NATURAL RESOURCES DEFENSE COUNCIL

Comments from NRDC on EPA's TSCA Systematic Review
EPA-HQ-OPPT-2018-0210

Comments on the application of the TSCA Systematic Review to the Exposure and Use Assessment and Human Health and Environmental Hazard Summary for Five PBT Chemicals
EPA-HQ-OPPT-2018-0314

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The Natural Resources Defense Council (NRDC) is a national, non-profit environmental organization of lawyers, scientists, and other professionals. NRDC presents these comments on behalf of our over three million members and online activists. NRDC does not have any financial interest in the topic of these comments.

Overview

The EPA TSCA program recently made public its approach for conducting its chemical assessments, called the "Application of Systematic Review in TSCA Risk Evaluations" (TSCA Systematic Review, May 2018, EPA Document# 740-P1-8001). See EPA's website for details.

A Systematic Review Protocol or Framework is *supposed to be* a systematic and transparent method to evaluate the quality of evidence and to support evidence-based decision making. With environmental health science, it is frequently the case that single studies have limits that make them insufficient on their own to provide reliable answers. Regulators, lawmakers, researchers, product manufacturers, and others want chemical assessments based on an evaluation and synthesis of all the evidence. This can include whole animal studies, cellular and in vitro studies (test tube and petri dish studies), and wide-ranging human data. All these study types have strengths and limitations; a systematic way to collect all the relevant information, assess the quality and reliability of each study, and then integrate all the studies together will lead to the most accurate assessment. A Systematic Review is a meant to be a systematic and transparent method to evaluate the quality of data and to support evidence-based decision making.

Unfortunately, the TSCA Systematic Review document is less about evaluating the quality of evidence, and more about eliminating it altogether. The document is incomplete, inconsistent with the state of the science, and too flawed to be used. Accordingly, use of the document violates TSCA and is otherwise arbitrary and capricious.

Given the serious flaws with the TSCA systematic review, it should not be used for any chemical assessments at EPA or any other agency. We are particularly concerned that in addition to chemicals being reviewed under TSCA, EPA is using it to assess the five PBT chemicals now under review. We therefore request that EPA consider the concerns detailed in these comments for its Exposure and Use Assessment and Human Health and Environmental Hazard Summary for Five PBT Chemicals (EPA-HQ-OPPT-2018-0314-0001).

We detail our main concerns below.

TSCA Systematic Review must be formally and rigorously peer reviewed

It is deeply concerning that the TSCA systematic review is already being applied to the TSCA chemicals, [1] including the ten chemicals that are the subject of these comments. It is still under development and has not been vetted by the EPA Science Advisory Board or any other appropriate scientific peer review committee, and has not undergone any public peer review, scientific scrutiny, or public comment before this comment period. This violates existing EPA peer review requirements as described in the EPA Peer Review Handbook (4th Edition, 2015), and the Final Information Quality Bulletin for Peer Review (OMB, 2004).[2] The Handbook and Bulletin require documents that are "highly influential," "novel, controversial, or precedent-setting," or have "significant interagency interest" to undergo peer review before being implemented. The peer review process that EPA should undertake if it is intending to use the TSCA Systematic Review should be transparent, include inter-agency input, and be accountable to the recommendations that arise from that process as described in the EPA Handbook and OMB Bulletin.

Since the TSCA Systematic Review has not undergone a formal rigorous transparent scientific review process yet, it would be inappropriate to apply it to any EPA chemical assessments at this time. Use of the document is procedurally flawed, and arbitrary and capricious.

Inconsistent or in conflict with state of the science

As pointed out in the comments here, and those of the University of California San Francisco Program on Reproductive Health and the Environment (UCSF PHRE) experts, the TSCA Systematic Review document seems to lack any linkages to the established worldwide leaders on systematic review. For example, it departs in significant and disturbing ways from approaches advanced by: National Academy of Sciences recent favorable review of the EPA IRIS program (NRC 2018);[3] the National Toxicology Program (NTP);[4] the international scientific collaboration that developed a framework for the "systematic review and integrated

[1] Application of Systematic Review in TSCA Risk Evaluations. May 2018. EPA Document# 740-P1-8001.Docket ID EPA-HQ-OPPT-2018-0210

[2] OMB Final Information Quality Bulletin for Peer Review. M-05-03. December 2004

[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. https://doi.org/10.17226/25086.

[4] 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; 2015

assessment" (SYRINA) of endocrine disrupting chemicals;[5] and the Navigation Guide systematic review method (NavGuide) developed by a collaboration of scientists led by the University of California San Francisco.[6] In fact, in many critical ways the TSCA Systematic Review is in direct conflict with these and other established Systematic Review frameworks, as detailed in these comments and comments from UCSF PHRE to this docket.

