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

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. Trichloroethylene (TCE) is one of the first ten chemical substances and the ninth of the 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 TCE. 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 TCE 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 TCE 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 Trichloroethylene: Supplemental File for the TSCA Scope Document, (EPA-HQ-OPPT-2016-0737)

- Trichloroethylene (CASRN 79-01-6) Bibliography: Supplemental File for the TSCA Scope Document, (EPA-HQ-OPPT-2016-0737)

- Trichloroethylene Problem Formulation (EPA-HQ-OPPT-2016-0737)

- 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 and Exposure:

EPA qualitatively analyzed the sediment, land application, and biosolids pathways based on TCE'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 (Section 2.1).

1.2. Please comment on the data, approaches, and/or methods used to characterize exposure to aquatic receptors (Section 2.2).

1.3 Please comment on EPA's assumption that TCE concentrations in sediment pore water are expected to be similar to the concentrations in the overlying water or lower in the deeper part of sediment, in which anaerobic conditions prevail. Thus, the TCE detected in sediments is likely from the pore (Section 4.1.3).

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 TCE in surface water and where possible compared those values to estimated release concentrations.

2.1. Please comment on the approaches, models, and data used in the water release assessment including comparison of modeled data to monitored data (Section 2.2).

2.2. Please provide any specific suggestions or recommendations for alternative data or estimation methods, including modeling approaches, that could be considered by EPA for conducting or refining the water release assessment and relation to monitored data (Section 2.2).

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 (Section 3.1)

3.2. Please comment on the use and interpretation of Species Sensitivity Distributions (SSDs) and hazardous concentrations ($HC_{05}s$) for ecological risk characterization and provide any specific suggestions or recommendations for how this information could inform EPA's risk assessment for TCE or other solvents (Section 3.1).

4. Occupational and Consumer Exposure:

Occupational 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 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, exposed via the inhalation and dermal pathways, would be adolescents and adults of both sexes (≥16 and older, including males and females of reproductive age, and pregnant women and their developing embryo and fetus).

4.1. Please comment on the approaches and estimation methods, models, and data used in the occupational exposure assessment (Section 2.3.1).

4.2. Please provide any specific suggestions or recommendations for alternative data (modeling or monitoring) or estimation methods that could be considered by the Agency for conducting the occupational exposure assessment. If so, please provide specific literature, reports, or data that would help us refine the exposure assessment (Section 2.3.1).

4.3. Please comment on assumptions used in the absence of specific exposure information (e.g., dermal surface area assumptions: high-end values, which represents two full hands in contact with a liquid: 890 cm^2 (mean for females), 1070 cm^2 (mean for males); central

tendency values, which is half of two full hands (equivalent to one full hand) in contact with a liquid and represents only the palm-side of both hands exposed to a liquid: 445 cm^2 (females), 535 cm^2 (males)). Please also consider these values in the context of different lifestages and body weights (Section 2.3.1.2).

4.4. Please comment on EPA's approach to characterizing the strengths, limitations and overall confidence for each occupational exposure scenarios presented in Section 2.3.1. Please comment on the appropriateness of these confidence ratings for each scenario. Please also comment on EPAs approach to characterizing the uncertainties summarized in Section 2.3.1.3.

To estimate occupational non-user (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 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.

4.5. Please comment on the adequacy, appropriateness, and transparency of EPA's approach and the assumptions EPA used to characterize ONU exposure via this approach (Section 2.3.1).

4.6. Are there other approaches or methods for assessing ONU exposure for the specific condition of use (Section 2.3.1)?

Consumer Exposure
Consumer exposure estimates were developed for the conditions of use for inhalation and dermal exposures to consumers. EPA performed systematic review, collected data from available sources and conducted modeling for estimating consumer inhalation and dermal exposures using the Consumer Exposure Model (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 a data from a comprehensive national survey 1987 as described and referenced within the TCE draft risk evaluation. The age, reliability, representativeness, and uncertainty of this survey is discussed in Sections 2.3.2.4.1, 2.3.2.5, 2.3.2.5.1, 2.3.2.6.1, 2.3.2.6.2, 2.3.2.7.1, 2.3.2.7.2, and 2.3.2.8. Weight fractions 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.

4.7. Please comment on the appropriateness of the approaches, models, exposure or use information and overall characterization of consumer inhalation and dermal exposures for users and bystanders for each of the identified conditions of use. What other additional information, or approaches, if any, should be considered (Section 2.3.2)?

4.8. Please recommend any additional data sources or studies that may be more reflective of current consumer use patterns for specific conditions of use (Section 2.3.2).

