February 29, 2016

The EPA/OPPT Work Plan Risk Assessment for 1-Bromopropane (1-BP) Draft Peer Review Charge Questions

Peer review charge questions are categorized into five main themes.

- General issues on the Risk Assessment
- Occupational Exposure Assessment
- Consumer Exposure Assessment
- Hazard and Dose-Response Assessments
- Risk Characterization

General Issues on the Risk Assessment

EPA/OPPT identified 1-BP as part of the TSCA Work Plan based on high hazard concerns, industrial use profiles which include scenarios with high exposure for workers, and concerns for consumer exposure due to chemical volatility and high content of 1-BP most consumer products contents ranging between 60-100%.

Based on the physical-chemical properties and use scenarios described in this assessment, EPA/OPPT expects inhalation to be the primary exposure route of concern for 1-BP. Because of limited toxicological data and the lack of toxicokinetic information needed to develop physiologically-based pharmacokinetic models for route-to-route extrapolations, EPA/OPPT did not evaluate dermal exposures.

1-BP exhibits a low ecological hazard profile and low persistence and bioaccumulation potential if released into aquatic or terrestrial environments. Therefore, a quantitative assessment of environmental risks was not included in this assessment.

Question 1-1: Please comment on whether the information provided in Section 1 (Background and Scope) is appropriate and accurately characterizes the fit for purpose nature of this assessment for TSCA related uses? Please provide any specific suggestions for improving the clarity and transparency of the background information that describes scope and limits of the assessment.

Question 1-2: Please comment on the scope of the assessment, in particular the conceptual model resulting from EPA/OPPT's problem formulation. Please provide any other significant literature, reports, or data that would be useful to complete this characterization and that may support expansion or refinement of the scope of this assessment.

Occupational Exposure Assessment

EPA/OPPT evaluated acute and chronic inhalation exposures to workers using 1-BP in degreasing (vapor, cold cleaning, and aerosol), spray adhesives and dry cleaning (used in dry-cleaning machines and spot cleaning). For each of the exposure pathways included in the assessment, EPA/OPPT quantified occupational exposures based on a combination of

monitoring data and modeled exposure concentrations. Inhalation exposures were assessed for both workers and occupational non-users.

EPA/OPPT assessed risks for workers using 1-BP following acute and chronic exposures in degreasing, spray adhesives and dry cleaning. EPA/OPPT assumed that workers would be adults of both sexes (≥16 and older, including pregnant workers) based on occupational work permits, although exposures to younger workers in occupational settings cannot be ruled out. Most monitoring data sources did not indicate whether exposure concentrations were for occupational users or nonusers. Therefore, EPA/OPPT assumed that occupational exposures were for a combination of users and nonusers when not specified.

EPA/OPPT assumed that direct contact or close proximity to the use would likely provide the highest exposures to 1-BP (i.e., for a commercial application with substantial frequency or duration of exposure).

Question 2-1: Please comment on the approaches used, and provide any specific suggestions or recommendations for alternative approaches, models, or information (references) that could be considered by EPA/OPPT for improving the workplace exposure assessment, including estimations for bystander/non-users (e.g., women of child-bearing age).

Question 2-2: Please comment on whether there are any additional occupational exposure scenarios that EPA/OPPT could address that have not already been quantified. Please also provide specific references and/or data to address such additional exposures.

Question 2-3: For the exposure assessments based on monitoring data, are you aware of any additional sources of occupational exposure monitoring data that EPA/OPPT could consider in its assessment? If so, please provide specific literature, reports, or data that would help us refine the exposure assessment.

Question 2-4: For the exposure assessments based on modeling, are you aware of any additional sources of data that EPA/OPPT could consider in deriving the parameter values used in the modeling? If so, please provide relevant literature, reports, or data that would help us refine the parameters used in the modeling

Consumer Exposure Assessment

Because of the relatively short half-life of 1-BP and its expected use pattern in consumer products, acute exposures to consumers using 1-BP in aerosol spray adhesives, aerosol spot removers and aerosol spray degreasers and cleaners were evaluated in this assessment. EPA/OPPT used data from literature sources where available. In the absence of data, EPA/OPPT relied on use patterns, physical-chemical properties of 1-BP and the Consumer Exposure Module of the Exposure and Fate Assessment Screening Tool or E-FAST to estimate acute exposure for consumers.

EPA/OPPT examined risks for consumers in residential settings following acute exposures. EPA/OPPT assumed that consumer users would be adult individuals (≥16 and older; including pregnant women) that intermittently use 1-BP, although exposures to younger users may be possible in residential settings. Bystanders would be individuals of any age group (e.g., children, adults, elderly) who are in a nearby area during product application.

EPA/OPPT assumed that direct contact or close proximity to the use would likely provide the highest exposures to 1-BP (i.e., for a consumer with substantial frequency or duration of exposure).

Question 3-1: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models, or use information (*e.g.*, information on duration, number of user events, amount used) that could be considered by EPA/OPPT in developing and /or refining the exposure assumptions and estimates for spray adhesives, aerosol spot removers and aerosol spray cleaners and degreasers.

Question 3-2: Exposure estimates were developed for three consumer uses: spray adhesives, aerosol spot removers and aerosol spray cleaners and degreasers. All products are aerosol sprays and appear to be available for sale and use by consumers in the U.S. There were no current reliable data regarding the consumer exposure scenarios. Please comment on the consumer uses selected for this assessment and provide any specific suggestions or recommendations for additional uses (including information on duration, number of user events, amount used) that could be considered for evaluation.

