

**EPA SCIENTIFIC ADVISORY COMMITTEE ON CHEMICALS CHARGE
TO THE PANEL – 1,4-DIOXANE REVIEW**

As amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act on June 22, 2016, the Toxic Substances Control Act (TSCA), requires the U.S. Environmental Protection Agency (EPA) to conduct risk evaluations on existing chemicals. In December of 2016, EPA published a list of the initial ten chemical substances that are the subject of the Agency's chemical risk evaluation process ([81 FR 91927](#)), as required by TSCA. 1,4-Dioxane is one of the first ten chemical substances and the second of the ten to undergo a peer review by the Scientific Advisory Committee on Chemicals (SACC). In response to this requirement, EPA released a scope document and a problem formulation document for 1,4-dioxane which solicited comments from the public and incorporated them as appropriate in the documents considered in this review. The documents that are part of this review include:

1. Draft Risk Evaluation for 1,4-Dioxane
2. Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies
3. Systematic Review Supplemental File: Data Quality Evaluation for Environmental Releases and Occupational Exposure Data Sources
4. Systematic Review Supplemental File: Data Quality Evaluation of Environmental Hazard Studies
5. Systematic Review Supplemental File: Data Quality Evaluation of Environmental Fate and Transport Studies
6. Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies, Animal and In Vitro Studies
7. Systematic Review Supplemental File: Data Quality Evaluation of Epidemiological Studies
8. Aquatic Exposure Screen Facility Information
9. Risk Calculator (Excel Spreadsheet)

1,4-Dioxane is a clear volatile liquid used primarily as a solvent and is subject to federal and state regulations and reporting requirements. 1,4-Dioxane has been reportable to Toxics Release Inventory (TRI) chemical under Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA) since 1987. It is designated a Hazardous Air Pollutant (HAP) under the Clean Air Act (CAA), and is a hazardous substance under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). It was listed on the Safe Drinking Water (SDWA) Candidate Contaminant List (CCL) and identified in the third Unregulated Contaminant Monitoring Rule (UCMR3).

1,4-Dioxane is currently manufactured, processed, distributed, and disposed of following use in industrial processes with industrial and commercial conditions of use. Manufacturing sites produce 1,4-dioxane in liquid form at concentrations greater or equal to 90% and 1,4-dioxane is also imported. EPA evaluated the following conditions of use: manufacturing; processing; functional fluids in open and closed systems; laboratory chemicals; adhesives and sealants (professional film cement); spray polyurethane foam; printing and printing compositions; disposal of waste materials containing 1,4-dioxane; and dry film lubricant. The total aggregate production volume is approximately 1 million pounds.

The draft risk evaluation contains the following components:

- Executive Summary
- Discussion of chemistry and physical-chemical properties
- Characterization of uses/sources
- A description of the systematic review process used to search, screen, and evaluate scientific literature
- Environmental fate and transport assessment
- Environmental exposure assessment
- Human exposure assessment
- Human health hazard assessment
- Environmental hazard assessment
- Risk characterization
- Risk determination
- Various technical appendices

The focus of this meeting is to conduct the peer review of the Agency's draft risk evaluation of 1,4-dioxane and associated supplemental materials. At the end of the peer review process, EPA will use the reviewers' comments/recommendations, as well as public comment, to finalize the risk evaluation.

CHARGE QUESTIONS:

EPA is seeking SACC advice on the clarity and scientific underpinnings of the overall assessment. The peer review should consider whether the conclusions presented in the draft risk evaluation are clearly presented, scientifically supported and based on the best available scientific information. The SACC should also consider whether the methods employed to generate the information are reasonable for and consistent with the intended use of the information. As per TSCA, where unreasonable risks are identified, once finalized the risk evaluation will be used to support rulemaking to mitigate identified risks.

Throughout the peer review, the SACC should be mindful that TSCA now requires that EPA use data and/or information in a manner consistent with the "best available science" and that EPA base decisions on the "weight of the scientific evidence". The EPA's Final Rule, [*Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* \(82 FR 33726\)](#), defines "best available science" as science that is reliable and unbiased. This involves the use of supporting studies conducted in accordance with sound and objective science practices, including, when available, peer reviewed science and supporting studies and data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data). The Final Rule also defines the "weight of the scientific evidence" as a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses 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.

Below, are a set of charge questions for each major analysis are presented. The SACC is expected to consider questions and issues raised during public comment as part of its deliberations.

1. *Content and Organization:*

EPA's Final Rule, [Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act \(82 FR 33726\)](#) stipulates the process by which EPA is to complete risk evaluations under the Frank R. Lautenberg Chemical Safety for the 21st Century Act.

As part of this draft risk evaluation for 1,4-dioxane, EPA evaluated potential environmental and occupational exposures. The evaluation considered reasonably available information, including manufacture, use, and release information, and physical-chemical characteristics. It is important that the information presented in the risk evaluation and accompanying documents is clear and concise and describes the process in a scientifically credible manner.

