UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Comments of Safer Chemicals Healthy Families et al. on Application of Systematic Review in Risk Evaluations under Section 6 of the Amended Toxic Substances Control Act

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Safer Chemicals Healthy Families and the undersigned groups submit these comments on EPA's June 11, 2018 document for applying "systematic review" methods in risk evaluations conducted under the Toxic Substances Control Act (TSCA).[1] The commenters listed below are public health and environmental organizations committed to assuring the safety of chemicals used in our homes, workplaces and the many products to which our families and children are exposed each day. We took a leadership role during the TSCA legislative process, advocating the most protective and effective legislation possible to reduce the risks of toxic chemicals in use today.

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Alliance of Nurses for Healthy Environments
Asbestos Disease Awareness Organization
Center for Environmental Health
Clean and Healthy New York
Clean Production Action
Clean Water Action
Clean Water Action (Connecticut)
Colorado PIRG (CoPIRG)
Environmental Health Strategy Center
Healthy Building Network
League of Conservation Voters
Learning Disabilities Association of America
Maryland PIRG
Natural Resources Defense Council
Science and Environmental Health Network
Texas PIRG (TexPIRG)
Toxic-Free Future
U.S. PIRG
WashPIRG
WE ACT for Environmental Justice
Women for a Healthy Environment

EPA is now conducting its first round of risk evaluations under the new TSCA section 6(b) requirements. These precedent-setting evaluations are addressing 10 major chemicals, including substances of long-standing concern such as asbestos, methylene chloride and trichloroethylene. The TSCA systematic review document will have far-reaching implications for the science judgments that inform these risk evaluations and determine how and whether EPA meets its obligation under section 26(h) of TSCA to base decisions on chemical risks on the "best available science" and the "weight of the scientific evidence."

We are very concerned that the TSCA systematic review document represents a deeply flawed and unscientific approach to systematic review that will compromise the quality, validity and public health value of the initial 10 risk evaluations.

"Systematic review" is a well-established framework for evaluating and integrating scientific evidence to arrive at judgments about hazard, exposure and risk. EPA's own risk evaluation process rule under TSCA section 6(b)(4) describes a systematic review methodology as --

> "a pre-established protocol to comprehensively, objectively, transparently, and consistently, identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance." 40 CFR § 702.33

However, the TSCA systematic review document departs radically from accepted scientific principles for systematic review adopted by the Institute of Medicine (IOM),[2] the National Toxicology Program (NTP)[3] and EPA's Integrated Risk Information System (IRIS)[4] and endorsed by the National Academy of Sciences (NAS)[5,6,7] and other peer review bodies.

Instead of establishing a multi-faceted and transparent process to evaluate and synthesize available data to reach broad scientific judgments about the evidence as a whole, the TSCA systematic review document will result in arbitrary judgments about study "quality" that narrow the range of factors on which EPA bases determinations of hazard and exposure and exclude relevant data from decision-making. Together with EPA's discredited proposed Science Transparency Rule[8] precluding reliance on studies unless all underlying data are available, the TSCA systematic review document will further restrict the body of evidence that informs EPA judgments about risk and hamper the Agency's ability to use the most relevant and meaningful data for decision-making.

EPA plans to release drafts of the 10 risk evaluations by the end of 2018. This means that, as a practical matter, EPA will complete the study reviews for the draft evaluations using the TSCA systematic review document in its current form – *before* any external peer review and without any consideration of public comments. As described below, we strongly oppose this approach and urge EPA to put the TSCA systematic review document on hold and instead conduct the risk evaluations using one of the available systematic review protocols that has been published in the scientific literature and peer reviewed. The absence of external peer review of the TSCA peer review method – an essential requirement applied by EPA and OMB for all major science products that will support regulatory decisions – is alone a bar to using the document for the ongoing risk evaluations.

EPA's Arbitrary Scoring System for Study Quality

As EPA acknowledges, its TSCA systematic review document only addresses one element of systematic review -- study quality. The document would apply a rigid scoring system to grade the quality of studies on chemicals against certain benchmarks and then calculate a composite score for the study as a whole. The TSCA benchmarks for study quality and formula for calculating a composite score lack any empirical support. 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. This system could result in many studies being arbitrarily classified as "poor"

or "unacceptable" based on a small number of reporting or methodology limitations that do not negate the studies' value in understanding a chemical's health risks.