Additionally, the TSCA Systematic Review is not harmonized with major hazard identification approaches described by the IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, California OEHHA chemical assessment approaches, and other globally-harmonized hazard ID approaches that enjoy widespread acceptance among the environmental health community. Accordingly, the TSCA Systematic Review violates Section 26(h) of TSCA requiring EPA to employ best available science when implementing Section 6 of the law.

The purpose of having a harmonized system is to promote common, consistent criteria for classifying chemicals according to their health, physical and environmental hazards, and to encourage the use of compatible hazard labels, material safety data sheets for workers, and other hazard communication information based on the resulting classifications, thus improving health protection.

The TSCA program should utilize a Systematic Review method that is already established, and that reflects the state of the science on systematic review, such as the NTP-OHAT or NavGuide methods.

TSCA Systematic Review shares similar problems with EPA's discredited Science Transparency Rule

Although the TSCA Systematic Review fails to align with established chemical assessment methods, it does manage to dovetail disturbingly well with the discredited Science Transparency Rule,[7] characterized by Reuters as a "concession to big business that has long requested such restrictions".[8] For reasons detailed in these comments, both the Censor Science rule and the TSCA Systematic Review would make it hard or impossible for EPA to

[5] Vandenberg LN, Ågerstrand M, Beronius A, Beausoleil C, Bergman Å, Bero LA,Bornehag CG, Boyer CS, Cooper GS, Cotgreave I, Gee D, Grandjean P, Guyton KZ, Hass U, Heindel JJ, Jobling S, Kidd KA, Kortenkamp A, Macleod MR, Martin OV, Norinder U, Scheringer M, Thayer KA, Toppari J, Whaley P, Woodruff TJ, Rudén C. A proposed framework for the systematic review and integrated assessment (SYRINA) of endocrine disrupting chemicals. Environ Health. 2016 Jul 14;15(1):74. Review.

[6] 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 Oct;122(10):1007-14. doi:10.1289/ehp.1307175. Epub 2014 Jun 25. Review.

[7] Strengthening Transparency in Regulatory Science, April 2018 RIN 2080–AA14. EPA–HQ–OA–2018–0259.

[8] U.S. environment agency proposes limits to science used in rulemaking. Valerie Volcovici, Timothy Gardner. Reuters, April 24, 2018. Available online at https://www.reuters.com/article/us-usa-epa-science/epa-set-to-unveil-policy-barring-secret-science-sources-idUSKBN1HV2DJ

include important human health and toxicology studies it its chemical hazard assessments if there is any information that is missing or not made public. Ultimately, both documents will hamstring EPA's use of scientific information, which will severely harm EPA's work quality and public credibility by producing inaccurate unprotective EPA chemical assessments. Both documents violate Sections 26(h) and (k) of TSCA by excluding valid scientific data from EPA's Section 6 risk evaluation process. See comments by NRDC submitted to Docket EPA-HQ-OA-2018-0259, incorporated here by reference.

Below we highlight some of the most serious problems with the TSCA Systematic Review:

Reporting quality is used as a false proxy for study quality

The systematic framework is almost wholly reliant on reporting as a measure of study quality, when in fact reporting and quality are not the same and are not even necessarily correlated. What information and how much is reported can be highly variable, depending on whether a study is published in a high-ranking generalist journal like Science or Nature with very severe space limits, or a discipline-specific journal like Environmental Health Perspectives that encourages lengthy descriptions of methods and results. Government reports may require even more detailed reporting, or less. And, conventions in reporting have changed over time, and especially with online journals having much less restrictive space constraints than even only a decade ago. Reporting differences will depend on the expected audience, where information needs and expectations between researchers and regulators can differ dramatically. The TSCA Systematic Review will not accurately determine study quality, as currently written.

For example, the TSCA Systematic Review's data screening approach to inclusion and exclusion criteria for identifying information relevant to the risk evaluation process includes seven bullet points, but only one that describes human health hazard data, and it contains only one simple requirement, that the data "meet minimum reporting elements" (TSCA SR Section 2.2.2. p. 22-23). In the flawed TSCA Systematic Review, failure to report some information will result in eliminating entire human health and environmental hazard studies. The whole approach appears to be designed to eliminate non-industry studies that do not have to adhere to regulatory reporting preferences or requirements.

The TSCA Systematic Review uses reporting in the Tables on data quality criteria for each data stream:

- For environmental fate assessments (see Table C-9, p. 51), almost every one of the eight domains in the first column – test substance, test design, test conditions, etc. – includes a statement that if some aspect of that domain is not reported, it would render the study unusable: "The study did not include or report control groups"; "The test method was not reported"; "Equilibrium was not established or reported", etc. Any one of these failures to report information is considered by the TSCA Systematic Review to be a "serious flaw that would make fate data unacceptable for use in the fate assessment". Presumably all studies with any one or more of these reporting gaps would be immediately and totally excluded from further consideration.

