# Comments of the American Chemistry Council on the TSCA Work Plan Chemical Draft Risk Assessment of 1-Bromopropane

## Docket No. EPA-HQ-OPPT-2015-0084

**May 9, 2016**

Christina Franz
Senior Director Regulatory & Technical Affairs
American Chemistry Council
700 Second Street, N.E.
Washington, DC 20002
(202) 249-6406
christina_franz@americanchemistry.com

# Table of Contents

# Comments of the American Chemistry Council on TSCA Work Plan Risk Assessment of 1-Bromopropane EPA-HQ-OPPT-2015-0084

## I. Introduction:

The American Chemistry Council (ACC)[1] appreciates the opportunity to comment on the draft chemical risk assessment for 1-bromopropane announced in the Federal Register on March 8, 2016. ACC has a longstanding and strong interest in risk assessments conducted by the Environmental Protection Agency (EPA), including those conducted under its Work Plan Chemical program under the Toxic Substances Control Act (TSCA).

ACC agrees with the general direction that EPA has taken in the Work Plan Chemicals program to prioritize chemicals for further review and conduct targeted assessments that may be used to consider whether regulatory action is warranted. In general, ACC agrees that this type of approach, with some important and essential refinements, will enable the Agency to evaluate existing chemicals in commerce effectively.

ACC commends the Agency for conducting targeted quantitative assessments that focus on the potential risks associated with certain uses and applications of the Work Plan chemicals, and for employing a margin of exposure (MOE) approach for human health evaluations. The MOE approach used for non-cancer assessments, consistent with the approach used by EPA's Office of Pesticide Programs (OPP), the European Union, and Canada, is a robust methodology that improves transparency and is preferable to those that use reference values (RfCs or RfDs).[2] Targeted quantitative assessments and use of the MOE are important steps for the Agency to take in its risk assessments. When properly implemented, these methodologies should allow EPA to

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is an $801 billion enterprise and a key element of the nation's economy. It is the nation's largest exporter, accounting for fourteen percent of all U.S. exports. Chemistry companies are among the largest investors in research and development. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against any threat to the nation's critical infrastructure.

[2] ACC prefers the use of the MOE for these assessments. When reference values are used they incorporate science policy judgments, in the form of uncertainty factors that are not immediately transparent to risk managers. Using an MOE approach, the risk manager can more clearly determine if the differential between the exposure level and the effect level is appropriate considering the populations exposed, endpoints of concern, strength of the evidence and other key factors that are often built into uncertainty factors but are not immediately transparent to the risk manager.

focus its resources confidently and consistently on uses that present the greatest potential for concern.

## II. Executive Summary:

ACC has a number of comments and suggestions to improve the overall risk assessment of 1-bromopropane and ensure a scientifically rigorous approach to evaluate risks associated with this chemical. In addition, in Section IV, we identify specific suggestions to improve the peer review charge questions. The key issues identified by ACC are:

- The 1-bromopane risk assessment uses methods consistent with a screening-level risk assessment, not a refined risk assessment, which must be reflected in the conclusions in the draft assessment. EPA should work with industry to refine the draft 1-bromopropane draft risk assessment.
- EPA's risk assessment fails to use "best science" approaches, which are critical to a scientifically defensible assessment. Failure to use best science approaches is a critical flaw in EPA's 1-bromopropane risk assessment. Specific comments relating to the benchmark dose modeling, the non-cancer and cancer risk assessments, and the exposure assessment components of the risk assessment are provided in these comments below.
- A systematic review of study quality, relevance, and reliability is missing from the assessment and must be included in order to adequately review and evaluate EPA's decisions. A systematic evaluation of each study used is a necessary part of a scientifically defensible risk assessment.
- The 1-bromopropane exposure assessment is outdated and does not reflect current exposures in occupational and consumer populations. ACC believes that EPA should work with industry to refine and update the 1-bromopropane exposure assessment.
- EPA has failed to describe adequately the scientific basis for decisions made when applying benchmark dose modeling to reproductive and developmental toxicity datasets. The risk assessment should incorporate significant additional discussion and explanation of the benchmark dose modeling process used. Without a discussion of the details of the modeling, risk assessors cannot judge the validity of certain modeling outputs and decisions.
- EPA has failed to consider its own guidance regarding developmental toxicity and relies on a study endpoint and dose where maternal toxicity was present. EPA has failed to discuss why this endpoint is appropriate in light of maternal toxicity. In addition, EPA has not articulated its consideration of study quality when selecting studies upon which to rely.
- EPA has used very conservative benchmark dose modeling response levels without describing the rationale for the choices made. EPA indicates that it followed its own

guidance, yet a review of the two documents cited reveals important differences between the recommendations contained in EPA's guidance and what EPA actually did in the 1-bromopropane risk assessment.

- The genotoxicity discussion in the 1-bromopropane risk assessment is incomplete. A weight-of-evidence assessment, which includes all available data, indicates that genotoxicity is not the mode of action for tumor induction in rodents exposed for a lifetime to 1-bromopropane by whole body inhalation. ACC agrees with EPA statements in the draft 1-bromopropane assessment that a mode of action for cancer is not known, based on available data.
- The female mouse lung tumor is not relevant for the 1-bromopropane human cancer risk assessment. EPA should refine the risk assessment to consider data related to this type of tumor as discussed at the 2014 EPA State-of-the-Science Workshop on Chemically-induced Mouse Lung Tumors.

