

EPA SCIENTIFIC ADVISORY COMMITTEE ON CHEMICALS CHARGE TO THE PANEL – PERCHLOROETHYLENE

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. Perchloroethylene (PCE) is one of the first ten chemical substances and the tenth of ten to undergo a peer review by the Scientific Advisory Committee on Chemicals (SACC). In response to this requirement, EPA has prepared and published a draft risk evaluation for PCE. The EPA has solicited comments from the public on the draft and will incorporate them as appropriate, along with comments from peer reviewers, into the final risk evaluation.

The focus of this meeting is to conduct the peer review of the Agency's draft risk evaluation of PCE 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.

This draft risk evaluation contains the following components:

- Discussion of chemistry and physical-chemical properties
- Characterization of uses/sources
- Environmental fate and transport assessment
- Environmental exposure assessment
- Human health hazard assessment
- Environmental hazard assessment
- Risk characterization
- Risk determination
- Detailed description of the systematic review process developed by the Office of Pollution Prevention and Toxics to search, screen, and evaluate scientific literature for use in the risk evaluation process.

CHARGE QUESTIONS:

Systematic Review (Section 1.5 of the Draft Risk Evaluation):

The Toxic Substances Control Act (TSCA) 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 the strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.

To meet these scientific standards, EPA applied systematic review approaches and methods to support the PCE draft risk evaluation. Information on the approaches and/or methods is described in the draft risk evaluation as well as the following documents:

- [*Strategy for Conducting Literature Searches for Perchloroethylene: Supplemental File for the TSCA Scope Document*, \(EPA-HQ-OPPT-2016-0732\)](#)
- [*Perchloroethylene \(CASRN 127-18-4\) Bibliography: Supplemental File for the TSCA Scope Document*, \(EPA-HQ-OPPT-2016-0732\)](#)
- [*Perchloroethylene Problem Formulation*, \(EPA-HQ-OPPT-2016-0732\)](#)
- [*Application of Systematic Review in TSCA Risk Evaluations*](#)

EPA has solicited peer review and public feedback on systematic review approaches and methods for prior evaluations. A general question on these approaches is not included in this charge; however, EPA will accept comment on the systematic review approaches used for this evaluation if provided.

1. Environmental Fate:

EPA qualitatively analyzed the sediment, land application and biosolids pathways based on PCE's physical/chemical and fate properties. Exposure estimates to the environment were developed for the conditions of use for exposures to aquatic organisms.

- 1.1 Please comment on EPA's qualitative analysis of pathways based on physical/chemical and fate properties.
- 1.2 Please comment on the data, approaches and/or methods used to characterize exposure to aquatic receptors.

2. Environmental Exposure and Releases:

EPA evaluated releases to water and aquatic exposures for conditions of use in industrial and commercial settings. EPA used Toxics Release Inventory (TRI) and Discharge Monitoring Report (DMR) data to provide a basis for estimating releases. EPA used these releases and associated inputs within EFAST 2014 to estimate instream chemical concentrations and days of exceedance. EPA also evaluated monitored values of PCE in surface water and where possible compared those values to estimated release concentrations.

- 2.1. Please comment on the data and approaches used to estimate the amounts of wastewater discharge for the different scenarios.
- 2.2 Please comment on the approaches, models, and data used in the water release assessment including comparison to monitored data.
- 2.3 Please provide any specific suggestions or recommendations for alternative data or estimation methods, including modeling approaches, that could be considered by the

Agency for conducting or refining the water release assessment and relation to monitored data.

3. Environmental Hazard:

EPA evaluated environmental hazards for aquatic species from acute and chronic exposure scenarios.

- 3.1. Please comment on EPA's approach for characterizing environmental hazard for each risk scenario (e.g. acute aquatic, chronic aquatic). What other additional information, if any, should be considered?

4. Occupational and Consumer Exposure

EPA evaluated acute and chronic exposures to workers for conditions of use in industrial and commercial settings. For exposure via the inhalation pathway, EPA quantified occupational exposures for both workers and occupational non-users (ONUs) based on a combination of monitoring data and modeled exposure concentrations. For exposure via the dermal route, EPA modeled exposure for workers, accounting for the effect of volatilization. EPA assumed dermal contact with liquids would not occur for occupational non-users. EPA assumed that workers and occupational non-users would be adults of both sexes (>16 and older, including women of reproductive age).

