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Comments on the Systematic Review Protocol for the Integrated Risk Information System (IRIS) Hexavalent Chromium Assessment

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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 that is the subject of these comments. 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 comment on the systematic review protocol for the IRIS Cr(VI) assessment.[1] Industrial processes including chrome plating can release the toxic metal Cr(VI) to the environment; an analysis of water quality tests from utilities nationwide found that Cr(VI) contaminates the drinking water of hundreds of millions of people in all 50 states.[2] As EPA's current drinking water standard is decades old and does not specifically address Cr(VI), the Agency expects the results of the IRIS assessment to inform a potential reevaluation of the standard.[3] As such, IRIS' work is vital to the health of families across the U.S. and it is critical for the evaluation to be comprehensive, transparent, and based on the most current science.

The IRIS program has clearly taken important steps to improve the transparency and rigor of its assessments and we commend these efforts. While on the whole we consider the protocol to be relatively comprehensive and robust there are several areas that need to be addressed. IRIS should modify its plan for dose-response assessment of oral Cr(VI) carcinogenicity to meet the National Academies' recommendation that the default approach to the dose-response for all modes of action be linear. Improvements are needed to the transparency and clarity of several points raised in the protocol, in particular in relation to the mechanistic studies. We have highlighted these below, followed by a more detailed discussion.

RECOMMENDATIONS

IRIS should:

1. Use a linear approach to dose-response analysis for health effects from oral or inhalation exposure to Cr(VI). The National Academies recommends a unified approach to analyzing health effects from chemical exposures that applies the methods used for mutagenic carcinogens to non-mutagenic carcinogens and non-cancer health effects as the default;
2. Instead of the "deprioritization" of studies for the mechanistic evaluation, use inclusion/ exclusion criteria;
3. Define criteria for "uninformative" and "less relevant" studies that were not selected for data extraction;
4. Use a more systematic approach that includes a quality evaluation of the relevant mechanistic evidence; and

[1] US EPA (2019) Systematic Review Protocol for the Hexavalent Chromium IRIS Assessment. Available: http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=538034

[2] Environmental Working Group (2019) Chromium (hexavalent). EWG's Tap Water Database. https://www.ewg.org/tapwater/contaminant.php?contamcode=1080#.WXe6WNMrJIY Accessed April 21, 2019.

[3] US EPA (2017) Chromium in Drinking Water. https://www.epa.gov/dwstandardsregulations/chromium-drinking-water Accessed April 21, 2019.

5. Incorporate the financial conflict of interest of study authors into the risk of bias assessment for included studies.
6. Additional minor comments.

DETAILED COMMENTS:

1. Use a linear approach to dose-response analysis for health effects from oral or inhalation exposure to Cr(VI). The National Academies recommends a unified approach to analyzing health effects from chemical exposures that applies the methods used for mutagenic carcinogens to non-mutagenic carcinogens and non-cancer health effects.

The protocol states "For cancer, it is acknowledged that the issue of whether Cr(VI) causes cancer by the oral route of exposure via a mutagenic mode of action is critical to address…"[4] with the underlying assumption that IRIS will take different approaches to the dose-response assessment based on the mode of action (MOA). But this approach is not supported by the science for several reasons, and the National Academies has recommended that the default approach to the dose-response for all MOAs be linear. [5] The current EPA practice for assigning "nonlinear" MOAs does not account for mechanistic factors that can create linearity at a low dose, such as when an exposure contributes to an existing disease process.[6] Specifically:

- Chemical exposures that add to existing (background) processes, endogenous and exogenous exposures lack a threshold if a baseline level of dysfunction occurs without the toxicant and the toxicant adds to or augments the background process.[7]
- Human variability with respect to the individual thresholds for a nongenotoxic cancer mechanism can result in linear dose-response relationships in the population.[8]
- In animal tests, a specific chemical may cause cancer through a nonlinear dose-response process. But for the human population, the dose-response relationship for the same chemical is likely a low-dose linear one, given the high prevalence of pre-existing disease and background processes that can interact with a chemical exposure, and given the multitude of chemical exposures and high variability in human susceptibility.[9]

Historically EPA has assumed a linear dose-response with no threshold of effect only for carcinogens that are mutagens or that have high human body burdens. But as detailed above, the science indicates that this linear presumption with no threshold is appropriate regardless of a carcinogen's MOA (mutagenic or non-mutagenic). IRIS should revise its dose-response approach to be consistent with the National Academies' recommendation for a unified, linear approach to dose-response analysis for mutagenic carcinogens, non-mutagenic carcinogens, and non-cancer health effects. Therefore, for calculating Cr(VI) oral carcinogenicity hazard based on a point of departure (POD), IRIS should use the same approach as for Cr(VI) by inhalation, which assumes a straight line from the POD.