## III. Discussion of Assessment:

ACC elaborates on each of the points raised in the Executive Summary as follows:

### A. The 1-Bromopropane Risk Assessment Employs Methods Consistent with Screening-Level Risk Assessment -- Not a Refined Risk Assessment -- Which Should be Reflected in the Risk Assessment Conclusions

The methodology described in the 1-bromopropane risk assessment consistently employs worst-case and high-end assumptions regarding both hazard and exposure throughout the assessment. This very conservative methodology is consistent with a screening-level assessment, where health protective assumptions are used for parameters employed to calculate hazards and exposures to assure that potential risks are not underestimated. Screening-level assessments are not designed to provide accurate estimates of risk. When a screening-level assessment indicates an acceptable level of risk, the Agency has a high degree of confidence that the potential risks are much lower than the calculation, and therefore, the actual risks are often much lower and/or perhaps non-existent. However, when a screening-level risk assessment indicates a potential concern for a health or environmental effect, this does not mean that the actual risks are significant and warrant action. Rather, it means that the risk evaluation should be refined using more realistic and accurate parameters in the methodologies to calculate risks.[3] The outcome is then a

[3] This well accepted approach is consistent with EPA's general approach to risk evaluation. This is perhaps best articulated in EPA's 2001 bulletin on ecological risk assessment, which states: "Screening-Level Ecological Risk Assessments are conservative assessments in that they provide a high level of confidence in determining a low probability of adverse risk, and they incorporate uncertainty in a precautionary manner. It must be stressed that SLERAs are not designed nor intended to provide definitive estimates of actual risk, generate cleanup goals and, in

refined risk assessment that more accurately quantifies actual risks. The screening-level assessment is, therefore, a "first look" at the available data to determine if more work is needed (the MOE was not adequate), or more work is not necessary with use of worst-case assumptions (MOE is adequate). Significantly, EPA fails to state throughout the assessment that this risk assessment is a screening-level assessment and must be refined before reliable and/or realistic conclusions about potential risks can be made.

For example, the Agency states in the Executive Summary: "The Agency is performing risk assessments for chemicals in the work plan. If an assessment identifies unacceptable risks to humans or the environment, EPA will pursue risk management." However, pursuing risk management after conducting a worst-case scenario risk assessment is not appropriate. Instead, refinement of the assessment should first be pursued for those exposures where 1-bromopropane MOEs have been found to be unreasonable.

The significance of the distinction between a screening-level and refined risk assessment is apparent in EPA's, *"Main Conclusions of this Risk Assessment."* (see page 25). The Agency discusses cancer risk and describes risks in the range of 1 in 100 for use of spray adhesives containing 1-bromopropane. However, given the use of outdated exposure data, as well as questionable cancer rodent data to define the hazard, the conclusions EPA should have described here would be the need to refine the cancer risk assessment in order to understand the magnitude of the risk.

In addition, EPA's discussion in Part 4 of the human health risk characterization for 1-bromopropane is inconsistent with EPA's own Risk Characterization Handbook (EPA, 2000)[4]. In Part 4 of the 1-bromopropane risk assessment, EPA presents only the findings for the 95th percentile. In contrast, EPA's Handbook states at page 40: *"Assessments should address the resulting variability in doses received by members of the target population. Individual exposure, dose, and risk can vary widely in a large population. Central tendency and high end individual risk descriptors capture the variability in exposure, lifestyles, and other factors that lead to a distribution of risk across a population."*

---

general, are not based upon site-specific assumptions. Rather, the purpose of SLE RAs is to assess the need, and if required, the level of effort necessary, to conduct a detailed or "baseline" ecological risk assessment for a particular site or facility. Therefore, refinement of contaminants of concern occurs in the baseline risk assessment rather than in the SLERA." Further details can be found here: https://www.epa.gov/sites/production/files/2015-09/documents/slera0601.pdf.

[4] EPA, 2000. Science Policy Council Handbook: Risk Characterization. Office of Science Policy. Office of Research and Development. EPA 100-B-00-002. December.

Furthermore, the National Academies reiterated the importance of providing central estimates for hazard values in 2014.[5] The EPA section on risk characterization in the draft assessment has not provided any central tendency estimates of risk. By failing to provide the full range of available risk estimates, risk managers will not have a complete and full understanding of the data and the findings. This critical information must be provided not only when conducting dose-response, but also in the final risk characterization section. This failure to discuss central tendencies, and presenting only the 95th percentile responses, is consistent with a screening-level approach.

Another example illustrating the significance of the important difference between screening-level and refined assessments is found in the Executive Summary of the assessment (see page 24), where EPA states: *"A concern for adverse developmental effects was identified for all acute consumer exposure scenarios (i.e., MOEs were below the benchmark MOE of 100), with 1-BP use in aerosol spray cleaners and degreasers showing the greatest risk."* However, if an adequate MOE is not achieved based on the use of worst-case assumptions in a screening-level assessment, this does not mean there is a risk. Instead, the conclusion properly drawn is that an adequate MOE was not achieved based on the use of worst-case, non-refined assumptions, and the assessment should be refined to understand whether a real concern exists or not.

Given that the 1-bromopropane risk assessment employs a methodology consistent with a screening-level assessment, EPA must very carefully describe any conclusions drawn in the draft risk assessment in order to avoid confusion and misinterpretation by overstating any potential risks identified. In addition, ACC strongly encourages EPA to refine the current risk assessment with participation from industry before finalizing the assessment and contemplating any risk management measures.