- 4.1. Please comment on the approaches and estimation methods, models, and data used in the occupational exposure assessment.
- 4.2 Specifically, please comment on the Occupational Near-Field/Far-Field models and their input parameters.
- 4.3 Please provide any specific suggestions or recommendations for alternative data or estimation methods that could be considered by the Agency for conducting the occupational exposure assessment.

To estimate ONU inhalation exposure, EPA reviewed personal monitoring data, area monitoring data and modeled far-field exposure concentrations. When EPA did not identify personal or area data on or parameters for modeling potential ONU inhalation exposures, EPA assumed ONU inhalation exposures could be lower than worker inhalation exposures however relative exposure of ONUs to workers could not be quantified. When exposures to ONUs were not quantified, EPA considered the central tendency from worker personal breathing zones to estimate ONU exposures.

- 4.3. Please comment on the assumptions and uncertainties of this approach.
- 4.4. Are there other approaches or methods for assessing ONU exposure for the specific condition of use?
- 4.5 Please comment on this and provide any suggestions and/or data for assessing dermal exposure to ONUs.

Consumer exposure estimates were developed for the conditions of use for inhalation and dermal exposures to consumers. EPA did systematic review, collected data from available sources and conducted modeling for estimating consumer inhalation and dermal exposures using the CEM model.

Product specific consumer monitoring information was not identified during the systematic review process; therefore, model inputs related to consumer use patterns (duration of use, mass of product used, room of use, and similar inputs) are based on survey data found in the literature as described and referenced within the perchloroethylene draft risk evaluation. Weight fraction of chemical within products are based on product specific safety data sheets (SDS). Default values utilized within the models are based on literature reviewed as part of model development as well as EPA's Exposure Factors Handbook.

- 4.5. Please comment on the approaches, models, exposure or use information and overall characterization of consumer inhalation exposure for users and bystanders for each of the identified conditions of use. What other additional information, if any, should be considered?
- 4.6. Please comment on the approaches, models, exposure or use information and overall characterization of consumer dermal exposure for each of the identified conditions of use.
- 4.7. Please comment on whether there are dermal models which would be appropriate to address evaporation during use and/or the amount of product absorbed into the skin during use when evaporation is not hindered. What other additional information or modeling approaches, if any, should be considered?
- 4.8. Please provide any other suggestions or recommendations for alternative approaches, dermal methods, models or other information which may guide EPA in developing and refining the dermal exposure estimates.

4 Human Health Hazard:

EPA used PODs and cancer slope factors (i.e., human equivalent concentration (HEC), inhalation unit risk (IUR) and dermal slope factor) for evaluating the non-cancer and cancer risks, respectively for chronic exposures to Perchloroethylene. PODs were derived from both animal and human studies.

- 5.1. Have the most scientifically robust critical health effects and corresponding PODs been identified for PCE? Are there additional data regarding other health effects for PCE that EPA needs to consider? If data gaps exist in the PCE database, how could the uncertainty about sensitive health effects and critical windows of exposure be better accounted for in the hazard characterization (Section 3.2)?

For the acute human study (Altmann et al, 1990) HECs were developed for both occupational and consumer exposure durations. For chronic PODs, the PBPK model provided HEC outputs for PODs from animal studies adjusted to 24-hr continuous exposure, which were compared to 24hr TWA exposure values during risk estimation. The chronic human

neurotoxicity POD was derived both based on continuous exposure and occupational exposure.

- 5.2. Please comment on EPA's approach for POD derivation, including selection of uncertainty factors and assignment benchmark MOEs for each endpoint. Please also include consideration of the methods and assumptions used for deriving Human Equivalent Concentrations (HECs) for each exposure scenario and receptor type (Section 3.2.5.3).
- 5.3. Please comment on EPA's application of the PBPK model to the dose-response analysis for all endpoints, and the selection of dose metrics when considering the sensitivity, uncertainty, and variability of the data (Sections 3.2.2.2 and 3.2.5.3).
- 5.4. EPA derived dermal HEDs by extrapolating from both oral and inhalation PODs, when available. Please comment on the transparency and clarity of EPA's methodology for deriving dermal PODs and the selection of particular values for risk estimation (Section 3.2.5.4.1).

EPA concluded that the reasonably available evidence supports a complex mode of action (MOA) for tumorigenesis, with contributions from both genotoxicity and non-genotoxic MOAs including cytotoxicity and PPAR α activation. EPA concluded that while these non-genotoxic mechanisms likely play a role in tumorigenesis, a causal link for necessity cannot be established. According to EPA's 2005 Guidelines for Carcinogen Risk Assessment ([U.S. EPA 2005a](#)), evidence for at least a significant contribution of a genotoxic MOA supports use of the low-dose linear assumption, while other mechanisms are not well-enough supported to suggest a potential threshold approach.