- Similarly, among the lengthy list of "serious flaws that would make epidemiological studies unacceptable" (TSCA SR Table H-8, p. 231) the failure to report on almost any aspect of the study is grounds for exclusion. If "Exposure variables were not well defined, and sources of data and detailed methods of exposure assessment were not reported" a study is excluded. If "Numbers of outcome events or summary measures, or diagnostic criteria were not defined or reported" a study is excluded. If "There are known [sample] contamination issues and no documentation that the issues were addressed" a study is excluded.
- Any epidemiology study of any type is scored as "unacceptable" for use in exposure assessment if "exposure misclassification is present and likely to impact results, but no attempt is made to address it" (TSCA SR Table E-13, p 120). This is despite the fact that many exposure misclassifications make it harder to detect a real effect (bias to the null, leading to false negatives); if an effect is observed it is therefore more likely to be real.

There is no evidence that any of these above reporting gaps would lead to reduced study quality, or an unacceptably high risk of bias. In fact, many of these things would lead to the discarding of reliable evidence of harm. For example, observational wildlife and epidemiology studies have many methodological features that tend to bias the direction of error away from detecting a real effect (bias to the null, leading to false negatives): nondifferential exposure misclassification, inadequate follow-up, lost cases, and simple models that fail to capture realistic complexity in the system.[9] Many excellent studies demonstrating links between environmental exposures and adverse health effects will be discarded under the TSCA Systematic Review, resulting in an inaccurate and unprotective chemical assessment.

Instead of simple reporting, established standards like NavGuide and NTP use more sophisticated and biologically sensitive systems for evaluating studies. For example, they recognize that an epidemiology study may be confidently used for developing an ever/never exposure analysis, but less so for a dose-response curve. It would be important to consider a study like this for making a determination about whether an agent is linked to elevated cancer risk, for example, instead of considering it 'unusable' with the TSCA Systematic Review approach.

<u>Bias against rare health outcomes – example of TCE cardiac effects</u>

Because the TSCA Systematic Review is structured to give studies a poor grade or designate them as low confidence without regard to biological understanding of the study outcome, the TSCA Systematic Review will result in discarding studies with particularly rare health outcomes. This conflicts with other established study assessment approaches that take into consideration that there may be *greater* confidence in an outcome due to the rarity of the effect, even with some study weaknesses. For example, the EPA Cancer Guidelines recognize this, and elevate the significance of rare tumors as follows:

[9] Gee D. Late Lessons from Early Warnings: Toward Realism and Precaution with Endocrine-Disrupting Substances. Environmental Health Perspectives. 2006;114(Suppl 1):152-160. doi:10.1289/ehp.8134.

- The Guidelines indicate that even a study with some limitations due to bias or confounding can be elevated if the adverse outcome endpoints are rare: "A unique feature that can be ascribed to the effects of a particular agent (such as a tumor type that is seen only rarely in the absence of the agent) can increase sensitivity by permitting separation of bias and confounding factors from real effects" (p. 2-10);
- The Guidelines require a (more lenient) lower statistical significance level for rare tumors, as compared to common tumors, recommending: "a statistical significance of 1% for common tumors or 5% for rare tumors" (p. 2-20);
- The Guidelines directs that a chemical should be classified as, "Likely to Be Carcinogenic to Humans" with evidence of a rare animal tumor response, even if it is in only "a single experiment that is assumed to be relevant to humans" (p. 2-55).

The TSCA Systematic Review fails to account for the significance of rare adverse outcomes in studies with limitations or a lower statistical significance. We are particularly concerned that the EPA Toxics Office plans to use its Systematic Review to discard the scientific evidence linking the rare outcome of congenital heart defects with trichlorethylene (TCE). The heart effects are rare but can be disabling or even deadly. Based on a transparent systematic review of the scientific evidence, EPA scientists determined that there were some uses of TCE in consumer and industrial products that were so dangerous they should be discontinued.[10] In particular, EPA scientists had raised concerns with low-dose exposures during pregnancy that could lead to permanent heart malformations in the developing fetus.[11]

However, recently the ToxStrategies consulting firm published a list of biases with the TCE heart studies that it contends should make the study unusable for regulatory purposes. Its analysis and conclusion follow the criteria laid out in the TSCA Systematic Review. Significantly, ToxStrategies received funding from Entek International, whose Oregon-based battery parts operations have been repeatedly fined for violations related to its TCE pollution including allegedly poisoning its workers (The Oregonian, May 5, 2017).[12] Thus, ToxStrategies itself also had a financial bias – something that the TSCA Systematic Review does not include in the risk of bias analysis, as discussed further below.