### B. EPA's Risk Assessment Fails to Use "Best Science" Approaches, Which Are Critical to a Scientifically Defensible Assessment

EPA's 1-bromopropane assessment applies inconsistent standards to existing scientific information, using methodology that does not comport with current "best science" approaches for the evaluation and integration of scientific information. For example, a systematic evaluation of the quality (including relevance and reliability) of each study is essential, but EPA has not included this review and evaluation in critical areas of the risk assessment (*e.g.,* genotoxicity, developmental toxicity). When evaluating both hazard and exposure for 1-bromopropane, it is critical that EPA rely on studies of the highest quality, not simply those studies that produce the lowest points of departure (POD) or the highest

[5] See: http://www.nap.edu/catalog/18764/review-of-epas-integrated-risk-information-system-iris-process.

exposure estimates. However, EPA consistently chose the lowest dose for each endpoint of toxicity and then drew conclusions based on results from the use of the lowest overall endpoint throughout the 1-bromopropane assessment, without any discussion at all regarding the quality of the available studies – with the exception of several cursory statements contained in tables.[6]

EPA has also failed to apply a weight-of-evidence approach to the studies available to it. In its assessment of 1-bromopropane, EPA had multiple studies for identified hazards, such as reproductive and developmental toxicity, and carcinogenicity. EPA also had multiple exposure studies to consider. When there are multiple studies available, the only scientifically-defensible approach, even with a screening-level risk assessment, is to weigh the studies by considering study characteristics and determining which studies are of higher quality and should be given greater weight in the assessment. Failure to employ a weight-of-evidence approach in the 1-bromopropane risk assessment is a critical deficiency that seriously limits any conclusions that can be drawn. This deficiency underscores the fact that EPA should clearly define the process used in this draft risk assessment as a screening-level assessment that cannot result in realistic estimates of risk.

### C. EPA Failed to Include a Systematic Review of Study Quality, Reliability, and Relevance

A systematic evaluation of the quality (including relevance and reliability) of each study is a necessary part of a scientifically defensible risk assessment process. When evaluating both hazard and exposure, it is critical that EPA rely on the studies of the highest quality, not simply those studies that produce the lowest points of departure, or the highest exposure estimates. EPA should develop, through an open and transparent process, clear procedures and protocols that will promote consistent and scientifically sound assessments that can be compared and evaluated.

Unfortunately, while EPA identifies inhalation endpoints that are considered suitable in Table 3-1, EPA fails to provide information regarding the quality of the individual studies. Appendix M does identify some quality considerations; however, EPA does not provide any information regarding its own findings from its quality review of the individual studies. No information is provided to describe how considerations were applied and what constitutes a study of "high quality" (as cited on page 100) or "good quality" (as cited on page 113). An evaluation of scientific evidence should begin with a

[6] For example, at page 120 of the draft assessment, EPA clearly states: "EPA/OPPT used margin of exposures (MOEs) to estimate acute or chronic risks for non-cancer based on the following:1. the lowest HECs within each health effects domain reported in the literature;…"

transparent application of clear criteria to evaluate the quality of individual studies. Simply referencing some considerations without describing how each relevant study compares to applicable criteria is neither transparent nor sufficient. Without a robust evaluation, studies of lower quality can be accorded too much weight in the overall assessment, leading to a flawed evaluation. It is very important that EPA rely on studies that are of the highest quality, not simply those studies that produce the lowest points of departure (as EPA states it has done on page 120). While it is possible that EPA has conducted such an evaluation, EPA should be transparent about how that evaluation was conducted and the criteria used. ACC strongly recommends that EPA include this information in its final risk assessment and provide evidence-based determinations of the chosen endpoints based on the quality of the data. Simply selecting the lowest value in not appropriate unless EPA acknowledges that this assessment of 1-bromopropane is strictly a screening-level assessment.

### D. The 1-Bromopropane Exposure Assessment Is Outdated and Does Not Reflect Current Exposures in Occupational and Consumer Populations

EPA's 1-bromopropane draft risk assessment identified occupational uses of concern, including its use in spray adhesives, dry cleaning (including spot cleaning), and degreasing (vapor, cold cleaning, and aerosol). The consumer uses of concern identified for 1-bromopropane included aerosol spray adhesives, aerosol spot removers, and aerosol cleaning and degreasing products. The Agency described (at page 24) a number of uncertainties associated with the available data and modeling approaches used, including *"the sites used to collect exposure monitoring data were not selected randomly, and the data reported therein may not be representative of all exposure scenarios. Further, of necessity, exposure modeling approaches employed knowledge-based assumptions that may not apply to all use scenarios. Because site-specific differences in use practices and engineering controls exist, but are largely unknown, this represents another source of variability that EPA/OPPT could not quantify in the assessment. Consumer exposures were estimated based on modeling approaches due to the lack of monitoring information that could be used to assess consumer products. In addition, the inability to include dermal exposures results in potential underestimation of overall exposure and risk."*

ACC believes that the exposure assessment data used by EPA are not representative of current workplace/occupational exposures in 2016. ACC believes that workplace exposures for 1-bromopropane have been rapidly declining based on changes in downstream applications. In a study previously conducted by Gradient Corporation, sponsored by Albemarle Corporation (see Albemarle comments submitted to EPA on the 1-BP Draft TSCA Work Plan Chemical Risk Assessment, May 9, 2016), workplace

exposures were shown to have been declining in several occupational sectors, namely the dry cleaning industry, the spray adhesives industry, and the industrial metal cleaning industry. The 1-bromopropane risk assessment should account for this change in 1-bromopropane use patterns in the workplace.