2. **Instead of the "deprioritization" of studies for the mechanistic evaluation, use inclusion/ exclusion criteria.**

[4] US EPA (2019) Systematic Review Protocol for the Hexavalent Chromium IRIS Assessment. pg. 78
[5] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009. Ch.5
[6] Id. pg. 129
[7] Id. pg. 130
[8] Id.
[9] Id.

The protocol states that "Due to the large number of studies, it was necessary to develop deprioritization criteria to begin to set aside studies that are potentially less impactful to the assessment of mechanistic events."[10] However, based on the criteria subsequently described, these studies do not appear to be "less impactful," rather they appear not to be relevant and should therefore be "excluded" rather than "deprioritized." The inclusion and exclusion criteria are robust and should therefore make this distinction straightforward to implement.

3. Define criteria for "uninformative" and "less relevant" studies that were not selected for data extraction.

In the description of studies selected for data extraction, the protocol states that "Studies evaluated as being *uninformative* are not considered further and would, therefore, not undergo data extraction." This statement additionally extends to "less relevant" studies.[11] IRIS needs to define criteria for studies excluded as "uninformative" and "less relevant" and include these as inclusion/ exclusion criteria in the protocol for data extraction.

4. Use a more systematic approach that includes a quality evaluation of the relevant mechanistic evidence.

Overall, the methods for assessing the mechanistic evidence are lacking in transparency, clarity and rigor, making it difficult to evaluate if this approach will lead to selection of the most informative and scientifically sound studies to inform evidence integration. Robust mechanistic data is valuable in the integration step and we strongly urge IRIS to take a more systematic approach and update the protocol accordingly to ensure strong and accurate conclusions.

We appreciate that the best method(s) for evaluating mechanistic data is unknown at this stage of the Cr(VI) review process. However, there are several steps that IRIS should take now that can be refined as more information becomes available.

Firstly, the protocol states "the mechanistic syntheses for most health outcomes will focus on a subset of the most relevant mechanistic studies."[12] It is unclear why the mechanistic evaluation would include only a subset of the relevant studies, and not all the relevant studies. The rationale for why only a subset will be included should be described, and consideration should be taken to assess whether it is justified in a systematic process. There also needs to be greater transparency in how the assessment will define "extensive high-confidence human or animal evidence,"[13] since the protocol states this would lead to a "diminished" need to synthesize all available mechanistic evidence.

Secondly, we note that IRIS has already developed categorizations for the mechanistic studies including by priority health endpoints and the key characteristics of carcinogens;[14] however this should be additionally detailed in section 8.2 of the protocol where it is relevant. Sufficient methodology should be provided to ensure this is reproducible.

Thirdly, the protocol states in Table 18 that mechanistic evaluation could be used to increase or decrease the strength of the animal or human evidence at the evidence integration step,[15] but the

[10] US EPA (2019) Systematic Review Protocol for the Hexavalent Chromium IRIS Assessment. pg. 20
[11] Id. pg. 69
[12] Id. pg. 77
[13] Id. pg. 78
[14] Id. pg. 21
[15] Id. pg. 87

protocol does not include an evaluation of the quality of the mechanistic evidence so there is the potential for this process to lead to erroneous conclusions. For example, a mechanistic evidence base that is overall high risk of bias could lead to inappropriately downgrading the strength of the evidence derived from high-quality human or animal studies. Therefore, we strongly recommend that IRIS implement, at a minimum, some basic criteria to determine the internal and external validity of the relevant mechanistic studies.