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[10] Regulation of Certain Uses under Toxic Substances Control Act: Methylene Chloride and N-Methylpyrrolidone. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0231-0001

Regulation of Certain Uses under Toxic Substances Control Act: Trichloroethylene. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0163-0001

Regulation of Certain Uses under Toxic Substances Control Act: Trichloroethylene; Vapor Degreasing. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0387-0001

[11] Trichloroethylene (TCE); Regulation of Certain Uses Under TSCA §6(a). December 2016. Pg 11-12. Docket EPA-HQ-OPPT-2016-0163. Available at https://www.epa.gov/sites/production/files/2016-12/documents/prepubcopy_tce-aerosolspotting_nprm_frdocument_2016-12-06.pdf

[12] Chemical linked to Entek air pollution also linked to employees' health problems. Rob Davis. The Oregonian. Updated May 5, 2017; Posted Apr 29, 2017. https://www.oregonlive.com/environment/index.ssf/2017/04/chemical_linked_to_entek_air_p.html

Instead of using reporting criteria to exclude studies, the EPA TSCA program should adopt an existing systematic review method that adheres to current state of the science, which dictates that reporting elements should be included in a risk of bias analysis through all the domains, not establishing a reporting requirement that would disqualify a study. Sections 26(h) and (k) of TSCA require such an approach.

TSCA Systematic Review is biased to score industry-sponsored studies higher than they deserve

As detailed in the previous section, by its heavy and inappropriate use of reporting criteria to exclude studies from a chemical assessment, the TSCA Systematic Review will provide an open door to regulatory studies sponsored by financially conflicted parties. This is because the only studies required to meet specific reporting requirements are the Guideline studies that are conducted for the purpose of gaining regulatory approval of products, and these are sponsored by the industry that has a financial interest in commercializing its product. The reporting requirements are described as Good Laboratory Practices (GLP). Neither Guideline methods nor GLP-compliance is necessarily associated with study quality; it may in fact be a very poor-quality study – but well reported - as described below.

Guideline studies are most often designed to identify major toxic effects (apical effects) like cancer, major organ weight gain or loss, body weight gain or loss, skeletal malformations, loss of fur, tremors and convulsions, diarrhea, and obvious signs of lethargy. However, by the time these major (apical) endpoints are observed, significant toxicity has already occurred. This is because Guideline studies must follow methods that are established over years of negotiated process between regulatory agencies and the regulated community, and thus almost by definition simply cannot reflect modern methods for evaluating chemicals. Guideline studies aren't designed to grapple with the issues of low-dose exposures, formulations and chemical mixtures, endocrine or hormonal effects, and subtle but significant neurobehavioral impacts like what are now known to be caused by even very low doses of lead during critical windows of development. In summary, Guideline studies are designed to observe obvious and significant toxicity, not to identify early warnings (upstream indicators) of potential harm, such as reduced anogenital distance which is a predictor of later-life infertility.

Good Laboratory Practices (GLP) establish standards for animal care and data collection and reporting. Guideline studies must be GLP-compliant. The GLP standards were established for industry laboratories in response to serious widespread fraudulent practices documented by government inspectors in the 1970s. This is why it is a requirement only for industry-sponsored studies. To be GLP compliant, studies must adhere to specified approaches to recordkeeping to facilitate audits and reduce fraud (54 Fed. Reg. 34034 Aug. 17, 1989). Since the requirements are primarily about reporting, and not study methods, the GLP requirements are not necessarily associated with higher quality research, proper study design or correct statistical analysis.[13] In

[13] Myers, J. P., F. S. vom Saal, et al. (2009). "Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case of bisphenol A." Environ Health Perspect 117 (3): 309-15.

many cases GLP and Guideline studies are not published, not subjected to public scientific scrutiny, and not independently peer reviewed.

Rather than being subject to GLP and Guidelines requirements, all academic research studies must instead adhere to the established standards of Institutional Review Boards (IRB) for both ethical and scientific conduct.[14] Like many aspects of GLP guidelines, IRB's ensure that the studies are conducted according to established and evolving best practices and legal requirements for animal care, human subject protections, and other ethical practices. However, unlike GLP, the IRB does not mandate specific reporting requirements. And, unlike Guideline studies which hamstring researchers into pre-set methods, IRB review will provide guidance to ensure sound research design while also encouraging cutting edge and exploratory research using novel methods to advance scientific knowledge.

The TSCA Systematic Review is inherently problematic and will yield poor-quality results by relying on criteria that favor regulatory studies over hypothesis-driven research.