Regarding EPA's modeling of consumer exposures, EPA used the E-FAST-2/CEM model, stating: "*CEM uses high-end input parameters/assumptions to generate conservative, upper-bound inhalation exposure estimates for aerosol spray products."(*See page 74). In particular, for the consumer behavior patterns EPA states (at page 274): *"By default, E-FAST2/CEM uses pre-set, high-end values for a variety of consumer use scenarios when use information is not available for specific products. Under these conditions, the model results tend to over predict the exposure."* Therefore, by EPA's own admission, it is very likely that EPA has overestimated consumer exposures.

A similar overestimation is likely to have occurred regarding workplace exposures. For instance, while EPA comments (at page 147) that *"the use of 8-hr TWA is not expected to present a "worst case" or conservative exposure estimate,"* EPA fails to mention that EPA is assuming that an individual is exposed at this level for an entire working life (40 years), as is reflected in Appendix H. By using only extreme values in a range, EPA fails to provide a sense of the average values of workplace exposure. Using central tendency estimates would be more useful and informative, particularly for the lifetime average daily concentrations (LADCs), which should be based on the average exposure concentration over time, rather than a single maximum eight-hour time-weight-average (TWA). A refined exposure assessment that uses central tendency values should be conducted for all possible exposure scenarios in order to provide for realistic estimates of risk – as opposed to only worst-case scenario.

While EPA provides inputs in Appendix L for the 50th and 90th percentiles of exposure, the Agency fails to identify clearly the exposure values actually used for the MOE derivations. Since only 95th percentile values are presented in the risk characterization section of the assessment, we must assume that EPA used only the 90th percentile exposure estimates. Further clarity is needed from EPA on this point before ACC can comment further on the outputs used to inform the MOE calculations.

EPA's reliance on outdated use and exposure data, in combination with estimated exposures and modeled data, very likely presents worst-case scenarios in the draft risk assessment. EPA should be very clear that the current draft risk assessment cannot identify *actual* risk, but rather can only identify exposure scenarios that require further

refinement. EPA should refine the assessment using current/more recent exposure data and provide estimates of the range of modeled exposures.

### E. EPA Has Used Very Conservative Benchmark Dose Modeling Response Levels without Describing the Rationale for Its Choices

EPA has used benchmark dose modeling (BMD) rather than NOAEL/LOAEL and RfD/RfC methods for dose-response assessment applied to 1-bromopropane datasets. EPA states at pages 100-101 of the assessment that it followed its 1991 EPA guidance (EPA, 1991)[7] and its 2012 BMD Technical Document (EPA, 2012)[8] regarding the selection of BMRs when developmental endpoints indicate increased severity. A review of both guidance documents, however, reveals important differences between what the guidance recommends and what EPA actually did in the 1-bromopropane risk assessment.

For instance, the 1991 guidance document refers to the use of BMD modeling, but states that its use in developmental toxicity datasets has not yet been validated. The 2012 Technical Document states that although use of BMD modeling for quantal datasets has been refined and the Agency provides specific guidance on its use for quantal datasets, EPA also cautions that use of the approach for continuous datasets is not straightforward (see page 20 of the guidance).

In addition, on page 19 of the 2012 Technical Document, Section 2.2., Selection of the Benchmark Response Level (BMR), EPA states: *"Selecting a BMR(s) involves making judgments about the statistical and biological characteristics of the dataset and about the applications for which the resulting BMDs/BMDLs will be used. The EPA does not currently have guidance to assist in making such judgments for the selection of the response levels, or BMRs, to use with BMD modeling for most applications (e.g., for calculating reference doses or relative potency factors), and such guidance is beyond the scope of this document."* EPA's lack of transparency regarding its justification for the choices of BMRs in the 1-bromopropane assessment makes it virtually impossible to understand the bases for EPA's decisions. Noting that EPA followed Agency guidance is not sufficient.

The choice of a BMR is critical to the MOE calculations presented. Therefore, additional details on why certain very conservative choices for BMR were made is very important to

[7] EPA, 1991. *Guidelines for Developmental Toxicity Risk Assessment*. Published on December 5, 1991, Federal Register 56(234):63798-63826.
[8] EPA, 2012. Benchmark Dose Technical Guidance. Risk Assessment Forum. EPA/100/R-12/001. June

understand how to interpret EPA's results, as well as to understand whether the risks presented are actually worst case, which appears to be the case, given the inadequate level of detail provided. For example, the EPA BMD modeling appears in some cases to represent a 1% response in rodents (see Table Apx P-2). This level is inconsistent with the Agency's guidelines, which state that the model should only be used within the range of observable effects (typically 10%) to determine a POD. As stated at page 20 of the EPA 2012 BMD Technical Document: "*It is important to recognize that the BMR need not correspond to a response that the study could detect as statistically significantly different from the control response, provided that the response is considered biologically significant*." Given the very low response level chosen, (below 5% in some cases), EPA should provide a discussion of why these response levels would be biologically significant and are superior to NOAEL/LOAEL methods with application of uncertainty factors.

## F. EPA Fails to Consider Its Own Guidance Regarding Developmental Toxicity Risk Assessment

EPA has developed guidance regarding developmental toxicity studies and risk assessment (EPA, 1991).[9] In that guidance, EPA discusses interpretation of fetal and pup study data in light of maternal toxicity (see pages 18-19 of EPA, 1991). In the 1-bromopropane risk assessment, EPA relies on study data from a rat reproduction study known as WIL (2001) in order to derive an acute toxicity BMDL (see page 117) for pregnant women. In the WIL (2001) study (see page 107), Sprague-Dawley rats were exposed to 1-bromopropane via inhalation exposure at levels from 100 to 500 ppm, 6 hours/day during mating, throughout mating, and up to gestation day (GD) 20 for first generation litters. In another study – Huntingdon (2001) (cited by EPA on page 315), Sprague-Dawley rats also were exposed to 1-bromopropane via inhalation at exposure levels of 103, 503 or 1005 ppm, 6 hours/day on GDs 6-19 (see page 315). In the Huntingdon study there was no effect on litter size, and just as was observed in WIL (2001), there was no significant effect on pre- or post-implantation loss. In fact, the only reported toxic effects in offspring in this study were non-specific effects seen in the presence of maternal toxicity. In comparison, WIL (2001) reported a statistically significant effect on live litter size only at an exposure level (500 ppm) that was also associated with signs of maternal toxicity. Therefore, using EPA guidance on developmental toxicity risk assessment, the data from both GLP quality rat studies, one a reproductive toxicity study (WIL, 2000) and the other a developmental toxicity study (Huntingdon, 2001), should be interpreted in light of the maternal toxicity data as

