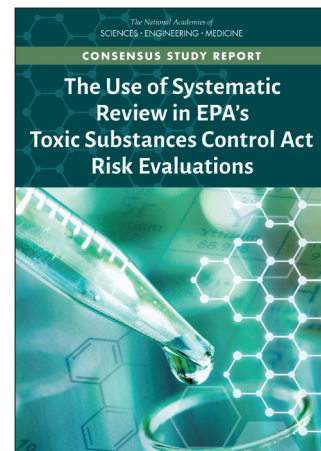




## The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations



Exposures to industrial chemicals in food, water, air, and in consumer products can cause harm to human health and the environment. Risk assessment is a key public-policy tool to inform decision-making to protect public health and ecological receptors from unsafe environmental exposures to chemicals. The U.S. Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) conducts chemical risk assessments to inform federal policy-making in accordance with the Toxic Substances Control Act (TSCA) of 1976.

Growing calls for reform of TSCA—which has not been updated to reflect both changes in chemical production and use or advances in understanding of exposure to and effects of chemicals in the environment—culminated in passage of the Frank R. Lautenberg Chemical Safety for the 21st Century Act in June 2016. The Lautenberg Act provides the OPPT increased authority to regulate chemicals existing before the original 1976 TSCA was amended.

The Lautenberg Act gave EPA new authority to regulate chemicals. Stakeholders called for the adoption of systematic review within these important risk evaluations. That new authority came with a timetable that imposed tight deadlines on OPPT as it assembled teams, promulgated rules, and drafted the guidance documents, and operating procedures that prescribe how OPPT exerts its new authority.

In 2018, after beginning the first ten chemical risk evaluations under the Lautenberg Act, OPPT released the document “Application of Systematic Review in TSCA Risk Evaluations” to guide the Agency’s selection and review of studies. The document details the agency’s new standard approach for systematic reviews used in TSCA chemical risk evaluations. This National Academies report reviews that document and other materials and provides an assessment of and recommendations on how to improve OPPT’s approach.

### USE OF SYSTEMATIC REVIEW IN HAZARD ASSESSMENT

Systematic review has become the foundation for assessing evidence to be used for decision-making in a variety of health contexts, including health care and public health. Well-conducted systematic reviews methodically identify, select, assess, and synthesize the relevant body of research, and clarify what is known and not known about the potential benefits and harms of the exposure being researched.

In recent years, there has been a trend to apply systematic review for gathering evidence to increase transparency, objectivity, and reproducibility of risk assessments. EPA has been using systematic review since the 2011 National Research Council review of

the Integrated Risk Information System’s formaldehyde assessment.

Figure S-1 provides a schema for how systematic review can be conducted to inform hazard assessment and make risk determinations. This synthesis of the various, specific streams of evidence is followed by hazard assessment with integration of the multiple evidence streams of human, animal or ecological receptors, and mechanistic evidence. Questions about human and ecological exposures could also be evaluated with systematic review, but systematic review tools for gathering and evaluating exposure data are not well developed. Exposure and hazard data are integrated to characterize risk (Figure S-1).

### OPPT APPLICATION OF SYSTEMATIC REVIEW TO EXPOSURE ASSESSMENT

Systematic review approaches have been used widely to assemble the evidence needed to assess human health and ecological receptors. Yet, the use of systematic review to collect, evaluate, and synthesize evidence streams that contribute to the exposure assessment of human and ecological receptors have not yet been established, and there is very little precedence for applying systematic review to these streams of evidence. The guidance that dictates how exposure, fate and transport, and physical chemical property data should be assembled for decisions about risks to human health and ecological receptors are contained in the Guidelines for Human Exposure Assessment, and the Guidelines for Ecological Risk Assessment.