In some places, the TSCA Systematic Review masks its bias towards reporting criteria. For example, it recommends that after the overall score is applied to a study, the final determination of study quality can be adjusted through use of the ToxRTool (TSCA SR p. 31, 34). However, since the ToxRTool was developed to assess the reporting quality of a study, its use simply perpetuates the existing flaws in the TSCR Systematic Review (the reliability categories utilized in the ToxRTool are the same as the Klimisch codes of reliability, developed over two decades ago by BASF employees).[15] Since the Klimisch codes favor Guideline and GLP studies, then using ToxRTool would be subject to the same criticism as over-relying on either Klimisch codes, Guideline studies or GLP – simply put, they are a measure of reporting, not of study quality.

<u>Use of scoring – an approach discredited by experts</u>

The TSCA Systematic Review is in direct conflict with best practices for systematic review by applying a scoring system to studies, and particularly to develop a "composite" quality score across all studies. It has been documented that the use of scoring in this manner will inevitably lead to a bias in study evaluation, based on pre-determined weighting strategies that fail to account for the complexity of study design, study conduct, how the study is being used, and other features. For example, authors published in JAMA reported that, "Our data indicate that the use of summary scores to identify [clinical] trials of high quality is problematic."[16] A medical journal review article titled, "No role for quality scores in systematic reviews of diagnostic

[14] More information about IRBs here: https://www.niehs.nih.gov/about/boards/irb/index.cfm

[15] Klimisch HJ, Andreae M, Tillmann U. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul Toxicol Pharmacol. 1997 Feb;25 (1):1-5

[16] Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA. 1999 Sep 15;282(11):1054-60.

accuracy studies" Concludes that scoring systems do not produce higher quality assessments; they simply don't work.[17] A recent publication of 29 collaborators on new tools to assess risk of bias in systematic review specifically emphasized that they, "should not be used to generate a summary 'quality score' because of the well-known problems associated with such scores".[18]

The US Institute of Medicine recommended standards for conducting high-quality systematic reviews that specifically warn against scoring systems, and particularly against ones relying on reporting: "Quality scoring systems have not been validated. Studies assessed as excellent quality using one scoring method may be subsequently assessed as lower quality using another scoring method (Moher et al., 1996).[19] Moreover, with an emphasis on risk of bias, the Systematic Review more appropriately assesses the quality of study design and conduct rather than the quality of reporting."[20]

In summary, experts warn against the scoring system promoted in the TSCA Systematic Review. The current state of the science for evaluating clinical and environmental health research is to describe or document each component of the assessment tool separately, without trying to calculate an overall numeric score. In accordance with Section 26(h)(and (k) of TSCA, EPA must use an existing Systematic Review method that adheres to these scientific standards, such as the NTP or NavGuide Systematic Review methods.

<u>TSCA Systematic Review fails to include a comprehensive risk of bias analysis</u>

EPA's TSCA Systematic Review does not address financial or other conflicts of interest at all, despite widespread acknowledgement across the scientific and medical community that regulated industry sponsorship can lead to biased study design, biased study conduct, and biased reporting of study results – all leading to a favorable outcome for the regulated industry sponsor.[21]

The National Toxicology Program Systematic Review states that, "It may be useful to pay attention to author affiliations and funding source which can contribute to selective outcome reporting when results are not consistent with expectations or value to the research

[17] Whiting P, Harbord R, Kleijnen J. No role for quality scores in systematic reviews of diagnostic accuracy studies. BMC Med Res Methodol. 2005 May 26;5:19. Review.

[18] Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, Shea B, Davies P, Kleijnen J, Churchill R; ROBIS group. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016 Jan;69:225-34. doi:10.1016/j.jclinepi.2015.06.005. Epub 2015 Jun 16.

[19] Moher D, Jadad AR, Tugwell P. Assessing the quality of randomized controlled trials. Current issues and future directions. Int J Technol Assess Health Care. 1996 Spring;12(2):195-208. Review.

[20] Eden J., Levit L., Berg A.O., Morton S., editors. Finding what works in health care: standards for systematic reviews. The National Academies Press; Washington, D.C: 2011.

[21] Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2017 Feb 16;2:MR000033.
https://www.ncbi.nlm.nih.gov/pubmed/?term=10.1002%2F14651858.MR000033.pub3

objectives."[22] The Agency for Healthcare Research and Quality recommends that: "(1) at a minimum, EPCs [Evidence-based Practice Centers] should routinely report the source of each study's funding; (2) EPCs should consider issues of selective outcome reporting at the individual study level and for the body of evidence; and (3) EPCs should conduct sensitivity analyses for the body of evidence when they have reason to suspect that the source of funding or disclosed conflict of interest is influencing studies' results".[23] Consideration of funding bias should be considered standard practice in all EPA systematic reviews, yet is wholly absent from the TSCA Systematic Review approach.