- Please comment on the overall content, organization, and presentation of the draft risk evaluation of 1,4-dioxane. Please provide suggestions for improving the clarity of the information presented in the documents.

2. *Systematic Review:*

To meet the scientific standards required by TSCA, EPA applied systematic review approaches and methods to support the draft risk evaluation of 1,4-dioxane. Information on the approaches and/or methods is described in the draft risk evaluation as well as the following documents:

- [1,4-Dioxane Problem Formulation](#)
 - [Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental file for the TSCA Scope Document](#)
 - [Application of Systematic Review in TSCA Risk Evaluations](#)
 - [1,4-Dioxane \(CASRN: 123-91-1\) Bibliography: Supplemental File for the TSCA Scope Document](#)
- Please comment on the approaches and/or methods used to support and inform the gathering, screening, evaluation, and integration of information used in the draft risk evaluation of 1,4-dioxane.
 - Please also comment on the clarity of the information as presented related to systematic review and suggest improvements as warranted.

3. *Exposure and Releases:*

Key data that informed the occupational exposure assessment include: the OSHA Chemical Exposure Health Data (CEHD), ATSDR assessments, ECHA dossiers, and NIOSH Health Hazard Evaluation (HHE), program data.

- Please comment on the characterization of occupational inhalation exposure for workers and occupational non-users for each of the identified conditions of use. What other additional information, if any, should be considered?
- Please comment on the characterization of occupational dermal exposure for workers. What other additional information, if any, should be considered?
- Please comment on the approach for characterizing the different use scenarios. Are there

any additional 1,4-dioxane specific data and/or information that should be considered?

4. *Environmental Fate, Exposure & Effects:*

As part of problem formulation, EPA qualitatively analyzed the sediment, land application and biosolids pathways based on 1,4-dioxane's physical/chemical and fate properties. EPA also quantitatively assessed environmental exposures and hazards to aquatic receptors. The results of the analyses are described in the 2018 problem formulation for 1,4-dioxane and presented again in Appendices C – E of the draft risk evaluation.

- Please comment on the data, approaches and/or methods used to characterize exposure to aquatic receptors.

5. *Human Health:*

The evaluation of human health hazards included:

- Reviewed reasonably available human health hazard data.
 - In evaluating reasonably available data, determined whether particular human receptor groups may have greater susceptibility to the chemical's hazard(s) than the general population.
 - Conducted hazard identification (the qualitative process of identifying non-cancer and cancer endpoints) and dose-response assessment (the quantitative relationship between hazard and exposure) for all identified human health hazard endpoints.
 - Derived points of departure (PODs) where appropriate and conducted benchmark dose modeling, when data supported the approach.
 - Adjusted the PODs to conform (e.g., adjusted for duration of exposure) to the specific exposure scenarios evaluated.
 - Considered the route(s) of exposure (inhalation and dermal) and route-to-route extrapolation approaches.
 - Evaluated the weight of the evidence of human health hazard data.
- Please comment on the evaluation of human health hazards including evaluation of portal of entry and systemic toxicity for cancer and non-cancer. Are there any additional 1,4-dioxane specific data and/or information that should be considered?
 - Please comment on any other aspects of the human health risk characterization that has not been mentioned above.

EPA has provided a summary of mode action information for a mutagenic mode of action and non mutagenic mode of action, in particular for rat liver tumors.

- Please comment on mode of action discussion and provide feedback on mode of action analysis.

EPA has provided alternative dose response analysis for non linear and linear extrapolation for cancer.

- Please provide comments on the approaches presented. Please provide comments on any

additional model consideration that EPA could include for cancer characterization.

7. Risk Characterization:

After consideration of all information identified by EPA that pertains to 1,4-dioxane, EPA concluded that 1,4-dioxane presents an unreasonable risk of injury to workers due to dermal exposure during particular conditions of use. Human health effects include non-cancer and cancer effects. EPA also concluded that 1,4-dioxane does not present an unreasonable risk of injury to workers and occupational non-users by inhalation exposure or to environmental receptors. EPA made these determinations considering risk to potentially exposed and susceptible subpopulations identified as relevant, under the conditions of use without considering costs or other non-risk factors.

- Please comment on the objectivity of the underlying data used to support the risk characterization and the sensitivity of the agency's conclusions to analytic assumptions made.
- Please comment on the characterization of uncertainties and assumptions including whether EPA has presented a clear explanation of underlying assumptions, accurate contextualization of uncertainties and, as appropriate, the probabilities associated with both optimistic and pessimistic projections, including best-case and worst-case scenarios. Please provide information on additional uncertainties and assumptions that EPA has not adequately presented.
- Please comment on whether the information presented supports the findings outlined in the draft risk characterization section. If not, please suggest alternative approaches or information that could be used to develop a risk finding in the context of the requirements of the EPA's Final Rule, [Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act \(82 FR 33726\)](#).