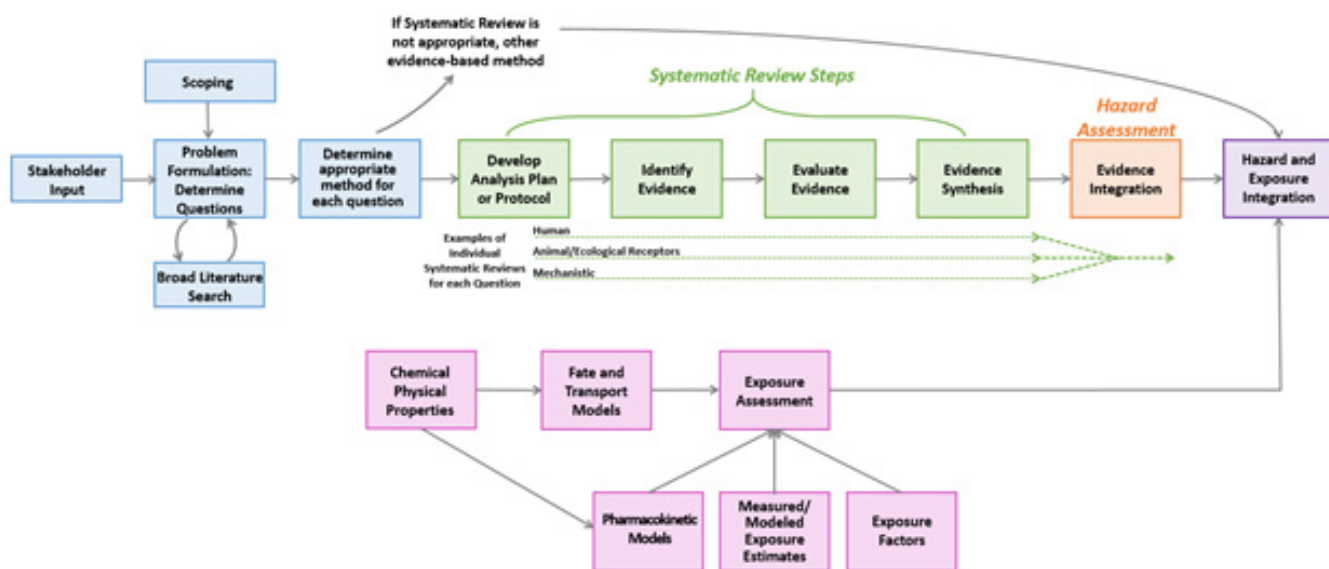
Figure S-2 illustrates the OPPT’s approach to systematic review, which differs to an extent from the above description and includes the systematic review as part of the broader process of risk evaluation. To evaluate the evidence, OPPT has developed an extensive de novo critical appraisal tool, termed TSCA’s “fit-for-purpose evaluation framework,” which is applied to human, animal or ecological receptors, mechanistic, as well as exposure, fate, and chemical-physical property studies. OPPT has stated that the evaluation strategies were developed after review of various qualitative and quantitative scoring systems. The critical appraisals for different types of studies use different domains and within each domain there are several metrics or questions.