[9] EPA, 1991. *Guidelines for Developmental Toxicity Risk Assessment*. Published on December 5, 1991, Federal Register 56(234):63798-63826.

discussed in EPA's own guidance. Yet, EPA fails to provide such study data discussion in its 1-bromopropane draft risk assessment.

### G. The Use of Non-GLP Study Data Instead of GLP Quality Data for the Reproductive Toxicity Hazard Assessment is Not Adequately Explained and Errors in the Risk Assessment Need Correction

EPA identifies reproductive toxicity in its draft risk assessment as one of the hazards of 1-bromopropane. As shown in Table 3-1, EPA identifies the available data used in its hazard assessment and non-cancer dose-response assessment. The key studies identified and used by EPA in its risk assessment for non-cancer effects include a guideline GLP study by WIL Research (2001) and a research study by a Japanese group referred to as Ichihara *et al.* (2000b). A careful review of the use of these two studies in EPA's risk assessment identified some important discrepancies that call into question the use of the Ichihara study over the WIL study for dose-response assessment of reproductive toxicity.

The Ichihara *et al.* (2000b) study is a non-GLP research study conducted in male Wistar rats only where animals were exposed by whole body inhalation exposure. The only details of the study available to EPA were those from the publication itself. In Appendix O of EPA's assessment, it states that this study is said to be a "GLP" study, but this conclusion is erroneous based on the published paper itself. Therefore, EPA has misstated a key quality concern for this study. Consequently, the Ichihara *et al.* study is not as robust as another GLP-guideline reproductive toxicity study, i.e., WIL (2001).

Another error exists in Table 3-4, where EPA identifies the lowest human equivalent concentrations (HECs) for non-cancer effects for 1-bromopropane. The entry in the table mistakenly identifies the WIL (2001) study as evidence supporting reproductive system toxicity, *i.e.*, the data presented in Table 3-4 actually relates to the Ichihara *et al.* (2002b) study; not the WIL study. These two errors lead us to question the quality of the study evaluation made by EPA and, given the significance of these studies to the risk assessment for 1-bromopropane, the assessment needs to be corrected.

The use of the Ichihara *et al.* (2000b) study for the 1-bromopropane assessment, rather than the more robust reproductive study known as WIL (2001), is never fully discussed, except to state that the Ichihara study apparently had a lower NOAEL. The Ichihara study tested exposures from 200 to as high as 800 ppm 1-bromopropane, and the authors reported that there was no NOAEL level identified for reproductive effects. Instead, the authors report a LOAEL of 200 ppm based on decreases in absolute and relative seminal vesicle weights. However, the WIL 2001 study identified a NOAEL of 250 ppm 1-

bromopropane in a whole body inhalation exposure study conducted in Sprague-Dawley rats exposed to levels from 100 ppm to as high as 750 ppm. The LOAEL of 500 ppm was associated with decreased percentage of motile sperm and an increase in estrous cycle length. The WIL study saw no significant effects on seminal vesicle endpoints at exposures up-to-and-including 250 ppm 1-bromopropane. It is also important to note that effects on sperm parameters are considered a more sensitive measure of toxicity and are typically associated with biologically relevant changes in reproductive organ effects (EPA, 1996)[10], such as were observed in the 2001 WIL study. Given the fact that Wistar rats are not the standard strain used in chemical toxicology testing in the United States, the possibility of strain-specific differences cannot be ruled out. EPA's risk assessment should explain why the more robust GLP study was set aside in favor of the non-GLP study.

It is also critical to emphasize that the use of the WIL (2001) reproductive toxicity study instead of the non-GLP study by Ichihara *et al.* (2000b) to choose a POD for use in the 1-bromopropane risk assessment would result in a 4-fold increase in the MOEs for adult workers based on reproductive endpoints (HEC of 200 ppm as compared to an HEC of 53 ppm), without refinements to the exposure assessment component of the 1-bromopropane risk assessment, which are also necessary (as discussed above).

## H. EPA's Benchmark Dose Modeling of Reproductive and Developmental Toxicity Datasets Is Inconsistent with EPA Guidance and Decisions that Depart from Guidance Are Not Explained Adequately

ACC has commented above regarding the reproductive toxicity endpoints and assessing risks of non-cancer effects in adult males. ACC reviewed EPA's use of the WIL study data in BMD modeling as applied to non-cancer risk assessment for adult males and pregnant women, for acute and chronic exposure scenarios, and has identified additional inconsistencies. ACC is concerned that EPA has failed to explain adequately the modeling and data choices/decisions it made in the 1-bromopropane risk assessment as it applies to both endpoints of toxicity (*i.e.*, reproductive and developmental endpoints). Consistent with comments above, the key issues ACC has identified concern EPA's choice of BMR levels for BMD modeling and the lack of consistency of those choices with current EPA Technical Guidance (EPA, 2012)[11].

