EPA SCIENTIFIC ADVISORY COMMITTEE ON CHEMICALS
CHARGE TO THE PANEL – METHYLENE CHLORIDE

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. Methylene chloride 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 has prepared and published a draft risk evaluation for Methylene Chloride. 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.

Methylene Chloride Scope Document
Methylene Chloride Problem Formulation Document

The documents that are part of this review include:

1. Draft Risk Evaluation for Methylene Chloride
2. Draft Methylene Chloride Charge
3. Draft Systematic Review Supplemental File: Data Quality Evaluation of Environmental Fate and Transport Studies
4. Draft Systematic Review Supplemental File: Data Quality Evaluation of Environmental Releases and Occupational Exposure Data
5. Draft Systematic Review Supplemental File: Data Quality Evaluation of Environmental Releases and Occupational Exposure Common Sources
6. Draft Systematic Review Supplemental File: Data Quality Evaluation on Data Sources on Consumer and Environmental Exposure
7. Draft Systematic Review Supplemental File: Data Extraction Tables for Consumer and Environmental Exposure Studies
8. Draft Systematic Review Supplemental File: Data Quality Evaluation of Environmental Hazard Studies
9. Draft Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies – Animal Studies
10. Draft Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies - Epidemiological Studies
11. Draft Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies - Human Controlled Experiments
12. Draft Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies
13. Draft Systematic Review Supplemental File: Data Extraction Tables for Human Health Hazard Studies
14. Draft Supplemental Information on Consumer Exposure Assessment
15. Draft Supplemental Information on Surface Water Exposure Assessment
16. Draft Supplemental Information on Releases and Occupational Exposure Assessment.

17. Draft Supplemental File: Methylene Chloride Benchmark Dose and PBPK Modeling Report
18. Draft Risk Evaluation for Methylene Chloride, Supplemental Information Risk Calculator for Occupational Exposures
19. Draft Risk Evaluation for Methylene Chloride, Supplemental Information Risk Calculator for Consumer Inhalation Exposures
20. Draft Risk Evaluation for Methylene Chloride, Supplemental Information Risk Calculator for Consumer Dermal Exposures
21. Draft Supplemental File: Methylene Chloride Consumer Exposure Assessment Model Input Parameters
22. Draft Supplemental File: Methylene Chloride Consumer Exposure Model Outputs
23. Draft Systematic Review Supplemental File: Data Quality Evaluation of Physical-Chemical Properties Studies

The focus of this meeting is to conduct the peer review of the Agency's draft risk evaluation of methylene chloride 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 the SACC advice on the clarity and scientific underpinnings of the overall methylene chloride risk evaluation. 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 in the final 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." 40 CFR 702.33

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

1. Environmental Fate and Exposure:

EPA qualitatively analyzed the sediment, land application, and biosolids pathways based on methylene chloride'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 methylene chloride 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 to monitored data.
2.2. 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 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. 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.
4.3. EPA assumed the following default surface area value for modeling dermal exposures for occupational exposure scenarios for which surface area data were not available: a high-end value of 1070 cm^2, which represents two full hands (mean value for males) in contact with a liquid. Please provide input on data sources and specific alternative values relevant to the uses.

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.

4.4. Please comment on the assumptions and uncertainties of this approach.
4.5. Are there other approaches or methods for assessing ONU exposure for the specific condition of use?

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 methylene chloride 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.

4.6. 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?
4.7. 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. What other additional information or modeling approaches, if any, should be considered?
4.8. Dermal exposure was evaluated using the absorption method submodel 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.

5. Human Health Hazard:

EPA used the acute point of departure (POD) to use to estimate risks from the human controlled experiment described by Putz et al. (1979). This study was rated as a medium quality study; it was a double-blind design but used a single exposure, which prevented the use of dose-response modeling. Given uncertainty regarding concentrations and exposure durations and the potential for a steep dose-response leading to death as suggested by these case reports and the analysis by Benignus et al. (2011), EPA considers Putz et al. (1979) to be the most relevant study for this risk evaluation.

5.1. Please comment on the appropriateness of the approach, including the data quality evaluation, and the approach's underlying assumptions, strengths and weaknesses.
5.2. Please provide any specific suggestions or recommendations for alternative approaches that should be considered by the Agency in characterizing the acute inhalation risks.
5.3. Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.
5.4. Please comment on the severity of the response used as the basis of the POD as well as the use of the result at 1.5 hours rather than at 4 hours.

For methylene chloride, exposure-versus-time data are limited. Therefore, EPA considers the Ten Berge equation using n = 2 as a valid method to convert the 1.5-hr POD value from Putz et al. (1979) to the 15-min, 1-hour and 8-hr PODs.

5.5 Please comment on the conversion of the 1.5 h time point in Putz to 15 min, 1-hour and 8-hour PODs.

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 methylene chloride.

5.6. Please comment on the appropriateness of the approach, including its underlying assumptions, strengths and weaknesses.
5.7. Please provide any specific suggestions or recommendations for alternative approaches that should be considered by the Agency in characterizing the chronic inhalation risks to workers.
5.8. Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.

EPA used a linear low-dose extrapolation for evaluating potential cancer risks from chronic exposures to methylene chloride.

5.9. Please comment on the appropriateness of using a linear low-dose extrapolation versus a non-linear or threshold approach, recognizing that methylene chloride is predominantly metabolized by cytochrome P450 2E1 to carbon monoxide at low concentrations (a high affinity, low capacity pathway) and by glutathione S-transferase T1-1 to two reactive intermediates (i.e., S-(chloromethyl)glutathione) and formaldehyde) at high concentrations (a low affinity, high capacity pathway).

EPA calculated a cancer slope factor by using a PBPK model that accounts for the internal dose of the amount of methylene chloride metabolized through the glutathione S-transferase T1-1 (GST) pathway.

5.10. Please comment on the appropriateness of applying the PBPK model and assumptions within the model, specifically using the internal dose metric of daily mass of methylene chloride metabolized via the GST pathway as the basis for performing a linear low-dose extrapolation for quantifying potential cancer risks from chronic exposures to methylene chloride.

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 methylene chloride poses a hazard to environmental aquatic receptors, with amphibians 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 30 was used with the acute POD based on 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 10 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. 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.
6.2. Please provide information on additional uncertainties and assumptions that EPA has not adequately presented.
6.3. Please comment on whether the information presented supports the findings outlined in the draft risk characterization section.
6.4. 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 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 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.

6.5. 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.

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 methylene chloride, 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 methylene chloride.
7.3. Please provide suggestions for improving the clarity of the information presented in the documents.