### CRITIQUING THE OPPT APPROACH

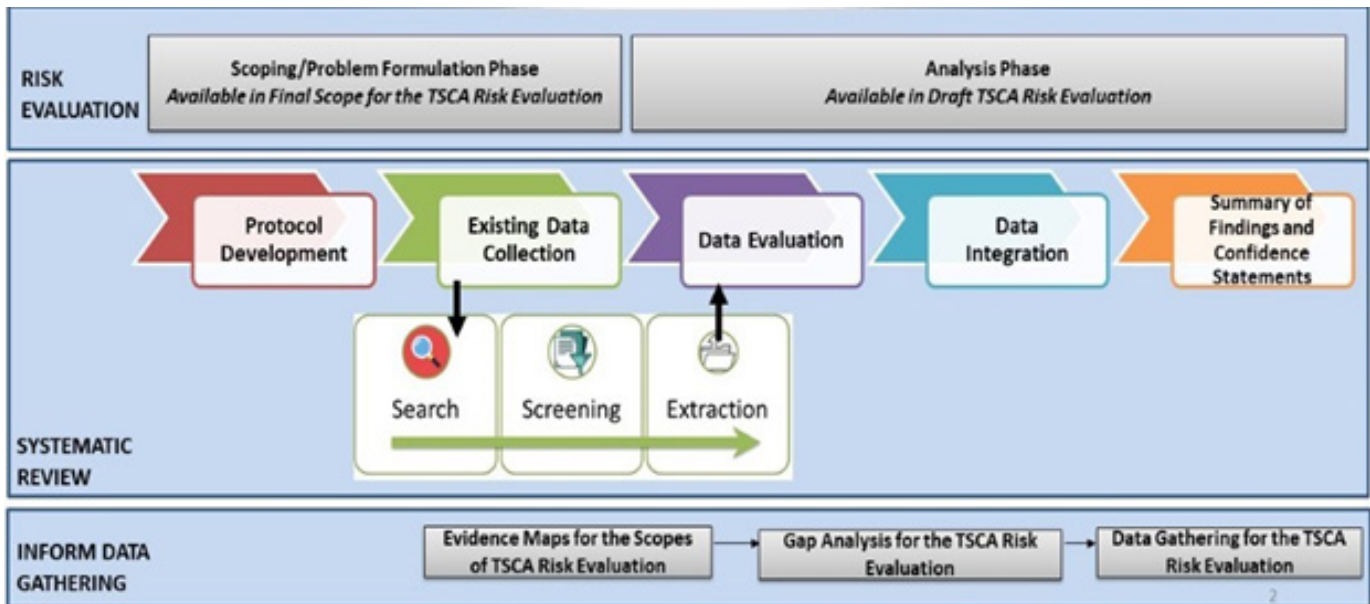
The committee that authored this report was asked to evaluate whether the TSCA approach to systematic review is “comprehensive, workable, objective, and transparent.” The committee concluded the approach presented by OPPT could be broadly improved to better meet these characteristics for the major review steps. The following problems were identified.

### Findings on Comprehensiveness

The OPPT approach was not comprehensive at each step. OPPT’s approach to problem formulation and protocol development did not result in refined research questions or a documented study protocol,



**FIGURE S-1** Example approach of systematic review in the context of risk assessment. The blue boxes refer to steps that are conducted prior to the systematic review, green denotes the systematic review process, orange denotes the hazard assessment, and purple the integration of hazard and exposure. The pink boxes refer to the exposure assessment, which is conducted outside of the systematic review, but is used to make the final risk characterization.



**FIGURE S-2** The systematic review process for TSCA risk evaluations.

which resulted in challenges to integration across evidence streams. While the OPPT approach for identifying the evidence is comprehensive in regard to searching for literature in many databases, it is less clear how comprehensive the searches are for data that support models for ecological assessment and human health exposure assessment. In the TCE evaluation, for example, the hydrology data and product use information were both decades old. Other issues include inadequate guidance on and evaluation of models used in the risk assessment, and shortcomings with including all of the elements important to addressing the research question.

### Findings on Workability

Considering whether the OPPT approach is workable, the report notes several concerns at each step. The current approach taken to problem formulation and protocol development is adding to a laborious process for searching, screening, and evaluating the literature. Although OPPT is using a number of validated artificial intelligence-based tools to help make the process of screening hundreds of references more efficient, their use requires that precise and explicit inclusion and exclusion criteria are used consistently by all reviewers.

The evidence evaluation step includes items that do not assess risk of bias, most notably relevance. Relevance should be handled prior to study evaluation. Later, relevance can also be addressed in the evaluation of the body of evidence. The use of numerical scoring in critical appraisal does not follow standards for the conduct of systematic reviews and no justifi-

fication is provided for the weighting of the specific metrics within the domains to create the overall quality score, making it hard to determine if the weights are appropriate.

Lastly, without a clear, documented approach to evidence synthesis and to integration, the risk evaluation process becomes unworkable because staff have to decide on approaches for these critical steps for each new evaluation rather than relying on a protocol or guidance.

### Findings on Objectivity

The committee found the OPPT approach to be lacking objectivity at each step, from not using a defined approach to documenting how the problem formulation and protocol are developed. Further examples include: having too broad inclusion and exclusion criteria when identifying the evidence; having little evidence that the evaluation metrics had been validated or tested for reliability, as well as allowing a single reviewer to override them; and the lack of a consistent approach for documenting the objectives or methods for synthesis and evidence integration. The committee found that many of these concerns were related to not having a protocol a priori or combining the traditionally discrete and distinct steps of a systematic review.