[10] EPA, 1996. *Guidelines for Reproductive Toxicity Risk Assessment*. Published on October 31, 1996, Federal Register 61(212):56274-56322.

[11] EPA, 2012. Benchmark Dose Technical Guidance. Risk Assessment Forum. EPA/100/R-12/001. June

As discussed on pages 102 and 103 in EPA's draft risk assessment for 1-bromopropane, the Agency indicates it will use "a BMR of 5%" to address the severity of the developmental endpoint for both acute and chronic exposures in humans. The endpoint selected is from the WIL 2001 study in rats and was described as "decreased live litter size" at post-natal day 0 (birth) in the $F_1$ generation (see Table 3-1, page 107). Given that this endpoint is a continuous endpoint, EPA's 2012 Technical Document indicates that a BMR of 1 standard deviation (1SD) from the control mean is recommended (EPA, 2012[12]). EPA also states that a justification should always be provided for the selected BMR. The 2012 Technical Document also indicates that a 0.5SD can be used for more severe effects (where a 0.5SD is assumed to correspond to a 5% BMR as may be applied to quantal datasets), yet the basis for such decisions should be discussed in the risk assessment. Interestingly, the support provided by EPA for the use of a 0.5 SD level, assumed to equate here to the 5% BMR, is a paper from 1995 (Kavlock, 1995)[13] (see page 323 of the 1-bromopropane risk assessment). However, Kavlock's paper addresses the issue of BMR choice by pointing out that in the analysis of the validity of BMR choices for developmental toxicity endpoints, the BMD calculations produced values that were similar to NOAELs observed in the same studies (see page 212, right hand column of Kavlock *et al.* 1995). This is not true of EPA's BMR choices and the resulting modeling where use of any standard other than the 1SD standard resulted in BMD and BMDL values that were very different from the NOAEL for live litter size from the WIL study (see values in Table Apx P-2 of the 1-bromopropane risk assessment).

ACC also notes that in Table Apx P-2, EPA indicates that they have used "relative deviation" instead of SD. The use of "relative deviation" is not mentioned or supported by the 2012 EPA Technical Guidance. Therefore, ACC questions the validity of any use of "relative deviation" in the 1-bromopropane assessment, particularly given the lack of discussion of modeling choices in the current draft assessment. The choice to use "relative deviation" in place of SD has a significant impact on the risk assessment and further justification is needed if EPA is going to rely on this endpoint.

Importantly, the Kavlock paper cited by EPA as support for its 1-bromopropane assessment states that the first step in the BMR assessment is to determine what change will be considered biologically significant, emphasizing the importance of this step to the validity of the BMD modeling (see page 216 under "Discussion" of Kavlock *et al.* 1995). Nowhere in the 1-bromopropane risk assessment does EPA provide a rationale or discussion of what change in live litter size would be considered biologically significant.

[12] EPA, 2012. Benchmark Dose Technical Guidance. Risk Assessment Forum. EPA/100/R-12/001. June (page 21).
[13] Kavlock *et al.* 1995. Dose-response assessment for developmental toxicity. IV. Benchmark doses for fetal weight changes. *Fund. Appl. Toxicol.* 26:211-222.

A search of the published literature by ACC failed to identify any specific guidance on this issue. What was found, as mentioned above, is a discussion of the fact that BMD modeling of developmental toxicity endpoints that are continuous data points, such as live litter size, are generally similar to NOAEL values for those same endpoints when robust developmental toxicity studies were evaluated in a meta-analysis (Kavlock, 1995; Kimmel, 1995[14]; Allen. 1994[15]).

Evaluating the actual data for live litter size as presented in Table Apx P-1 (see page 323), and the results of modeling in Table Apx P-2 (page 324), it is clear that EPA has not provided adequate explanation for the choices made in terms of modeling the WIL study data. For example, the live litter size data demonstrates that the control mean litter size was 14.4 with a SD of 2.21. This means that there was a 15% difference in the mean value and the value representing 1SD from that mean in the control group. Yet, a 5% BMR value as used by EPA represents only 0.72, or less than one fewer rat pups per litter, a value that is unlikely to be biologically relevant given that the control group varied by much more than one rat pup from litter to litter. EPA should provide a scientifically-based discussion, not a statistical discussion, of the biological relevance of 0.72 as the 5% BMR for the dataset. If EPA were to use the approach from its 2012 Technical Guidance, the BMR representing 1SD would be applied, which would result in estimates of a BMD that is essentially identical to the NOAEL of 250 ppm identified in the study (see EPA calculations in Table Apx P-2). Moreover, the $BMDL_{1SD}$ of 158 ppm (see Apx P-2) would make logical sense as well, given that 100 ppm was also a NOAEL exposure level in the study. EPA must provide a rationale for use of a BMD and BMDL other than 256 ppm and 158 ppm in the 1-bromopropane risk assessment.

ACC notes that use of the BMD of 256 ppm and a BMDL of 158 ppm would result in increases in the HEC values for the 1-bromopropane risk assessment that are at least 3-fold higher. Given the 2012 Technical Guidance and publications concerning the use of BMD modeling for developmental toxicity study data, ACC finds no support for the use of an alternative approach, including the inappropriate use of the "relative deviation", particularly given the lack of discussion of biological relevance of the very small changes in live litter size of 0.7.

[14] Kimmel et al. 1995. The application of benchmark dose methodology to data from prenatal developmental toxicity studies. *Toxicol. Lett.* 82/83:549-554.
[15] Allen et al. 1994. Dose-response assessment for developmental toxicity. III. Statistical models. *Fund. Appl. Toxicol.* 23:496-509.

