimates.[21,22] However, such empirical examinations of the association between the methods and results for each risk of bias domain in the ROBINS-I, and the Methylmercury protocol's subsequent adaptation of ROBINS-I, have not been conducted and it is unclear whether these tools would stand up to such an empirical assessment. Therefore, to rate a study as overall 'low' or 'medium' confidence based on arbitrary measures lacks validation and is concerning as it would likely result in exclusion of studies that would be informative to the risk assessment.

Further, although the Methylmercury protocol's risk of bias evaluation does not explicitly use scores, the use of a rating system that generates an overall rating based on an individual domain or several domains combined essentially acts as a quantitative score and assumes that we know empirically how much each risk of bias domain contributes to the overall rating. Furthermore, this essentially weights certain domains as more important than other domains in contributing to the overall evaluation of

[18] US EPA (2020) Systematic Review Protocol for the Methylmercury IRIS Assessment (Preliminary Assessment Materials) [CASRN 22967-92-6], EPA/635/R-19/243. Page 21. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345309

[19] US EPA (2020) Systematic Review Protocol for the Methylmercury IRIS Assessment (Preliminary Assessment Materials) [CASRN 22967-92-6], EPA/635/R-19/243. Page 23. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345309

[20] US EPA (2020) Systematic Review Protocol for the Methylmercury IRIS Assessment (Preliminary Assessment Materials) [CASRN 22967-92-6], EPA/635/R-19/243. Page 23. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345309

[21] Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, Gluud C, Martin RM, Wood AJ, Sterne JA. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ. 2008;336(7644):601–5.

[22] Page MJ, Higgins JP, Clayton G, Sterne JA, Hrobjartsson A, Savovic J. Empirical evidence of study design biases in randomized trials: systematic review of meta-epidemiological studies. PLoS One. 2016;11(7):e0159267.

quality. The use of 'quality scores' has not been able to distinguish between studies with a high and low risk of bias in meta-analyses [23] and empirical evidence is lacking to establish how each risk of bias item should be weighted.[24] The use of scores falsely implies a relationship between scores (i.e. high vs low) and effect or association and therefore the use of only 'high' quality studies will lead to a biased evaluation of the evidence. The NAS in its review of the EPA's IRIS program's method for systematic review, strongly supported a methodology that did not incorporate quantitative scoring:

> *"…there is no empirical basis for weighting the different criteria in the scores. Reliability and validity of the scores often are not measured. Furthermore, quality scores have been shown to be invalid for assessing risk of bias in clinical research (Juni et al. 1999)."*[25]

Overall, there is no scientific justification for EPA to assign these scoring measures to the individual domains and thus will lead to a biased evaluation of the studies. We therefore strongly recommend against the use of an overall score and instead recommend that the ratings of each domain of the risk of bias tool are reported for each study to clearly highlight the different sources of bias in the study, similar to the approaches used in the Navigation Guide and OHAT Systematic Review Method.[26,27]

b) The Methylmercury protocol risk of bias method should not exclude research based on one "critically deficient" methodological limitation.

The Methylmercury protocol states that "*Studies with critically deficient judgments in any evaluation domain are almost always classified as uninformative… Uninformative studies will not be considered further in the dose-response analysis."* [28] The Science Advisory Committee on Chemicals (SACC) has highlighted concerns on using a weighted scoring system that may lead to the exclusion of a study, due to one 'fatal flaw' in its peer review of the TSCA (Toxic Substances Control Act) Draft Risk Evaluation of C.I. Pigment Violet 29 (PV29).[29] Further, in its Peer Review of the Draft Risk Evaluation of 1,4-Dioxane the SACC recommended that EPA *"…not be overly stringent and exclude studies based on a single criterion."*[30] While we recognize the overall approach to assessing study quality in the Methylmercury protocol is significantly different from the TSCA systematic review method, the exclusion of a study based on one "critically deficient" domain is a problematic similarity.

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[23] Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA. 1999;282(11):1054–60.

[24] Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Chichester: The Cochrane Collaboration and Wiley-Blackwell; 2008.

[25] National Research Council. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press; 2014

[26] Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect. 2014;122(10):1007-1014.

[27] National Toxicology Program (NTP). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Research Triangle Park, NC: National Toxicology Program; 2019.

[28] US EPA (2020) Systematic Review Protocol for the Methylmercury IRIS Assessment (Preliminary Assessment Materials) [CASRN 22967-92-6], EPA/635/R-19/243. Page 23. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345309

[29] US EPA (2019) Peer Review of the Draft Risk Evaluation for Pigment Violet 29 (PV29). Pp 26. Available: https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2018-0604 D=EPA-HQ-OPPT-2018-0604

[30] US EPA (2019) SACC July 2019 Meeting Minutes and Final Report Docket. Pp 38. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0063.