There is recognition that financial bias is most evident in industry-sponsored studies that are conducted to gain regulatory approval. For example, a survey of the pharmaceutical company funding on clinical research concluded that, "Bias in favour of industry is apparent in every one of the themes examined with the result that research funded by industry undermines confidence in medical knowledge."[24] Medical journals are extremely concerned about industry-bias leading to poor quality or even inaccurate studies, and have worked hard to tighten up their disclosure requirements for authors, peer reviewers, and even editors of journals. The Institute of Medicine includes an extensive discussion of the problems of financial conflict in its report on systematic review, citing recommendations of the International Committee of Medical Journal Editors that highlight relationships with commercial entities as of concern. [25] [26]

Yet, despite the tremendous global effort that biomedical and other journals have undertaken to require study authors to disclose financial interests, because it is a recognized source of potential bias, the TSCA Systematic Review and other government Systematic Review methods continue to ignore this information in an analysis of bias.
Considerations of funding from the regulated industry must be included in a comprehensive risk of bias analysis in any systematic review method that is used for TSCA chemical assessments. This would be consistent with recommendations of the National Academies review of the IRIS program: "funding sources should be considered in the risk-of-bias assessment conducted for systematic reviews that are a part of an IRIS assessment".[27]

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[22] NTP Systematic Review risk of bias tool. https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf

[23] Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov

[24] Lexchin J. Sponsorship bias in clinical research. Int J Risk Saf Med. 2012;24(4):233-42. doi: 10.3233/JRS-2012-0574.

[25] Eden J., Levit L., Berg A.O., Morton S., editors. Finding what works in health care: standards for systematic reviews. The National Academies Press; Washington, D.C: 2011. p. 52

[26] Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. ICMJE, 2010.

[27] National Research Council. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. P. 79 https://doi.org/10.17226/18764

TSCA Systematic Review is incomplete

The evidence integration process is a critical part of a systematic review method. It describes the selection of a hazard identification category. For example, NTP has the following hazard categories: known, presumed, suspected, and not classifiable. There is a narrative that accompanies each of these categories. The hazard identification categories used by NTP are comparable to those used in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Both the NTP and NavGuide systematic review methods are designed to effectively address the full range of data relevant to environmental health assessments (e.g., human, animal, and in vitro/mechanistic studies), and include tools to assess potential bias of studies.

However, although the TSCA Systematic Review discusses how to evaluate (and score) individual studies, it has no method for integrating different streams of evidence to make a risk determination. The TSCA Systematic Review explains that this is because its timeframe for conducting its assessments has been compressed, and it has simply not completed the development of its systematic review protocols (TSCA SR, Section 3.1, p. 19). EPA writes that the data integration portion of the method is still under development.

Among many disturbing elements of this document is the fact that it is acknowledged to be both incomplete and already being applied to the chemicals under review. Even more unsettling is the disturbing claim in the TSCA Problem Formulation documents that the TSCA program plans to undo years of work by EPA IRIS and other programs by subjecting the ten TSCA chemicals to a re-do using this just-released TSCA Systematic Review method. This exclusion of valid scientific information based upon an incomplete and deeply flawed TSCA Systematic Review Method is a serious, immediate, and ongoing violation of Section 26(h) and (k) of TSCA, and the Administrative Procedures Act.

Inappropriate and inaccurate use of mechanistic information

We support the TSCA Systematic Review insofar as it indicates that mechanistic information is not necessary for interpreting or evaluating other data: “Although highly preferred, the availability of a fully elucidated mode of action (MOA) or adverse outcome pathway (AOP) is not required to conduct the human health hazard assessment for a given chemical.” (TSCA SR, p. 172). This is consistent with the EPA Cancer Guidelines: “A lack of mechanistic data, however, is not a reason to reject causality” (EPA Cancer Guidelines, p. 2-14).[28]

We are concerned, however, that the chemical industry and its paid consultants have been arguing for over a decade that MOA conclusions be rendered separately from other data

[28] EPA 2005. Guidelines for Carcinogen Risk Assessment EPA/630/P-03/001B. https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf

streams, as if it were stand-alone information (see, for example, Meek et al 2003).[29] This is also the approach in the TSCA Systematic Review: "EPA/OPPT plans to prioritize the evaluation of mechanistic evidence instead of evaluating all of the identified evidence upfront. This approach has the advantage of conducting a focused review of those mechanistic studies that are most relevant to the hazards under evaluation." (TSCA SR p. 172). This is in direct contradiction with the EPA Cancer Guidelines, which state that mechanistic data, "are incorporated into the context of all of the data regarding weight of the evidence for carcinogenicity" (EPA Cancer Guidelines, p. 2-39).[30] The TSCA Systematic Review is therefore in conflict with EPA Guidelines which are peer-reviewed and finalized, and inconsistent with Section 26 of TSCA.

