

December 23, 2019

## Comments on the Systematic Review Protocol for the PFDA, PFNA, PFHxA, PFHxS, and PFBA IRIS Assessments

Submitted online via *Regulations.gov* to docket EPA-HQ-ORD-2019-0275

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 PFBA, PFHxA, PFHxS, PFNA, and PFDA IRIS Assessments (which we will refer to as the "PFAS protocol").<sup>1</sup> To date, there is only a draft version of the IRIS systematic review handbook, which has not been subject to public comment or peer review and is currently not publicly available.

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.<sup>2,3</sup> 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.*"<sup>4</sup> 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 PFAS 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 PFAS protocol is unvalidated 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 PFAS 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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<sup>1</sup> US EPA (2019) Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA IRIS Assessments. EPA/635/R-19/049. Available: <https://www.regulations.gov/document?D=EPA-HQ-ORD-2019-0275-0002>

<sup>2</sup> 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>.

<sup>3</sup> 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

<sup>4</sup> 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. Pp 1

1. **The PFAS 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 Academy of Sciences and is not used by the National Toxicology Program’s Office of Health Assessment and Translation.**
  - b) **The PFAS protocol risk of bias method should not exclude research based on one “critically deficient” methodological limitation.**
  - c) **The PFAS protocol should require at least two reviewers to make risk of bias study determinations and potentially relevant evidence should not be excluded prior to the actual review.**
2. **The PFAS 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. The PFAS 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 Academy of Sciences and is not used by the National Toxicology Program's Office of Health Assessment and Translation.**

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.<sup>5</sup> The approach to risk of bias in the PFAS protocol is inconsistent with two previously validated methods used to evaluate the risk of bias in human epidemiological studies recommended by the NAS, the Navigation Guide and the Office of Health Assessment and Translation (OHAT).<sup>6,7</sup> The PFAS 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.*"<sup>8</sup> As shown in Figure 5b reproduced from the PFAS protocol below, there are seven domains for epidemiology studies and reviewers would need to assign a consensus judgment of *good, adequate, deficient, not reported, or critically deficient* for each domain.<sup>9</sup> 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.<sup>10</sup> This step is not part of the risk of bias evaluation in either Navigation Guide or OHAT and has some fundamental scientific flaws described below.

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<sup>5</sup> A.A. Rooney, G.S. Cooper, G.D. Jahnke, 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

<sup>6</sup> 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.

<sup>7</sup> 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.

<sup>8</sup> U.S. EPA. Systematic Review Protocol for the Pfas IRIS Assessments. U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-19/050, 2019. Pp 60

<sup>9</sup> U.S. EPA. Systematic Review Protocol for the Pfas IRIS Assessments. U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-19/050, 2019. Pp 58

<sup>10</sup> U.S. EPA. Systematic Review Protocol for the Pfas IRIS Assessments. U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-19/050, 2019. Pp 59

**(b) Individual evaluation domains**

Animal	Epidemiology
Selection and performance • Allocation • Observational bias/blinding	Participant selection
Confounding/variable control	Confounding
Selective reporting and attrition	Selective reporting
Exposure methods sensitivity • Chemical administration and characterization • Exposure timing, frequency, and duration	Exposure measurement
Outcome measures and results display • Endpoint sensitivity and specificity • Results presentation	Outcome ascertainment Analysis
Reporting quality	Other sensitivity

**Domain judgments**

Judgment	Interpretation
Good	Appropriate study conduct relating to the domain and minor deficiencies not expected to influence results.
Adequate	A study that may have some limitations relating to the domain, but they are not likely to be severe or to have a notable impact on results.
Deficient	Identified biases or deficiencies interpreted as likely to have had a notable impact on the results or prevent reliable interpretation of study findings.
Critically Deficient	A serious flaw identified that makes the observed effect(s) uninterpretable. Studies with a critical deficiency will almost always be considered "uninformative" overall.