The approach to risk of bias in the Methylmercury protocol is again inconsistent with two previously validated methods used to evaluate the risk of bias in human epidemiological studies recommended by the NAS, the Navigation Guide[31] and OHAT.[32] Neither method recommends excluding a study based on a single measure. While the Navigation Guide does not exclude any studies based on the risk of bias assessment, OHAT "*favors inclusion of studies unless they are problematic in multiple key aspects of study quality, an approach that offsets concerns about potentially excluding studies based on a single measure, which could seriously limit the evidence base available for an evaluation, given the type of studies available in environmental health*."[33]

While we understand that there will be variation in the internal validity and thus quality across studies, it is more appropriate to exclude studies based on pre-defined inclusion/exclusion criteria when there is a large database (such as only evaluating cohort studies), rather than an arbitrary rating of the evidence, based off one domain that is not empirically supported. Further, there are various strategies that EPA should use to evaluate quantitatively the influence of the levels of bias across the studies via meta-analysis. These strategies include: restricting the primary analysis to those studies with a lower risk of bias and demonstrating how conclusions might be affected by the inclusion of high risk of bias studies, performing a sensitivity analysis; presenting multiple (stratified) analyses; or presenting every included study and summarizing the risk of bias, using structured approaches like GRADE. [34]

We therefore strongly recommend against the exclusion of a study based on one "critically deficient" domain and support the use of either of these methods recommended by the NAS, to evaluate the quality of human epidemiological evidence.

4. The Methylmercury protocol should consider financial conflicts of interest as a potential source of bias in research.

In its 2018 evaluation, the 'NAS Committee Findings Regarding its 2014 Recommendations to IRIS' that "*Funding sources should be considered in the risk-of-bias assessment conducted for systematic reviews that are part of an IRIS assessments*" found that "*EPA documents funding source, but it is unclear how the data are used*."[35] The NAS recommendation is based on empirical evidence that non-methodological characteristics, including author conflicts of interest (COI) and industry sponsorship, can also influence the findings of a study. It has been demonstrated across several areas of research that even when studies have the same methodological risk of bias or internal validity, studies with industry sponsorship

[31] Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect. 2014;122(10):1007-1014.

[32] National Toxicology Program (NTP). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Research Triangle Park, NC: National Toxicology Program; 2019.

[33] National Toxicology Program (NTP). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Pp38. Research Triangle Park, NC: National Toxicology Program; 2019.

[34] National Toxicology Program. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. In: U.S. Department of Health and Human Services, editor.: Office of Health Assessment and Translation, Division of National Toxicology Program, National Institute of Environmental Health Sciences; 2019. Pp 38

[35] National Academies of Sciences, Engineering, and Medicine. 2018. Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press.

are associated with more favorable outcomes towards the study sponsor.[36,37] In studies of harmful exposures such as chemicals, this funding bias would be expected to be associated with a bias towards the null (finding that the chemical does not have a toxic effect). The need to account for this potential bias is empirically supported. Thus, it is quite concerning that the Methylmercury protocol does not mention consideration of study funding sources anywhere in the document.

The ROBINS-I tool, on which EPA's IRIS Assessments study evaluation of epidemiological evidence is based, focuses on a narrow definition of bias based on a methodological flaw that may lead to an error in quantitative effect estimates.[38] The Navigation Guide assesses financial conflicts of interest as a separate domain within its risk of bias evaluation.[39] OHAT, however, *"collects information about funding source during data extraction and considers it at multiple points in the evaluation"* as financial COI can be accounted for at various time points throughout the review process including in an assessment of the selective reporting of results, publication bias, and in assessing inconsistency in a body of evidence.[40,41,42] However, it is not always possible to identify such biases due to a lack of study registries and the publication of protocols for the types of evidence used in systematic reviews to assess the harms of chemicals. Therefore, the simplest way to identify such potential biases is by assessing funding source and author COI as a specific risk of bias domain as recommended by the Navigation Guide.[43]

Importantly, including funding as a risk of bias domain *does not lead to the exclusion of industry sponsored studies*, it only means identifying it as a domain of potential bias and then evaluating its impact on the overall quality of the body of evidence. Therefore, we again support the recommendation made by the NAS to IRIS that "*Funding sources should be considered in the risk-of-bias assessment conducted for systematic reviews that are part of an IRIS assessments*."

[36] Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2017;2:MR000033.

[37] White J, Bero LA. Corporate manipulation of research: strategies are similar across five industries. Stanford Law Policy Rev. 2010;21(1):105–34.

[38] Bero, L., Chartres, N., Diong, J. et al. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. Syst Rev 7, 242 (2018) doi:10.1186/s13643-018-0915-2

[39] Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environmental Health Perspectives. 2014;122(10):A283.

[40] National Toxicology Program. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. In: U.S. Department of Health and Human Services, editor.: Office of Health Assessment and Translation, Division of National Toxicology Program, National Institute of Environmental Health Sciences; 2019.

[41] Viswanathan M, Ansari M, Berkman N, Chang S, Hartling L, McPheeters L, Santaguida P, Shamliyan T, Singh K, Tsertsvadze A, Treadwell J. Assessing the Risk of Bias of Individual Studies

[42] National Toxicology Program. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. In: U.S. Department of Health and Human Services, editor.: Office of Health Assessment and Translation, Division of National Toxicology Program, National Institute of Environmental Health Sciences; 2019.

[43] Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environmental Health Perspectives. 2014;122(10):A283.