We are additionally concerned that the TSCA program may prematurely and inappropriately rely on some of the new tools in hazard, exposure, and risk assessment that have developed rapidly over the last decade. For example, EPA's Toxicity ForeCaster (ToxCast™) is billed by EPA as its "most updated, publicly available high-throughput toxicity data on thousands of chemicals".[31] The chemical screening results from ToxCast are shared by EPA with the inter-agency collaboration called Toxicology in the 21st Century (Tox21) which includes EPA, NIH, and FDA. Federally sponsored programs like Tox21[32] have exponentially increased the amount of molecular information available for environmentally-relevant chemicals. While there are important potential benefits to faster, cheaper testing methods for evaluating environmental chemicals, their ultimate usefulness resides in their ability to be protective of the health of populations and ecosystems. To be fully protective, TSCA requires these non-animal methods to be (1) scientifically reliable, (2) relevant, and (3) capable of providing information of equivalent or better scientific reliability and quality to that which would be obtained from vertebrate animal testing. Reliability, relevance, and providing equal or better information than vertebrate tests represent independent criterion that must be established prior to their use in lieu of whole-animal based tests. The overzealous deployment of tests that may underestimate or completely miss toxicity or exposure (high false negative rate) would result in risk evaluations and determinations that are not consistent with the requirements of the revised TSCA – particularly for vulnerable populations including children, pregnant women and workers. Non-animal test methods and strategies must be proven to be reliable, relevant, and able to provide information of equivalent or better scientific reliability and quality prior to being included on a list of acceptable tools to aide decision making.

We are additionally concerned that much of the methods and raw data for ToxCast and Tox21 are generated by outside contractors including private for-profit entities that are holding

[29] M Meek ME, Bucher JR, Cohen SM, Dellarco V, Hill RN, Lehman-McKeeman LD, Longfellow DG, Pastoor T, Seed J, Patton DE. A framework for human relevance analysis of information on carcinogenic modes of action. Crit Rev Toxicol. 2003;33(6):591-653. Review.653.

[30] EPA 2005. Guidelines for Carcinogen Risk Assessment EPA/630/P-03/001B. https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf

[31] EPA website on Toxicity ForeCaster (ToxCast™) Data. Accessed 5/24/2018. https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data

[32] https://ntp.niehs.nih.gov/results/tox21/index.html

portions of the models and raw data as proprietary. For example, a private company called BioSeek is contracted to EPA to use its proprietary BioMAP® system to generate ToxCast data.[33] [34] According to a 2012 article, "The new agreement [with EPA] covers the use of BioSeek's unique BioMAP® Systems human primary cell assay platform to help predict the biological activity and potential toxicity of up to 60,000 additional samples, including environmental chemicals, pesticides, failed pharmaceuticals and nanomaterials… Under the agreement, BioSeek will receive up to $46,770,000 over the next five years for testing up to 60,000 samples. The specific value of the award will depend on the volume of testing required during the contract period. The company's previous contract with the EPA awarded in 2007 was for up to $12.8 million over five years..." [35] In addition to BioSeek, some cell-based assays run by Odyssey Thera, Novascreen, Attagene and other contractors also used a proprietary process, where the raw data and models are not fully disclosed to the public.[36] The proprietary nature of tests and data supporting the ToxCast and Tox21 platforms means that the entire platforms are not fully transparent.

A major challenge in using any of these methods to test for chemical toxicity is that different systems can react to chemicals in different ways. These differences should not be used to dismiss evidence of toxicity. In fact, strong evidence from mechanistic/MOA studies could support a conclusion and raise it to a level of increased concern. The TSCA program should rely on a Systematic Review method such as NTP or NavGuide that provides a robust credible method for integrating multiple streams of data, including mechanistic information, to elevate the level of concern with a chemical hazard.

When information is missing or unreliable, EPA should use established defaults that will protect health, and set stringent criteria for when to depart from health-protective defaults

The TSCA Systematic Review is noticeably silent on the issue of health-protective default assumptions. When information is missing or unreliable, the framework should be clear and consistent that its approach is to use scientifically-based default assumptions that will protect health to improve the timeliness of the chemical assessment and decision-making process, and

[33] Powerpoint presentation. BioSeek - ToxCast Phase I Project Update. Ellen Berg, PhD, BioSeek, Inc. EPA Chemical Prioritization Community of Practice. Monthly Meeting January 24, 2008. https://www.epa.gov/sites/production/files/2014-08/documents/bioseek_toxcast_summary_24jan08.pdf

[34] BioSeek Awarded New Five-Year Contract from EPA ToxCast™ Program: Up to 60,000 Additional Samples to be Screened Using BioSeek's BioMAP® Systems. Oct 04, 2012 from BioSeek, LLC. Accessed 5/24/2018. https://www.prnewswire.com/news-releases/bioseek-awarded-new-five-year-contract-from-epa-toxcast-program-172642451.ht