**Overall study rating for an outcome**

Rating	Interpretation
High	No notable deficiencies or concerns identified; potential for bias unlikely or minimal; sensitive methodology.
Medium	Possible deficiencies or concerns noted, but resulting bias or lack of sensitivity is unlikely to be of a notable degree.
Low	Deficiencies or concerns were noted, and the potential for substantive bias or inadequate sensitivity could have a significant impact on the study results or their interpretation.
Uninformative	Serious flaw(s) makes study results unusable for hazard identification or dose response.

**Figure 5b.** 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).<sup>11</sup>

The PFAS protocol provides guidance in addition to Figure 5b 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 outcome-specific results.”* Finally, studies with *“critically*

<sup>11</sup> U.S. EPA. Systematic Review Protocol for the Pfas IRIS Assessments. U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-19/050, 2019. Pp 59

*deficient judgements in any evaluation domain are almost always classified as “uninformative” and **are excluded from further data synthesis and integration of evidence.**”(emphasis added)<sup>12</sup>*

The PFAS protocol’s system for assigning an overall study rating is confusing, ambiguous and not empirically based. Firstly, the PFAS 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 the outcome-specific results.”* 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.<sup>13,14</sup> However, such empirical examinations of the association between the methods and results for each risk of bias domain in the ROBINS-I, and the PFAS 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 is unvalidated and concerning and would likely result in exclusion of studies that are informative to the risk assessment.

Further, although the PFAS 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 score and assumes that we know empirically how much each risk of bias domain contributes to the overall rating. The use of ‘quality scores’ has not been able to distinguish between studies with a high and low risk of bias in meta-analyses<sup>15</sup> and empirical evidence is lacking to establish how each risk of bias item should be weighted.<sup>16</sup> 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 National Academy of Sciences (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).”<sup>17</sup>*

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

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<sup>12</sup> U.S. EPA. Systematic Review Protocol for the Pfas IRIS Assessments. U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-19/050, 2019. Pp 59

<sup>13</sup> 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.

<sup>14</sup> 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.

<sup>15</sup> 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.

<sup>16</sup> Higgins J, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: The Cochrane Collaboration and Wiley-Blackwell; 2008.

<sup>17</sup> National Research Council. *Review of EPA’s Integrated Risk Information System (IRIS) Process*. Washington, DC: National Academies Press; 2014

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.<sup>18,19</sup>

**b) The PFAS protocol risk of bias method should not exclude research based on one “critically deficient” methodological limitation.**

The PFAS protocol states that “*studies with a determination of critically deficient in an evaluation domain will not be used for hazard identification or dose-response analysis.*”<sup>20</sup> 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).<sup>21</sup> 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.*”<sup>22</sup> While we recognize the overall approach to assessing study quality in the PFAS 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.

The approach to risk of bias in the PFAS 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<sup>23</sup> OHAT.<sup>24</sup> Neither method recommends excluding a study based on 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.*”<sup>25</sup>

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,

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<sup>18</sup> 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.

<sup>19</sup> 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.

<sup>20</sup> U.S. EPA. Systematic Review Protocol for the Pfas IRIS Assessments. U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-19/050, 2019. Pp 58

<sup>21</sup> 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

<sup>22</sup> 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>.

<sup>23</sup> 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.

<sup>24</sup> 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.

<sup>25</sup> 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.

performing a sensitivity analysis; presenting multiple (stratified) analyses; or presenting every included study and summarizing the risk of bias, using structured approaches like GRADE.<sup>26</sup>

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 before making final determinations on the hazards of these PFAS.