### Findings on Transparency

The committee found that transparency of the entire risk evaluation process is compromised across all of its elements. In addition to not developing clear questions for the systematic reviews, there are no

protocols for the reviews. Consequently, the review process is not documented from its start, and clarity is lacking when the review is finished and published. Overall, the committee found that the lack of information and needed details about the specific processes used for the identification of evidence reduced confidence in the findings.

## CONCLUSIONS AND RECOMMENDATIONS

The report's authoring committee concludes that the process outlined in the guidance document, and as elaborated and applied in the example evaluations considered by the committee, does not meet the criteria of "comprehensive, workable, objective, and transparent."

The committee also concludes that the systematic reviews within the draft risk evaluations considered did not meet the standards of systematic review methodology. The report makes the following suggestions to improve the OPPT approach.

- The OPPT approach to systematic review does not adequately meet the state-of-practice. OPPT should reevaluate its approach to systematic review methods, addressing the comments and recommendations in this report.
- With regard to hazard assessment for human and ecological receptors, OPPT should step back from the approach that it has taken and consider components of the OHAT, IRIS, and Navigation Guide

methods that could be incorporated directly and specifically into hazard assessment.

- OPPT's use of systematic review for the evidence streams for which it has not been previously adapted have been particularly unsuccessful. Given these novel applications of systematic review, OPPT should elaborate plans for continuing the refinement of methods, ideally in collaboration with internal and external stakeholders. OPPT also should evaluate how the existing OHAT, IRIS, and Navigation Guide methods could be modified for the other evidence streams. In addition, OPPT should use existing guidance within the agency such as the Guidelines for Human Exposure Assessment, the Guidelines for Ecological Risk Assessment, and the operating procedures for the use of the ECOTOX knowledgebase. Following existing guidelines would improve transparency of the assessments.
- OTTP should create a handbook for TSCA review and evidence integration methodology that details the steps in the process. The effort to develop and publicly vet a handbook could help make the process more straightforward, transparent, and easier to follow.

Finally, OPPT should engage in on-going cross-sector efforts on developing and validating new tools and approaches for exposure, environmental health, and other new areas of application of systematic review.

---

## COMMITTEE TO REVIEW EPA'S TSCA SYSTEMATIC REVIEW GUIDANCE DOCUMENT

**Jonathan M. Samet** (NAM) (Chair), Colorado School of Public Health; **Deborah H. Bennett**, University of California, Davis; **Bryan W. Brooks**, Baylor University; **Jessica L. Myers**, Texas Commission on Environmental Quality; **Kristi Pullen Fedinick**, Natural Resources Defense Council; **Karen A. Robinson**, Johns Hopkins University School of Medicine; **Joseph V. Rodricks**, Ramboll, Arlington, VA; **Katya Tsaioun**, Johns Hopkins Bloomberg School of Public Health; and **Yiliang Zhu**, University of New Mexico. Staff of the National Academies of Sciences, Engineering, and Medicine: **Elizabeth Barksdale Boyle** (Project Director); **Andrea Hodgson** (Senior Program Officer); and **Tamara Dawson** (Program Coordinator).

**For More Information . . .** This Consensus Study Report Highlights was prepared by the National Academies of Sciences, Engineering, and Medicine based on the Consensus Study Report *The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations* (2021). The study was sponsored by the U.S. Environmental Protection Agency. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project. Copies of the Consensus Study Report are available from the National Academies Press, (800) 624-6242; <http://www.nap.edu> or via the Board on Environmental Studies and Toxicology web page at <http://www.nationalacademies.org/best>.

---

Division on Earth and Life Studies

*The National Academies of*  
SCIENCES · ENGINEERING · MEDICINE

The nation turns to the National Academies of Sciences, Engineering, and Medicine for independent, objective advice on issues that affect people's lives worldwide.

[www.national-academies.org](http://www.national-academies.org)