4.9. Dermal exposure was evaluated using the permeability sub-model within CEM. Please comment on the suitability and use of this modeling approach for this evaluation. Please provide any suggestions or recommendations for alternative approaches, dermal methods, models or other information which may guide EPA in developing and refining the dermal exposure estimates (Section 2.3.2.4.1).

4.10. Please comment on EPAs approach to characterizing the strengths, limitations and overall confidence for each consumer exposure scenarios presented in Section 2.3.2. Please comment on the appropriateness of these confidence ratings for each scenario. Please also comment on EPA's approach for characterizing the uncertainties summarized in Section 2.3.2.7.

5. __Human Health Hazard:__

For hazard identification and dose-response, EPA reviewed the evidence for TCE toxicity and selected liver toxicity, kidney toxicity, reproductive toxicity, developmental toxicity, neurotoxicity, immunotoxicity, and cancer, that taken as a whole, demonstrated the most robust, sensitive and consistent adverse human health effects for risk characterization. EPA used benchmark dose (BMD) modeling where practicable and, when BMD values were adequate, they were used to generate the Point of Departure (POD) for characterizing chronic and acute exposure scenarios.

5.1. Please comment on the appropriateness of the approach, including the data quality evaluation, and the underlying assumptions, strengths and weaknesses (Section 3.2).

5.2. Have the most scientifically supported health effects and PODs been identified for TCE? Are there additional data regarding sensitive life stages or health effects for TCE that EPA needs to consider? If data gaps exist in the TCE database, how could the uncertainty about sensitive health effects and critical windows of exposure be better accounted for in the risk characterization (Sections 3.2 and 4.3.2)?

5.3. Please comment on EPA's application of the PBPK model to the dose-response analysis for all endpoints. Was the selection of dose metrics and percentile output selection appropriate when considering the sensitivity, uncertainty, and variability of the data (Sections 3.2.2 and 3.2.5)?

Non-Cancer

5.4. EPA performed a weight of evidence assessment for the endpoint of developmental cardiac defects based on available epidemiological, *in vivo* animal*,* and mechanistic data. EPA concluded that the available literature overall supported positive overall evidence that TCE may produce cardiac effects in humans (Section 3.2.4.1.6 and Appendix G.2); however cardiac defects after developmental exposure were not observed consistently across the available *in vivo* animal studies. The Charles River dissection methodology

differed from Johnson et. al. (2003), resulting in reduced sensitivity to the full range of cardiac defects compared to Johnson et al. (2003) and other studies. Therefore, EPA concluded that the Charles River study did not adequately recapitulate the methodology of the Johnson et al. (2003) study. Please comment on EPA's Weight of Evidence (WOE) analysis approach and conclusions for this endpoint, including EPA's analysis of the Charles River (2019) and Dawson (1993)/Johnson (2003) studies.

5.5. Please comment on the assumptions, strengths and weaknesses of the non-cancer dose-response approaches used to estimate the non-cancer and cancer risks to workers, occupational non-users, and consumers. Please also comment on whether EPA sufficiently justified its selections of BMRs for BMD modeling results and uncertainty factor values in deriving the PODs and benchmark margin of exposures (MOEs) (Sections 3.2.5.3.2 and 3.2.5.3.3). As part of this discussion, please comment on EPA's justification for selecting a 1% BMR for the cardiac malformation endpoint based on the severity of the endpoint (i.e. potential mortality).

5.6. EPA determined that the immune effects from Selgrade and Gilmour (2010) represent the best representative dataset to use for evaluating acute effects and the autoimmunity effects from Keil et al (2009) represent the best data set to use for evaluating chronic non-cancer effects (Section 3.2.6.4).

 a. Please comment on EPA's selection of these studies as the best representative endpoints, including consideration of the POD derivation and benchmark MOEs.

 b. EPA did not input the data on response to pulmonary infection from Selgrade and Gilmour (2010) into the TCE PBPK model due to uncertainty over the proper dose metric to be used. Therefore, EPA relied on standard methods for cross-species scaling (i.e., blood:air partition coefficient for HEC, allometric scaling for HED) and accordingly reduced the default 10X UF_A uncertainty factor to 3 (see Section 3.2.5.3.2). Please comment on whether this approach is appropriate and whether the UF is sufficient.

 c. EPA acknowledges that in using the Keil et al (2009) study, EPA is relying upon an early clinical marker to account for susceptibilities, and the endpoint is a precursor to adverse effects for autoimmunity. This LOAEL was considered in this context and the LOAEL to NOAEL uncertainty factor was reduced from 10 to 3X. In light of this, please comment on EPA's use of a 3x Uncertainty Factor for human variability and LOAEL to NOAEL extrapolation.