Other systematic review methodologies do not use numerical scoring systems for assessing study quality and in fact expert bodies strongly recommend against numerical scoring for this purpose. As stated by the Institute of Medicine, "… systematic review teams have moved away from scoring systems to assess the quality of individual studies toward a focus on the components of quality and risk of bias." The Cochrane Collaboration, founded in 1993, is an international non-profit and independent organization that possesses the world's most authoritative expertise on systematic review methods. This organization states: "The current standard in evaluation of clinical research calls for reporting each component of the assessment tool separately *and not calculating an overall numeric score* (emphasis added)."[9] The National Academy of Sciences (NAS) recently reviewed the systematic review method of the EPA Integrated Risk Information System (IRIS) and strongly argued against quantitative scoring, stating:

> … Cochrane discourages using a numerical scale because calculating a score involves choosing a weighting for the subcomponents, and such scaling generally is nearly impossible to justify (Juni et al. 1999). Furthermore, a study might be well designed to eliminate bias, but because the study failed to report details in the publication under review, it will receive a low score. Most scoring systems mix criteria that assess risk of bias and reporting. However, there is no empirical basis for weighting the different criteria in the scores. Reliability and validity of the scores often are not measured. Furthermore, quality scores have been shown to be invalid for assessing risk of bias in clinical research (Juni et al. 1999). The current standard in evaluation of clinical research calls for reporting each component of the assessment tool separately and not calculating an overall numeric score (Higgins and Green 2008) (Pg. 69).[5]

The TSCA scoring system will mean that important evidence of public health impacts – particularly epidemiological studies demonstrating harm in human populations – will be unjustifiably disregarded or given limited weight in the 10 risk evaluations. Long-standing scientific and regulatory findings about these chemicals' risks may then be reversed or called into question, weakening protections of health and the environment.

Over-reliance on Reporting of Data as an Indicator of Study Quality

The TSCA scoring system is heavily weighted toward using the completeness of reporting of study methods and data as a proxy for study quality. However, reporting is not in itself an indicator of study quality and the TSCA reporting metrics do not directly correlate with the reliability and relevance of study findings. Moreover, there are no precise conventions for how much and what type of information should be reported on studies. The level of reporting has varied over time, depending on the audience for a study, its purpose, perceived information needs of peer reviewers and users of the data, and the presence or absence of regulatory requirements. A mechanical scoring system that overlooks these factors and does not consider reporting as part of a holistic evaluation of study quality will erroneously disregard or downgrade studies that contribute significantly to an understanding of risk.

The TSCA reporting benchmarks are skewed toward industry studies conducted to satisfy regulatory requirements, which demand compliance with Good Laboratory Practice (GLP) standards and "guidelines" prescribing study protocols. Researchers in an academic setting are not subject to these requirements and may employ different standards for reporting study methods and results. Yet through the selection of doses and test species and criteria for interpreting histopathological findings, the industry-sponsored studies may be designed to avoid adverse findings. This evidence of bias may call into question the relevance and quality of the findings, despite adherence to GLPs and established protocols. A scoring system fixated narrowly on reporting will overlook these concerns.

The authors of the STROBE guidelines for improving reporting of epidemiology studies specifically note that adequacy of reporting should not be equated with the quality of the underlying research:

> "The STROBE Statement is a checklist of items that should be addressed in articles reporting on the 3 main study designs of analytical epidemiology: cohort, case control, and cross-sectional studies. *The intention is solely to provide TSCA systematic review on how to report observational research well; these recommendations are not prescriptions for designing or conducting studies. Also, while clarity of reporting is a prerequisite to evaluation, the checklist is not an instrument to evaluate the quality of observational research* (emphasis added). … Our intention is to explain how to report research well, not how research should be done. We offer a detailed explanation for each checklist item. Each explanation is preceded by an example of what we consider transparent reporting. This does not mean that the study from which the example was taken was uniformly well reported or well done; nor does it mean that its findings were reliable, in the sense that they were later confirmed by others: it only means that this particular item was well reported in that study"(emphasis added)."[10]

The TSCA systematic review document uses its checklist of reporting practices in exactly the way that STROBE cautions against.