- c) The PFAS protocol should require at least two reviewers to make risk of bias study determinations and potentially relevant evidence should not be excluded prior to the actual review.**

The Navigation Guide and OHAT both recommend the use of two assessors to conduct risk of bias assessments, independently, with conflicts resolved by consensus and the use of a third member for arbitration if required.<sup>27,28</sup> This is based on the Institute of Medicine (IOM) highlighting the need of two assessors as “Quality assurance and control are critical during data collection and extraction because of the substantial potential for errors.”<sup>29</sup>

In section 5. *Refined Evaluation Plan*, the PFAS protocol states:

*“To make the systematic review of the epidemiology literature more pragmatic and efficient and focus the set of studies undergoing study evaluation a systematic map of the available evidence was developed after literature screening.....one epidemiologist per outcome reviewed the available evidence and summarized at a high level the direction and consistency of observed associations. In the systematic map, the summary of available evidence for each outcome is shaded based on the consistency of direction of association in the studies. These summaries do not account for study risk of bias, with the exception of easily identified critical deficiencies that would make a study or set of studies uninformative (e.g., considerable concern for exposure measurement, confounding, or reverse causation).”<sup>30</sup>*

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<sup>26</sup> 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

<sup>27</sup> 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.

<sup>28</sup> 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.

<sup>29</sup> Institute of Medicine. 2011. *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/13059>.

<sup>30</sup> U.S. EPA. Systematic Review Protocol for the Pfas IRIS Assessments. U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-19/050, 2019. Pp 44

The above indicates that IRIS relied on the risk of bias determinations of only one epidemiologist to “exclude a study or set of studies as uninformative due to a critical deficiency” before even publishing this PFAS protocol describing the risk of bias tool used. We strongly recommend against such premature exclusions and instead recommend using two assessors to conduct the evaluations. Further, EPA should immediately publish what, if any, studies have already been excluded due to “critical deficiencies” and their rationale for doing so, as they have done in the study flow diagrams in the preceding sections.

The PFAS protocol goes on to state:

*“Based on the systematic map, outcomes were classified into one of three different tiers of further review based on the likely impact of the outcome on hazard identification and dose-response analyses: (1) systematic review with formal study evaluation with at least two reviewers and evidence synthesis; (2) systematic review with formal study evaluation with one reviewer and evidence synthesis; or (3) systematic map (SM) only.”<sup>31</sup>*

To justify tier (2), conducting a systematic review with formal study evaluation with only one reviewer, the PFAS protocol references the 2014 NAS report by stating that:

*“This approach of tiered reviews is consistent with recommendations from the National Academies of Science encouraging the U.S. Environmental Protection Agency (EPA) to explore ways to make systematic review more feasible, including conducting a rapid review in which components of the systematic review process are simplified or omitted (e.g., the need for two independent reviewers)” (NAS, 2014).<sup>32</sup>*

However, this quote and recommendation was not found in the 2014 report or in the 2018 NAS Evaluation of the IRIS program.<sup>33</sup> Rather, it is described in the NAS report ‘Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals.’<sup>34</sup> In describing the ‘Lessons Learned and Reflections on the Statement of Task’ in this report, the NAS states:

*“One form of accelerated evidence synthesis that has been suggested by practitioners of systematic review is a rapid review..... The committee recognizes the need to streamline the process; however, evidence suggests that rapid reviews should not be viewed as a substitute for a systematic review and that the time savings correlate with decreased methodologic quality or robustness (Harker and Kleijnen 2012; Featherstone et al. 2015).”*

Therefore, it is deeply concerning that EPA is decreasing the ‘methodologic quality or robustness’ of its review process on these exposures which can have potentially important health effects for the population. EPA should also clearly state that it is not conducting ‘systematic reviews’ which have now

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<sup>31</sup> U.S. EPA. Systematic Review Protocol for the Pfas IRIS Assessments. U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-19/050, 2019. Pp 44

<sup>32</sup> U.S. EPA. Systematic Review Protocol for the Pfas IRIS Assessments. U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-19/050, 2019. Pp 45

<sup>33</sup> 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.