Hazard and Dose-Response Assessments

For hazard identification and dose-response, EPA/OPPT reviewed the evidence for 1-BP toxicity and selected liver toxicity, kidney toxicity, reproductive/developmental toxicity, neurotoxicity, and cancer, that taken as a whole, demonstrated the most robust, sensitive and consistent adverse human health effects for risk characterization. EPA/OPPT used benchmark dose (BMD) modeling where practicable and, when BMD values were adequate, they were used to generate the POD for characterizing chronic and acute exposure scenarios. EPA/OPPT determined that using developmental toxicity and neurotoxicity endpoints for dose-response calculation would be protective of the most sensitive life stages, including the developing fetus for non-cancer points of departure and risk estimates.

For the cancer risk assessment, EPA/OPPT derived the inhalation unit risk (IUR) based on lung tumors in female mice. The exact mechanism/mode of action of 1-BP carcinogenesis is not clearly understood. There are, however, an abundance of data that may provide a basis for weight-of-evidence (WOE) considerations; these include in vitro tests, similarity in metabolism across species, SAR and other potential mechanisms of action. Other possible mechanisms of action – oxidative stress, immunosuppression, and cell proliferation—can act synergistically to complete the multi-stage process of carcinogenesis. 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 probable mutagenic mode of action for 1-BP carcinogenesis.

Question 4-1: EPA/OPPT concluded in the risk assessment that 1-BP carcinogenesis occurs through a probable mutagenic mode of action based on the totality of the available data/information and the WOE. Please comment whether the cancer hazard assessment has adequately described the WOE regarding the mutagenic mode of action.

Question 4-2: EPA/OPPT identified liver toxicity, kidney toxicity, reproductive/developmental toxicity, and neurotoxicity in the risk assessment as adverse human health effects for risk characterization. EPA/OPPT used these endpoints to calculate PODs to assess non-cancer risks associated with chronic inhalation exposures. As part of the review, please comment on the choice of these endpoints as PODs for assessing risks in humans associated with acute and chronic inhalation exposures to 1-BP. Are there other data that EPA/OPPT could have considered for the hazard identification and dose response associated with chronic inhalation exposures? If so, please provide specific data and references.

Question 4-3: Please comment on the WOE analysis for the choices of non-cancer endpoints for the acute and chronic risk scenarios. Please provide additional data, data interpretation or information that would have informed the WOE analysis and selection of critical studies for the PODs.

Question 4-4: Typically, EPA uses the benchmark dose modeling software (BMDS) with a BMR of 10% and the models are restricted to multistage models or the broader suite of dichotomous models in BMDS and a single best model is chosen for the POD. EPA/OPPT used an alternative approach to calculate the cancer POD versus the standard approach of choosing best fit model. Briefly, EPA/OPPT used a model averaging approach considering multiple benchmark dose models to calculate the POD at a benchmark response (BMR) level of 0.1%. Please comment on the assumptions, strengths and weaknesses of the model averaging approach for determining the POD in the cancer assessment.

Risk Characterization EPA/OPPT quantified non-cancer risks based on the Margin of Exposure (MOE), which is the product of dividing the scenario specific exposure into the hazard point of departure which is no adverse effect level, based on animal and/or human studies. EPA/OPPT calculated MOEs for acute or chronic exposures separately based on the appropriate non-cancer POD and estimated exposure concentrations adjusted for durations. To determine if unacceptable risks were present for relevant exposure scenarios, the endpoint-specific MOEs were compared to the endpoint-specific benchmark MOEs. The benchmark MOEs were the product of all of the relevant UFs identified for each non-cancer POD. If the MOE estimate was less than the benchmark MOE, the exposure scenario for non-cancer endpoints was interpreted as a human health risk.

Cancer risk estimation consisted of multiplying the occupational scenario-specific exposure estimates by the cancer IUR to estimate the added cancer risk. Added lifetime cancer risk

estimates from 1-BP exposure were compared to benchmark cancer risk levels of 10^{-6}, 10^{-5} and 10^{-4} (i.e., 1 in 10,000, 1 in 100,000 and 1 in 1,000,000).

Question 5-1: EPA/OPPT interpreted the endpoint of decreases in live litter size following exposure to 1-BP before and during gestation, as a surrogate for frank developmental effects in relevant to humans per EPA's Guidelines for Developmental Toxicity Risk Assessment. EPA/OPPT used this endpoint to calculate a point of departure (POD) to assess non-cancer risks associated with acute inhalation exposures to 1-BP. Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the non-cancer risks to workers and occupational non-users following acute inhalation exposures to 1-BP, including the MOEs presented in the document. Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate risks to consumers following acute inhalation exposures; including non-users (e.g., bystanders who may be children, or women of childbearing age). Specifically, please comment on the decision to limit the analysis to acute exposures without residual concerns between events and what data could critically inform modifying this approach for consumers. Please comment on the selection of uncertainty factor values in deriving the benchmark MOE for acute inhalation exposures.

Question 5-2: Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the non-cancer risks to workers and occupational non-users following chronic inhalation exposures to 1-BP, including the MOEs presented in the document. Please comment on the selection of uncertainty factor values in deriving the benchmark MOE for chronic inhalation exposures.

Question 5-3: Please comment on the assumptions, strengths and weaknesses of the approach used to estimate added lifetime cancer risks to workers which EPA/OPPT-derived from an inhalation unit risk based on lung tumors in female mice for estimating incremental or added individual lifetime cancer risk.

Question 5-4: Please comment on whether the risk characterization has adequately described the assumptions, uncertainties and data limitations in the methodology used to assess risks from 1-BP. Please comment on whether this information and risk conclusions are presented in a logical, transparent manner and provide suggestions that could increase clarity in the risk characterization.