Lack of Critical Systematic Review Elements

The TSCA systematic review document is also fundamentally incomplete because it focuses on one limited aspect of systematic review – study quality – but fails to address other critical elements that the Agency itself recognizes are essential for science-based risk judgments. EPA's July 2017 risk evaluation framework rule defines systematic review as a comprehensive, consistent and transparent process to "identify and evaluate each stream of evidence" and "to integrate evidence as necessary and appropriate based on strengths, limitations, and relevance."[11] Yet the TSCA systematic review document lacks any protocol for determining the strengths and relevance of individual studies, grouping them into streams of evidence and integrating these streams into a set of judgments about the weight of the evidence as a whole.

EPA admits that it is proceeding with its first 10 risk assessments in the absence of a pre-defined protocol that addresses all the elements of systematic review:

> … the purpose of the document is internal TSCA systematic review that … sets out general principles to guide EPA's application of systematic review in the risk evaluation process for the first ten chemicals … *EPA had limited ability to develop a protocol document detailing the systematic review approaches and/or methods prior to the initiation of the risk evaluation process for the first ten chemical substances. For these reasons, the protocol development is staged in phases while conducting the assessment work" (emphasis added).* Additional details on the approach for the evidence synthesis and integration will be included with the publication of the draft TSCA risk evaluations.[1]

It is universally recognized that systematic review methods need to be established in advance of individual evaluations to eliminate the potential for bias and to assure that evidence reviews are conducted using consistent, well-defined criteria. Yet the TSCA program is conducting its risk evaluations **before** these methods are in place, will develop them in parallel with the evaluations, and will document them only in its final risk evaluations, requiring the public and peer reviewers to comment on EPA's approach only after-the-fact.[1] Not only is this a violation of the systematic review principles the Agency has adopted in the framework rule, but it also heightens the danger that EPA's arbitrary scoring system for study quality – and not a broad process of evaluating and integrating streams of evidence – will drive EPA's judgments about risk, raising serious doubt whether EPA has in fact relied on the "best available science" as required by TSCA.

Absence of Intra-agency, Interagency and External Peer Review

Disturbingly, despite its lack of consistency with both IRIS and NTP protocols, the TSCA systematic review document was rushed out the door without the in-depth intra-agency and inter-agency review and external peer review required for major science policies under EPA and OMB guidelines.

Because it "involves a significant new use of science" and "science issues [that] are controversial, unresolved or unaccepted," the TSCA systematic review document should have been designated as a Tier 2 action under EPA's Action Development Process (ADP).[12] This would have resulted in a robust cross-agency workgroup process in which experts could examine the relative merits of the IRIS and TSCA approaches to systematic review. Similarly, OMB and EPA should have treated the TSCA systematic review document as "significant" under Executive Order 13422[13] and convened an inter-agency process that enabled HHS/NTP to critique the TSCA approach based on their extensive systematic review expertise.

Most importantly, because it is "novel, controversial, [and] precedent setting [and] has significant interagency interest," the TSCA systematic review document clearly qualifies as a Highly Influential Scientific Assessment (HSIA) and Influential Scientific Information (ISI) under the EPA Peer Review Handbook[14] and the OMB Peer Review Bulletin.[15] Thus, external peer review with public participation was required to determine the scientific validity and reliability of the TSCA document – a step that plainly did not occur despite the long-standing commitment of EPA and OMB to rigorous peer review to assure that agencies meet the highest scientific standards in making regulatory decisions. It would be a violation of this commitment to implement the TSCA systematic review document in conducting the 10 risk evaluations.

Next Steps: Assuring that EPA Applies Scientifically Acceptable Peer Reviewed Systematic Review Methods in the 10 Ongoing Risk Evaluations

With impending deadlines to complete the 10 evaluations, EPA should withdraw the TSCA systematic review document and instead implement systematic review methods that have been demonstrated for use in environmental health assessments and endorsed by the NAS. Examples include the NTP Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration[3] and the Navigation Guide Systematic Review Method.[16] These protocols can be applied immediately because they have already been peer reviewed and represent a broad scientific consensus.

We appreciate this opportunity to comment on the TSCA systematic review. Please contact SCHF counsel Bob Sussman at bobsussman1@comcast.net with any questions.

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