

To Ensure Transparent and Unbiased Evaluation of Chemical Harms, EPA Should Use Science-Based Systematic Review Methods

RECOMMENDATION

To ensure EPA is making decisions based on the best available science, EPA must implement a science-based, validated systematic review method to inform policy and decision-making to save lives and money.

ISSUE SUMMARY

Systematic review methods are used to collect and evaluate scientific evidence using transparent, consistent methods that reduce bias in evidence evaluation. They have been implemented in clinical medicine because it has been demonstrated that these methods produce a less-biased evaluation of evidence for making decisions about patient care that saves lives and money. They set the “rules” of the game for assembling and interpreting the scientific evidence.^{1,2,3}

Scientifically valid systematic reviews are recommended by the National Academies of Sciences, Engineering, and Medicine (NASEM) to better evaluate environmental chemicals and inform policy and decision-making.^{4,5,6}

The Toxic Substances Control Act (TSCA) requires that EPA make decisions about chemical risks based on the “best available science” and use of systematic reviews to evaluate the weight of the scientific evidence.⁷ These systematic review “rules” will determine what evidence EPA will consider, and how it will evaluate that evidence when making decisions about potentially hazardous chemicals. However, the TSCA method does not comply with current, established, best-available empirical methods for systematic review and has resulted in underestimating risks of environmental chemicals and pollutants; this noncompliance has been identified by EPA’s Science Advisory Committee on Chemicals (SACC).

With the public’s health at stake, EPA’s incomplete TSCA method (see TCE case study below) is deeply concerning as it has excluded quality research that found health effects from exposures to toxic chemicals from EPA’s decision-making. Thus, continued use of this method would mean that risks from industrial chemicals and pollutants could be undervalued and underestimated — leaving the public and the most vulnerable populations that Congress explicitly mandated EPA to protect at risk from harmful chemical exposures.

PROPOSED ACTIONS

- 1. EPA should implement a science-based systematic review method** that aligns with the National Academy of Medicine’s definition of a systematic review, including but not limited to, using explicit and pre-specified scientific methods for every step of the review.
- 2. EPA should immediately implement a science-based systematic review method for the ongoing TSCA risk evaluations** and use the same systematic review method for hazard identification, characterization and risk assessment across the Agency that has been demonstrated for use in environmental health, and which has been endorsed and utilized by the National Academies of Sciences, Engineering, and Medicine (NASEM) i.e., the National Toxicology Program’s OHAT method and the Navigation Guide developed by the University of California, San Francisco.
- 3. EPA should invest in training and implementation for risk assessors in best practices in systematic review** across the Agency. This would allow for greater consistency across the Offices within the Agency for how these assessments are conducted, the ability to share knowledge, learning and resources, and allow the Agency to be at the forefront of cutting-edge methodological advancements for systematic review methods globally. It would allow for consistency across Agency offices that conduct hazard identification, hazard characterization and risk assessment.

HOW HAS THE TSCA METHOD EXCLUDED QUALITY RESEARCH FROM EPA'S DECISION-MAKING?

Example: Failure to Consider Prenatal Exposures to TCE and Fetal Heart Defects in Draft Risk Evaluation for Trichloroethylene⁸

- Scientific evidence and EPA scientists find that TCE can increase the risk of fetal heart malformations and that this is the most sensitive outcome (endpoint) for exposure to TCE.
- However, EPA's conclusions about the science ignore this evidence and instead focus on immunosuppression and autoimmunity as the key endpoints for determining whether or not a condition of use presents "unreasonable risks." The critical exposure level for immunological effects occur almost 500x higher than for fetal heart malformations. Thus, using the immunological endpoint will put pregnant women and their fetuses at risk.
- If EPA had used a systematic review method that complied with current, established, and best-available empirical methods, EPA could not ignore the fetal heart defect endpoint, as there was **sufficient to high evidence** to show these harms. EPA stated that there was "medium confidence" in the relevance of the endpoint to human toxicity based on the results of the Weight of Evidence analysis⁹ and that the Johnson et al., 2003 study considered in the dose-response analysis for acute exposure scenarios, measuring the effect on congenital heart defects, was of medium quality.¹⁰ Instead, **EPA created arbitrary decision-making criteria after the evidence** had already been evaluated to select a far less sensitive endpoint. **There is no credible scientific justification for ignoring evidence of fetal heart defects in evaluating TCE's risks to health.**

explicit, **pre-specified scientific methods** to identify, select, assess, and summarize the findings of similar but separate studies."¹¹ However, the TSCA method does not comply with these current, established, empirical methods for systematic review and could result in underestimating risks to environmental chemicals and pollutants. Several of these fundamental systematic review deficiencies in the TSCA method have been identified by EPA's Science Advisory Committee on Chemicals (SACC). The SACC has made several comments and critical recommendations necessary to improve the TSCA method, which EPA has not addressed in the draft risk evaluations to date; therefore, the scientific flaws in the TSCA method persist.^{12,13,14,15,16}