[35] BioSeek Awarded New Five-Year Contract from EPA ToxCast™ Program: Up to 60,000 Additional Samples to be Screened Using BioSeek's BioMAP® Systems. Oct 04, 2012 from BioSeek, LLC. Accessed 5/24/2018. https://www.prnewswire.com/news-releases/bioseek-awarded-new-five-year-contract-from-epa-toxcast-program-172642451.ht

[36] Kleinstreuer NC, Ceger P, Watt ED, Martin M, Houck K, Browne P, Thomas RS, Casey WM, Dix DJ, Allen D, Sakamuru S, Xia M, Huang R, Judson R. Development and Validation of a Computational Model for Androgen Receptor Activity. Chem Res Toxicol. 2017 Apr 17;30(4):946-964.

set clear scientifically-based criteria for when to depart from these assumptions.[37] In the landmark "Science and Decisions" report (NAS, 2009), the NAS committee concluded that, "established defaults need to be maintained for the steps in the risk assessment that require inferences."[38] The NAS committee recommended that EPA and other agencies update default factors and assumptions based on the best current science, identify where unstated or implicit assumptions are used, and replace these with explicit assumptions wherever possible. These recommendations push Agencies to, "continue and expand use of the best, most current science to support or revise its default assumptions,"[39] making the assumptions stronger, rather than reducing reliance on them. In fact, the committee specifically recommended that EPA develop "clear standards for departures from defaults."[40] The committee also noted that establishing, "clear criteria for departure from defaults can provide incentives for third parties to produce research" that can reduce uncertainty and, over time, result in more accurate assessments. Importantly, by using the established defaults more often, EPA could avoid "the delay entailed by having to re-examine generic information with every new risk assessment."[41] EPA should also evaluate and quantify, when possible, the impact of the uncertainty associated with a default assumption, including a description of how using a default versus the chosen alternative assumption affects the decisions that protect the environment and public health.

EPA should keep the scientific and regulatory work of TSCA in separate offices

EPA should keep chemical assessments in the science office with the EPA staff that have established expertise in this area. A recent National Academies report of the IRIS chemical assessment program specifically supported current best practices recommended by the Institute of Medicine that, "the IRIS teams involved in the systematic-review process should be independent of those involved in regulatory decision-making who use the products of the systematic-review teams. The committee notes that the current organizational structure of the IRIS program in the EPA Office of Research and Development is consistent with those best practices."[42] Placing chemical assessments within the OCSPP regulatory office will compromise the independence and public trust in the final product.

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[37] NRDC Issue paper. Strengthening toxic chemical risk assessments to protect human health. S Janssen, J Sass, T Schettler, G Solomon. February, 2012. http://switchboard.nrdc.org/blogs/jsass/nrdc_issue_paper_better_risk_a.html

[38] Science and Decisions: Advancing Risk Assessment. National Research Council of the National Academies. (2009), p. 7.

[39] NRC 2009 Science and Decisions, p. 207.

[40] NRC 2009 Science and Decisions, p. 199.

[41] NRC 2009 Science and Decisions, p. 191.

[42] 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. Page 8. https://doi.org/10.17226/25086

In summary, EPA should heed the recommendations of the National Academies and leave the IRIS program with its independence, and the resources and ability to do its work without political interference by the regulated industries whose toxic chemical products are being assessed.

Conclusion

A Systematic Review Protocol or Framework is *supposed to be* a systematic and transparent method to evaluate the quality of evidence and to support evidence-based decision making. Fundamentally, however, the TSCA Systematic Review document describes a head-in-sand approach to any evidence that a toxic chemical is toxic. Such evidence will be excluded from further consideration by the TSCA program, to almost guarantee that the resulting chemical assessment will be as chemical-friendly as possible, enabling chemical manufacturers to avoid restrictions and regulations and dodge legal liability. The TSCA Systematic Review is incomplete, in conflict with best practices and the state of the science, and in conflict with recommendations from the IOM and National Academies. It is too flawed to be used, and EPA's application of the document in its current form constitutes a serious, immediate, and ongoing violation of TSCA and the Administrative Procedures Act.

We recommend that the EPA TSCA program employ an existing credible peer-reviewed Systematic Review method that conforms with the state of the science, such as the National Toxicology Program Systematic Review, or the Navigational Guide. This is consistent with recommendations from the National Academies and other expert scientific reports.

We also recommend that the EPA TSCA program use existing assessments from the IRIS program and continue to support the IRIS program with independence and resources adequate for it to complete its mission, including conducting chemical assessments for the TSCA program. This is consistent with recommendations from the 2018 National Academies in its recent favorable review of the IRIS program.[43]

Thank you for the opportunity to provide comments.

Respectfully,

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[43] 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. https://doi.org/10.17226/25086