## I. There Are Insufficient Data to Establish a Mode of Action for 1-Bromopropane Carcinogenicity

The EPA draft risk assessment states: *"1-BP is expected to be a good alkylating agent because bromine is a good leaving group." "Four possible mechanisms---genotoxicity, oxidative stress, immunosuppression, and cell proliferation—have been suggested." "The exact mechanism/mode of action for 1-BP carcinogenesis is not clearly understood. More research (e.g., organ-specific in vivo DNA adduct studies, oxidative stress) is needed to identify key molecular events"* (page 322).

The limited toxicokinetic data indicate that glutathione (GSH) conjugation and oxidation via cytochrome P450 (CYP450) significantly contribute to the metabolism of 1-bromopropane. As discussed by EPA in the draft 1-bromopropane risk assessment (see page 84), 1-bromopropane is rapidly absorbed and eliminated from the body following inhalation in humans. The metabolism of the chemical in mammals involves: (1) conjugation, principally with glutathione, leading to release of the bromide ion and formation of mercapturic acid derivatives; and (2) oxidation (catalyzed by cytochrome P-450) of parent material and metabolites leading to metabolites with hydroxyl, carbonyl, and sulfoxide groups, and to $CO_2$.

According to EPA, over 20 metabolites have been identified or hypothesized in rodent studies, including four metabolites that have been identified in human urine. While glycidol and propylene oxide have been identified as reactive intermediate, and have been reported to be genotoxic, as discussed above, a weight-of-evidence assessment of the genotoxicity potential of 1-bromopropane indicates that the compound is most likely non-genotoxic. As a result, there is no sound basis for any specific mode of action for 1-bromopropane, and any statements based on the available data are pure speculation. As EPA states in the draft risk assessment: "*The exact mechanism/mode of action for 1-BP carcinogenesis is not clearly understood. More research (e.g., organ-specific in vivo DNA adduct studies, oxidative stress) is needed to identify key molecular events."* ACC encourages EPA to make these conclusions clear as the draft risk assessment is revised.

Regarding mechanism/mode of action, EPA repeatedly states in the draft assessment (at pages 95, 99, 152, and 322 of 403, and in the charge questions to the Peer Review Panel[16]) that *"oxidative stress, immunosuppression and cell proliferation can act synergistically to complete the multi-stage process of carcinogenesis."* EPA provides no scientific support for this sweeping statement and has not connected this finding to any of

[16] The EPA/OPPT Work Plan Risk Assessment for 1-Bromopropane (1-BP)
Draft Peer Review Charge Questions dated February 29, 2016

the 1-bromopropane experimental data. These statements do not support a mutagenic mode of action for 1-bromopropane. ACC recommends that EPA either delete these statements or conduct a more robust scientific review to provide justification for them.

## J. The Discussion of the Potential Genotoxicity of 1-Bromopropane in the EPA Risk Assessment Is Incomplete

EPA's 1-bromopropane draft risk assessment indicates that genotoxicity studies have demonstrated mixed results in tests using bacteria. 1-Bromopropane was stated to be a dose-dependent mutagen in *in vitro* studies with *Salmonella typhimurium* (*S. typhimurium*) strains TA100 and TA1535 when the assay was conducted using closed chambers/desiccators specifically designed for testing volatile substances (Barber *et al.*, 1981). While other Ames tests cited in EPA's assessment were identified as negative for mutagenicity, the Agency noted that a major deficiency in these negative studies was the fact that the system was an "open" rather than "closed" system. However, there is additional Ames test data now available that have not been considered by EPA in its draft risk assessment (BioReliance, 2014)[17]. This new study replicated the closed system used by Barber *et al.* (1981), but demonstrated that 1-bromopropane was not mutagenic *in vitro*, either with or without metabolic activation. These data impact the weight-of-evidence for genotoxicity of 1-bromopropane and should be considered by EPA in its assessment.

With respect to the available genotoxicity data in assays other than the Ames assay, an *in vitro* L5178Y mouse lymphoma cell assay was also positive; however, the increased mutation frequency was noted only at levels that produced cytotoxicity. Therefore, these data do not provide strong evidence for genotoxicity potential of 1-bromopropane. The only other *in vitro* assay suggesting 1-bromopropane may be genotoxic was a Comet assay for DNA damage that employed human leukocytes from venous blood of unexposed workers. This assay had several experimental limitations that affect the interpretation of study results and the weight accorded to the study in any genotoxicity assessment. First, the assay did not include a S9 fraction; without the S9 fraction data, the effect of metabolic capacity as observed *in vivo* was not examined, limiting the utility of the data in the weight-of-evidence assessment. In addition, leukocytes of one donor only were used and no positive control was included in the assay. Overall, the quality of this Comet assay is questionable. All of the *in vivo* mutagenicity studies, including three micronucleus assays, two dominant lethal mutation assays, and one *in vivo* Comet assay were negative. ACC believes that the weight-of- evidence for a mutagenic mode of

[17] The study sponsor, Albemarle, has included this study as part of their comments to this docket (comments dated May 9, 2016).

action for 1-bromopropane does not exist. The EPA draft risk assessment should be revised to reflect the new data and to re-evaluate the issue of mutagenic mode of action.