Cancer

5.7. EPA performed a meta-analysis on the published database for liver cancer, kidney cancer, and non-Hodgkins lymphoma (NHL), concluding that there was a statistically significant association between TCE exposure and all three cancers when accounting for various sensitivity analyses. Please comment on EPA's methodology and conclusions (Sections 3.2.4.2.1 and Appendix H).

5.8. For the cancer dose-response assessment, EPA derived an inhalation unit risk (IUR) and

oral cancer slope factor (OSF) based on epidemiological kidney cancer data from Charbotel et al, 2006, adjusted upward to also account for the relative contribution NHL and liver cancer. Per EPA Guidelines for Carcinogen Risk Assessment, overall, the totality of the available data/information and the WOE analysis for the cancer endpoint was sufficient to support a linear non-threshold model (Section 3.2.4.2.2). Please comment whether the cancer hazard assessment has adequately described the methodology and justification for the cancer dose-response approach, including the use of a linear model and the adjustments made for the other tumor sites (Section 3.2.5.3.4).

6. **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 TCE poses a hazard to environmental aquatic receptors, with invertebrates and fish 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 an MOE, which is the ratio of the hazard value to the exposure. EPA evaluated potential risks for workers and ONUs, consumer users, and bystanders/non-users (e.g., children, women of childbearing age). For the most sensitive endpoint of congenital heart defects, a benchmark MOE of 10 was used for both acute and chronic risks. An IUR and OSF that account for the combined extra risk kidney cancer, liver cancer, and NHL 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.

After consideration of all identified information, EPA concluded that TCE presents an unreasonable risk of injury to workers, ONUs, consumers, and bystanders by inhalation and dermal exposure based on the potential for adverse human health effects (See Section 4.2). EPA also concludes that TCE does not present an unreasonable risk to environmental receptors exposed via surface water (see Section 4.1). EPA makes this determination considering risk to potentially exposed and susceptible subpopulations identified as relevant, under the conditions of use without considering costs or other non-risk factors.

6.1. Please comment on whether the information presented to the panel supports the conclusions outlined in the draft risk characterization section concerning TCE. If not, please suggest alternative approaches or information that could be used to further develop risk estimates within the context of the requirements stated in EPA's Final Rule, Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act (82 FR 33726) (Section 4).

6.2 EPA presented human health risk conclusions based on the endpoints that it believes are best representative of acute and chronic scenarios (see Question 5.7 - immunosuppression for acute exposure, autoimmunity for chronic exposure). Please comment on EPA's approach and endpoint selections including any potential alternative considerations for presenting risk conclusions and the risk summary tables (Table 4-54 and 4-55).

6.3. Please comment on the calculation of risk derived from different exposure data sources (e.g. modeling tools and monitored datasets) and how they account for variability in environmental and human exposure. Please provide specific recommendations as needed for improving the risk characterization and references to support any recommendations (Section 4).

6.4. Please comment on whether the risk evaluation document has adequately described the uncertainties and data limitations associated with the methodologies used to assess the environmental and human health risks. Please comment on whether this information is presented in a clear and transparent manner (Section 4.3).

6.5. Please comment on the validity of specific confidence summaries presented in Section 4.3.

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 has led to the identification and characterization of all PESS (Sections 2.3.3, 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 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 or 50 and the glove protection factors of 5, 10, or 20. EPA also characterized exposure scenarios in which respirator use was unlikely. EPA did not assume occupational non users (ONUs) or consumers used personal protective equipment (PPE) 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 and ONUs using PPE (exposure - Sections 2.3.1.2.6 and 2.3.1.3, Table 2-20; risk - Sections 4.2.2 and 4.3.2.1).

6.8. Please comment on any other aspect of the environmental or human health risk characterization that has not been mentioned above (Section 4).

7. 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 TCE, 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.

To increase the quality and credibility of scientific information disseminated by EPA, EPA uses the peer review process specifically as a tool for determining fitness of scientific information for the intended purpose. The questions below are intended to guide the peer reviewers toward determining if EPA collected, used and disseminated information that is 'fit for purpose' based on utility (the data's utility for its intended users and for its intended purpose), integrity (the data's security), and objectivity (whether the disseminated information is accurate, reliable, and unbiased as a matter of presentation and substance). The peer reviewers' critical focus should pertain to recommendations of the technical information's usefulness for intended users and the public.

7.1. Please comment on the overall content, organization, and presentation of the TCE draft risk evaluation. Please provide suggestions for improving the clarity of the information presented.

7.2. 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.