The National Toxicology Program (NTP) has done some method development in this area from which IRIS can draw.[16] NTP's initial work has determined that for mechanistic studies with *in vivo* exposures, existing tools for human and animal studies that consider domains such as randomization, blinding, incomplete reporting and conflicts of interest are appropriate to apply. These tools use study design to determine the applicable risk of bias questions, and NTP adapted this approach for *in vitro* studies. NTP found that, similar to human and animal studies, relevance of the risk of bias domains depended on the study design for *in vitro* studies. For example, for *in vitro* studies using homogenous cell suspensions, randomization is not relevant because there is no variation or difference between the groups, as there may be with individual animals or humans.[17] IRIS should build on NTP's work to develop some basic criteria to assess the internal and external validity of the mechanistic studies determined to be relevant. This will allow IRIS to assess the overall quality of the mechanistic evidence base as it feeds into the evidence integration.

5. Incorporate the financial conflict of interest of study authors into the risk of bias assessment for included studies.

This is the same recommendation that we have made in our previous comments on the chloroform IRIS Assessment protocol.[18] For the reasons detailed below this is still critical to include in a risk of bias assessment.

In Appendix B (Typical Data Extraction Fields, page 128), IRIS includes "Funding" as one data extraction field, which contains the elements "Funding source(s)" and "Reporting of conflict of interest by authors." However, the protocol does not discuss how these particular data extraction fields are incorporated into the assessment.

We 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 as an important risk of bias,[19] based on empirical data from studies of the health effects of tobacco,[20,21]

[16] Rooney, A. (2018) Consideration of Internal and External Validity in Mechanistic Studies. Presentation at National Academies of Sciences Workshop on Strategies and Tools for Conducting Systematic Reviews of Mechanistic Data to Support Chemical Assessments. December 10, 2018. Available: http://dels.nas.edu/Upcoming-Workshop/Strategies-Tools-Conducting-Systematic/AUTO-5-32-82-N

[17] NTP (National Toxicology Program). 2016. Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Research Triangle Park, NC: National Toxicology Program.

[18] UCSF PRHE (2018) Comments on the Systematic Review Protocol for the IRIS Chloroform Assessment (Inhalation). Available: https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/UCSF%20comments%20on%20chloroform%20protocol%202018-03-01%20FINAL.pdf

[19] 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

[20] 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.

[21] 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.

the safety and efficacy of pharmaceuticals,[22,23,24] and medical procedures,[25,26] 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.[27,28,29,30,31,32,33,34] 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.[13,14,15,16,17,18,19,20]

6. Additional minor comments:

1. On page 13, one of the aims is to "Extract data on relevant health outcomes from selected epidemiological and toxicological studies based on the study evaluations." It is not clear if the authors intend to selectively include or exclude studies based on study evaluations (for example based on quality) rather than including all of the studies that met the inclusion criteria. Rewording for clarity would be helpful. If the authors are intending to selectively

[22] 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.

[23] 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.

[24] Lundh, A., Sismondo, S., Lexchin, J., Busuioc, O.A. and Bero, L., 2012. Industry sponsorship and research outcome. *Cochrane Database Syst Rev*, *12*(12).

[25] 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.

[26] 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.

[27] 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.

[28] 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.

[29] 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.

[30] 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.

[31] 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.

[32] 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.

[33] 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.

[34] 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.

include studies based on factors other than the inclusion criteria, then this would be a potential methodological flaw.

2. Page 13, the protocol states that reviewers will synthesize evidence across studies using a narrative approach. Clarity on why a quantitative approach will not be considered would be helpful.
3. Page 15, for the population element, were authors including pregnancy- and fetal-related outcomes? The animal population specifically mentions in utero and preconception. It would improve clarity to align the animal and human population descriptions where possible.
4. Page 18, regarding point 1 ("studies previously determined not to be pertinent…"), can the protocol authors confirm that the PECO / inclusion / exclusion criteria have not changed?
5. Page 23, Figure 1. It is not clear how the results were distilled from 12728 to 137 with 10328 excluded and 2587 potentially included; how many of the "potentials" were actually relevant? Also, under Excluded, there are 324 "Not peer reviewed" exclusions; however, it was our understanding that these would be included if they were relevant as they would be peer reviewed by EPA consultants.
6. Section 8 – p.80/140 – the method of contacting authors differs from other parts of the protocol where they stated they would consider an attempt unsuccessful after 1 month (page 36) or ambiguously "after one or two attempts" (page 70).

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,

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