## K. The Female Mouse Lung Tumor is of Limited Relevance for Human Cancer Risk Assessment

A cancer risk assessment was performed in EPA's risk assessment based on an increased incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in female B6C3F1 mice that had been exposed to 1-bromopropane via inhalation for two years (NTP, 2011)[18]. This result was limited to one species (only mice) and only one sex (female). Mouse lung tumors have been the subject of scientific discussion in recent years, with significant investigation and discussion around the relevance of these tumors to human cancer risk assessment. EPA held a "State-of-the-Science Workshop on Chemically-induced Mouse Lung Tumors" (Workshop) in 2014.[19] At that Workshop, data was presented addressing the issue of human relevance (presentation by Dr. Daniel Krewski). After performing an analysis of known human carcinogens as identified by the International Agency for Research on Cancer (IARC) and comparing human and animal data, Dr. Krewski reported that the concordance of human and mouse lung tumors was only "slight," while the concordance of human and rat lung tumors was only somewhat better and ranked as "moderate." Therefore, positive lung cancer results for 1-bromopropane, which were limited to female mice only, occurred in the rodent species that was found to only slightly correlate with human cancer occurrence. This lack of human concordance should be considered as part of the 1-bromopropane risk assessment process.

In order to determine why there is a lack of concordance between mouse and human lung tumor occurrence, researchers at the EPA Workshop suggested several factors may be involved. In a presentation by Dr. Gary Boorman (Covance), the pathology of human versus mouse lungs was discussed. Dr. Boorman described a series of potentially important differences between the lungs of humans and mice that included: 1) differences in the gross anatomy of the mouse lung and human lung; 2) dominance of the Clara cell in epithelial cells lining mouse lung; and 3) metabolic differences between mouse, rat and human lung. Each of these factors indicates that mouse lung tumors are not relevant for quantitative cancer risk assessment and for predicting human risk. These issues are

[18] NTP, 2011. NTP Technical Report on the Toxicology and Carcinogenesis Studies of 1-Bromopropane (CAS No. 106-94-5) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). (NTP TR 564; NIH Publication No. 11-5906). Research Triangle Park, NC.

[19] http://www2.epa.gov/iris/mouse-lung-tumor-workshop

discussed in detail in comments provided by Albemarle (dated May 9, 2016) and ACC believes they provide important support for the lack of relevance of mouse lung tumors to human cancer risk.

## L. Comments on 1-Bromopropane Draft Peer Review Charge Questions

Consistent with EPA's Scientific Advisory Board practices, we recommend that the peer review discussions begin with a robust discussion of each of the charge questions and allow stakeholder comment as part of this discussion. ACC has a number of comments and concerns regarding the 1-bromopropane draft peer review charge questions. In general, the draft charge questions frequently fail to solicit direct opinions concerning the specific scientific issues that are critical to the risk assessment. For example:

- In the "Hazard and Dose-Response Assessment" and "Rick Characterization" sections, EPA should include the following key question: *"Did we choose the appropriate critical GLP studies that were available and present a sound scientifically balanced weight-of- evidence discussion of the key critical endpoints for the non-cancer and cancer assessments as well as the acute and chronic risk scenarios?"*

- Questions 2-1, 2-3, 2-4 and 3-1: EPA should specifically request comment regarding the inputs used in the exposure modeling and subsequent calculations.

- The introduction to the hazard and dose-response charge questions discusses EPA's review of the evidence. EPA should explicitly state that its calculations were based on the lowest human equivalent concentrations (HECs) rather than on the quality of the individual studies, and request comment on this approach.

- Question 4-1: EPA should revise this question to ensure that it accurately reflects the assessment and ensure that comment is requested on whether EPA's finding is appropriate. We suggest the following replacement language:

  "EPA/OPPT concluded that 1-BP carcinogenesis occurs through a ***possible*** mutagenic mode of action based on the totality of the available data/information and the WOE. Please comment on whether the cancer hazard assessment has described adequately the relevance of the animal tumors to human risk assessment? Has the Agency adequately described the WOE, using all appropriate critical GLP studies, to address the proposed mutagenic mode of action?"

- Question 4-2: In framing this question, EPA should state that the endpoints chosen were those with the lowest HECs. EPA should specifically take comment on the scientific robustness of this approach.

- Question 4-3: We suggest that EPA add the following question: "Did the Agency choose the appropriate critical GLP studies for this analysis"

- Question 4-4: This question should explicitly request comment on EPA's use of the "relative deviation" in place of the standardized "standard deviation." The question should also request comment on all aspects of the BMR modeling, not only the model averaging approach.

- Risk Characterization: In the introductory section to the charge questions concerning risk characterization, EPA states in the first paragraph, second sentence that "EPA/OPPT calculated MOEs for acute or chronic exposure separately based on the appropriate non-cancer POD and estimated exposure concentrations adjusted for durations." We suggest that the word **"lowest"** be substituted for "appropriate" in that sentence.

## IV. Conclusion:

In conclusion, ACC strongly urges EPA to:

- Acknowledge that its assessment of 1-bromopropane is a screening-level assessment that should be refined to determine if unreasonable risks exist in the occupational and/or consumer applications that are the focus of the assessment;
- Refine the 1-bromopropane assessment using "best science" approaches in all aspects of the assessment, i.e., benchmark dose modeling, non-cancer and cancer risk assessments, and the exposure component;
- Conduct a systematic review of study quality, relevance, and reliability of each study used in the revised and refined assessment;
- Refine the exposure assessment with current data and information in both occupational and consumer settings with the assistance of industry stakeholders;
- In a refined assessment of 1-bromopropane, describe in adequate detail the scientific basis for decisions made when applying modeling to reproductive and developmental toxicity datasets;
- Consider its own guidance regarding developmental toxicity and explain the endpoints relied upon for its conclusions; and
- Consider all available data regarding genotoxicity and apply a weight-of-evidence approach in drawing conclusions from the data;