- 5.5. Please comment whether the cancer hazard assessment has adequately described and supported the MOA conclusions and the selection of a low-dose linear model and discuss any potential alternative approaches.
- 5.6. Please comment on any other aspects of the human health hazard assessment that have not been discussed, including the data quality evaluation and the characterization of all assumptions and uncertainties (Section 3.2).

5 Risk Characterization:

EPA calculated environmental risk using exposure data (e.g. modeling tools and monitored datasets) and environmental toxicity information, accounting for variability within the environment. EPA concludes that perchloroethylene poses a hazard to environmental aquatic receptors, with algae being the most sensitive taxa identified for aquatic exposures. Risk Quotients (RQs) and the number of days a concentration of concern (COC) was exceeded were used to assess environmental risks. The risk characterization section provides a discussion of the risk and uncertainties around the risk calculations.

EPA calculated human health risks for acute and chronic exposures. For non-cancer effects EPA used a margin of exposure (MOE), which is the ratio of the hazard value to the exposure to calculate human health risks. Using an acute non-cancer POD, EPA evaluated potential acute risks for workers for certain scenarios, consumer users and bystanders/non-users (e.g., children, women

of childbearing age). A benchmark MOE of 10 was used with the acute POD based on neurological (central nervous system (CNS)) effects. For chronic occupational risks, EPA used a POD for liver effects as the basis of the chronic non-cancer MOE calculations. A benchmark MOE of 100 was used to interpret chronic risks for workers. An IUR for liver and lung tumors was used to evaluate potential chronic risks to cancer endpoints for the worker exposure scenarios. The risk characterization also provides a discussion of the uncertainties surrounding the risk calculations.

- 6.1. EPA provided separate chronic inhalation risk estimates for the key chronic endpoint of neurotoxicity using occupational HECs (i.e. assuming 1.25 m³/hr inhalation rate). Please comment on whether EPA sufficiently characterized and evaluated considerations for the effects of differing breathing rates on risk estimates, especially in the context of occupational scenarios. Additionally, please provide any suggestions for adjusting risk estimates from other 24 hr PBPK-derived HECs for occupational scenarios (Appendix G and Supplemental Engineering Report, Appendices B-C).
- 6.2. 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. Are the approaches used for animal-to-human and route-to-route extrapolation adequately supported?
- 6.3. Please provide information on additional uncertainties and assumptions that EPA has not adequately presented.
- 6.4. Please comment on whether the information presented supports the findings outlined in the draft risk characterization section.
- 6.5. 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.

The Frank R. Lautenberg Chemical Safety for the 21st Century Act (2016) (amended TSCA) states that “potentially exposed or susceptible subpopulations” (PESS) be considered in the risk evaluation process. PESS is defined in the Lautenberg Act to include populations with greater exposure or greater response, including due to lifestyle, dietary, and biological susceptibility factors, than the general population.

- 6.6. Has a thorough and transparent review of the available information been conducted that led to the identification and characterization of all PESS (Sections 2.4.3, 3.2.5.2, and 4.4.1)? Do you know of additional information about PESS that EPA needs to consider? Additionally, has the uncertainty around PESS been adequately characterized?

The EPA risk characterization of human health risk from inhalation exposure to workers includes estimates of risk for respirator use. These estimates are calculated by multiplying the high end and central tendency MOE or extra cancer risk estimates without respirator use by the respirator assigned protection factors (APFs) of 10, 25 and 50 (air-supplied respirators). EPA did not assume

occupational non users (ONUs) or consumers used personal protective equipment in the risk estimation process.

- 6.7. Please comment on whether EPA has adequately, clearly, and appropriately presented the reasoning, approach, assumptions, and uncertainties for characterizing risk to workers using air-supplied respirators and to ONUs and consumers who would not be expected to use PPE.

6 Overall 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 perchloroethylene, EPA evaluated potential environmental, occupational and consumer 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.

- 7.1. Please comment on the overall quality and relevance of the resources used in this draft risk evaluation; describe data sources or models that could improve the risk evaluation.
- 7.2 Please comment on the overall content, organization, and presentation of the draft risk evaluation of perchloroethylene.
- 7.3. Please provide suggestions for improving the clarity of the information presented in the documents.