<sup>34</sup> National Academies of Sciences, Engineering, and Medicine. 2017. Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, DC: The National Academies Press. <https://doi.org/10.17226/24758>.



been classified as ‘tier 2,’ as the rapid review IRIS is proposing in the protocol for certain outcomes “should not be viewed as a substitute for a systematic review” according to EPA’s own source citation. Finally, the references to the NAS report should be corrected.

In the 2014 report referenced in this PFAS protocol, the NAS recommended (item 3 Chapter 2):

*“When extracting data for evidentiary tables, EPA should use **at least two reviewers** to assess each study independently for risk of bias. The reliability of the independent coding should be calculated; if there is good agreement, multiple reviewers might not be necessary. (emphasis added)”*

Therefore, EPA needs to clearly state 1) the reliability of the independent coding that was calculated demonstrating good agreement to justify multiple reviewers are not necessary in their tiered approach and 2) as stated above report what, if any, studies have already been excluded due to “critical deficiencies”. Further, in its 2018 evaluation of the IRIS Program, the Committee Findings Regarding 2014 Recommendations reported that “EPA also uses two people to complete the risk-of-bias evaluation.”<sup>35</sup> It is disappointing and concerning that IRIS has now deviated from what they reported to the NAS in 2018.

The PFAS protocol goes on to state that:

*“the systematic review with one reviewer category was used for outcomes in which the available evidence was sparse or the reported results were inconsistent (but for which there was still a need to conduct a review to provide an informed summary of the available data to support other parts of the assessment...Generally, outcomes with some or more consistency (shaded light or dark pink in the systematic map) were classified as systematic review with two reviewers, but in a few cases, outcomes with some consistency were classified as requiring one reviewer if the complexity appeared to be low (e.g., a small number of studies).”*

While we recognize that a small number of studies may be less time and resource intensive, the number of available studies does not change the degree of complexity a study may present in assessing its risk of bias.

Accurate evaluation of risk of bias even for outcomes with a small number of studies is important because a hazard determination can be made even with a single study. In the evidence integration step, the PFAS protocol notes a finding of ‘Sufficient Evidence’ can be based on *“A single high or medium confidence study without supporting coherent evidence or concern for unexplained inconsistency. Specifically, there are no comparable studies of similar confidence and sensitivity providing conflicting evidence, or the differences can be reasonably explained by, e.g., the populations or exposure levels studied (U.S. EPA, 2005a).”*<sup>36</sup> Therefore the risk of bias assessment of ‘this small number of studies’ becomes critically important in determining if an exposure presents a hazard to human health. We therefore strongly recommend that EPA use more than one reviewer to assess the risk of bias of the studies as recommended by two previously validated methods recommended by the NAS, the

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<sup>35</sup> 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.

<sup>36</sup> U.S. EPA. Systematic Review Protocol for the Pfas IRIS Assessments. U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-19/050, 2019. Pp 123.

Navigation Guide<sup>37</sup> and OHAT.<sup>38</sup> Neither method recommends the use of a single reviewer to assess the risk of bias of the included studies.

## **2. The PFAS 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.”*<sup>39</sup> 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 are associated with more favorable outcomes towards the study sponsor.<sup>40,41</sup> 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 PFAS protocol does not mention 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.<sup>42</sup> The Navigation Guide assesses financial conflicts of interest as a separate domain within its risk of bias evaluation.<sup>43</sup> 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.<sup>44,45,46</sup>

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<sup>37</sup> 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.

<sup>38</sup> 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.

<sup>39</sup> 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.

<sup>40</sup> Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev.* 2017;2:MR000033.

<sup>41</sup> White J, Bero LA. Corporate manipulation of research: strategies are similar across five industries. *Stanford Law Policy Rev.* 2010;21(1):105–34.

<sup>42</sup> 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

<sup>43</sup> 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.

<sup>44</sup> 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.

<sup>45</sup> 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

<sup>46</sup> 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

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.<sup>47</sup>

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.”*

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Assessment and Translation, Division of National Toxicology Program, National Institute of Environmental Health Sciences; 2019.

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