CRITICAL CONCERNS IN THE TSCA SYSTEMATIC REVIEW METHOD IDENTIFIED BY THE EPA'S SCIENCE ADVISORY COMMITTEE ON CHEMICALS (SACC) INCLUDE:

- Failure to use a published protocol for any of the chemicals that have undergone draft risk evaluations
- Failure to use a complete literature review process, which incorporates only select best practices for conducting a systematic and transparent literature review
- The use of a quantitative scoring method that is incompatible with the best available science in fundamental ways and can exclude relevant studies from consideration in the risk evaluation
- Failure to adequately define how EPA integrates the evidence from different streams to come to a determination on whether a chemical exposure presents an "unreasonable risk"

We recommend EPA implement a systematic review method that is compatible with empirically based existing methods and aligns with the National Academy of Medicine's definition of a systematic review, including but not limited to, using explicit and pre-specified scientific methods for every step of the review.

EPA should immediately implement a science-based systematic review method for the ongoing TSCA risk evaluations and use the same systematic review method for hazard identification, characterization and risk assessment across the Agency that has been demonstrated for use in environmental health, and which has been endorsed and utilized by the National Academies of Sciences, Engineering, and Medicine (NASEM) i.e., the National Toxicology Program's OHAT method and the Navigation Guide developed by the University of California, San Francisco.

SUPPORTING EVIDENCE

EPA should implement a science-based systematic review method that aligns with the National Academy of Medicine's definition of a systematic review, including but not limited to, using explicit and pre-specified scientific methods for every step of the review.

The National Academy of Medicine, which has 21 standards covering the entire systematic review process that, if adhered to, result in a scientifically valid, transparent, and reproducible systematic review, defines a systematic review as a "scientific investigation that focuses on a specific question and uses

Almost a decade ago, these empirically proven methods for research synthesis were adapted through an interdisciplinary collaborative effort for environmental health beginning with the development and implementation of the University of California, San Francisco (UCSF) "Navigation Guide Systematic Review Method."¹⁷ This was followed by the publication of the National Toxicology Program's Office of Health Assessment and Translation (OHAT) "Approach for Systematic Review and Evidence Integration for Health Effects Evaluations."¹⁸ Both the Navigation Guide and the OHAT method have been used or recommended by the National Academies of Sciences, Engineering, and Medicine (NASEM), and demonstrated in six case studies^{19,20,21,22,23,24,25,26} in the peer-reviewed literature. The World Health Organization and International Labor Organization (WHO/ILO) are using the Navigation Guide to conduct systematic reviews to assess the global burden of work related injury and disease due to exposure to occupational risk factors.²⁷ Therefore, these proven methods could be easily transferred and used immediately for all ongoing evaluations conducted under TSCA.

Further, EPA should use the same systematic review method for hazard identification, characterization and risk assessment across the Agency. The NASEM has cited both of these systematic review methods as exemplary of the type of methods EPA should use in hazard and risk assessment.^{4,5,6} Further, the NASEM utilized both methods in its 2017 assessment of the potential health impacts of endocrine active environmental chemicals.⁴ Specifically, in its 2017 review the NASEM found:

"The two approaches [OHAT and Navigation Guide] are very similar... and they are based on the same established methodology for the conduct of systematic review and evidence assessment (e.g., Cochrane Collaboration, AHRQ Evidence-based Practice Center Program, and GRADE). Both the OHAT and Navigation Guide methods include the key steps recommended by a previous National Academies committee (NRC 2014) for problem formulation, protocol development, specifying a study question, developing PECO statement, identifying and selecting the evidence, evaluating the evidence, and integrating the evidence."²⁸

To assess the harms in human studies, instead of conducting an entirely new review, NASEM used the Navigation Guide published systematic review on PBDE flame retardant exposure and IQ and concluded that:

"To assess the human evidence, the committee critically evaluated the methods of a recent systematic review conducted by Lam et al... Judging that this existing review fulfilled the requirements of a systematic review and that there was no evidence of risk of bias in the assessment, the committee used the Lam et al. review as a basis for its own assessment."²⁹

Further, systematic reviews have been adopted by EPA's Integrated Risk Information System (IRIS) program and in 2014, NASEM recommended that the IRIS Program use the OHAT method.

EPA should invest in training and implementation for risk assessors in best practices in systematic review across the Agency. This would allow for greater consistency across the Offices within the Agency for how these assessments are conducted, the ability to share knowledge, learning and resources, and allow the Agency to be at the forefront of cutting-edge methodological advancements for systematic review methods globally. It would allow for consistency across Agency offices that conduct hazard identification, hazard characterization and risk assessment.

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