



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 22 2016

OFFICE OF
CHEMICAL SAFETY AND POLLUTION
PREVENTION

MEMORANDUM

SUBJECT: Transmittal of Minutes of the May 24-25, 2016 Chemical Safety Advisory Committee (CSAC) Meeting Regarding the Draft Risk Assessment for TSCA Work Plan Chemical 1-Bromopropane (CASRN-106-94-5)

TO: Wendy Cleland-Hamnett
Director
Office of Pollution Prevention and Toxics

FROM: Steven M. Knott, M.S.
Designated Federal Official, CSAC Staff
Office of Science Coordination and Policy *Steven M. Knott*

THRU: Laura E. Bailey, M.S.
Supervisory Physical Scientist/Executive Secretary, FIFRA SAP
Office of Science Coordination and Policy *Laura Bailey*

Stanley Barone, Ph.D.
Acting Director
Office of Science Coordination and Policy *Stanley Barone*

Attached, please find the minutes of the May 24-25, 2016 CSAC open public meeting held in Arlington, VA. This report addresses a set of scientific issues being considered by the Environmental Protection Agency regarding the Draft Risk Assessment for TSCA Work Plan Chemical 1-Bromopropane (CASRN-106-94-5).

Attachment (1)

cc:

Jim Jones
Louise Wise
Jeff Morris, Ph.D.
Tala Henry, Ph.D.
Alva Daniels, Ph.D.
OPPT Docket

CSAC Members

Kenneth Portier, Ph.D.

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CSAC Subcommittee Members for Review of the Draft Risk Assessment for TSCA Work Plan Chemical, 1-bromopropane (CASRN-106-94-5)

James Blando, Ph.D.

Muhammad Hossain, D.V.M., Ph.D.

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Chemical Safety Advisory Committee
Minutes No. 2016-02

**A Set of Scientific Issues Being Considered by the
Environmental Protection Agency Regarding
The Draft Risk Assessment for TSCA Work Plan
Chemical 1-Bromopropane (CASRN-106-94-5)**

**May 24-25, 2016
CSAC Meeting
Held at the
Crystal City Marriott
1999 Jefferson Davis Highway
Arlington, VA**

The Chemical Safety Advisory Committee (CSAC) is a Federal advisory committee operating in accordance with the provisions of the Federal Advisory Committee Act (FACA), 5 U.S.C. App.2 § 9 (c). The CSAC supports the Environmental Protection Agency (EPA) in performing its duties and responsibilities under the Toxic Substances Control Act (TSCA), 15 U.S.C. 2601 et seq., the Pollution Prevention Act, 42 U.S.C. 13101 et seq., and other applicable statutes. The CSAC provides scientific advice, information, and recommendations to the EPA Administrator on the scientific basis for risk assessments, methodologies, and pollution prevention measures or approaches. The meeting minutes represent the views and recommendations of the CSAC and do not necessarily represent the views and policies of the EPA or of other agencies in the Executive Branch of the Federal government. Mention of trade names or commercial products does not constitute an endorsement or recommendation for use. The meeting minutes do not create or confer legal rights or impose any legally binding requirements on the EPA or any party.

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1. NOTICE

The CSAC serves as the primary scientific peer review mechanism of the Environmental Protection Agency (EPA), Office of Pollution Prevention and Toxics (OPPT), and is structured to provide independent expert assessment of chemical and chemical-related matters facing the Agency. These meeting minutes have been written as part of the activities of the CSAC. In preparing the meeting minutes, the CSAC carefully considered all information provided and presented by EPA, as well as information presented in public comments.

The meeting minutes of the May 24-25, 2016 CSAC meeting held to consider and review scientific issues associated with the draft risk assessment for TSCA Work Plan chemical 1-bromopropane were certified by Dr. Kenneth Portier, CSAC Chair, and Steven Knott, CSAC Designated Federal Official. The minutes were reviewed by Laura E. Bailey, M.S., FIFRA SAP Executive Secretary. The minutes are publicly available on the CSAC website (<https://www.epa.gov/csac>) under the heading of "Meetings" and in the public e-docket, Docket No. EPA-HQ-OPPT-2015-0805, accessible through the docket portal <https://www.regulations.gov>. Further information about CSAC reports and activities can be obtained from its website at <https://www.epa.gov/csac>. Interested persons are invited to contact Steven Knott, Designated Federal Official, via e-mail at knott.steven@epa.gov.

CSAC Minutes No. 2016-02

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding the Draft Risk Assessment for TSCA Work Plan Chemical 1-Bromopropane (CASRN-106-94-5)

May 24-25, 2016
CSAC Meeting
Held at
Crystal City Marriott
1999 Jefferson Davis Highway
Arlington VA



Kenneth Portier, Ph.D.
CSAC Chair
Chemical Safety Advisory Committee
Date:

AUG 22 2016



Steven Knott, M.S.
Designated Federal Official
Chemical Safety Advisory Committee
Date:

AUG 22 2016

2. COMMITTEE ROSTER

Chemical Safety Advisory Committee (CSAC) Chair

Kenneth Portier, Ph.D., Vice President, Statistics and Evaluation Center, American Cancer Society, Atlanta, GA

CSAC Members

Holly Davies, Ph.D., Senior Toxicologist, Department of Ecology, State of Washington, Olympia, WA

Panos G. Georgopoulos, Ph.D., Professor of Environmental and Occupational Health, Rutgers Biomedical and Health Sciences - School of Public Health, Rutgers, The State University of New Jersey, Piscataway, NJ

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Daniel Schlenk, Ph.D., Professor of Aquatic Ecotoxicology and Environmental Toxicology, University of California, Riverside, Riverside, CA

Kristina Thayer, Ph.D., Deputy Division Director of Analysis and Director, Office of Health Assessment and Translation, National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC

CSAC Subcommittee Members for Review of the Draft Risk Assessment for TSCA Work Plan Chemical, 1-bromopropane (CASRN-106-94-5)

James Blando, Ph.D., Associate Professor, School of Community & Environmental Health, Old Dominion University, Norfolk, VA

Muhammad Hossain, D.V.M., Ph.D., Assistant Professor, Department of Pharmaceutical Sciences, Northeast Ohio Medical University, Rootstown, OH

Melanie Marty, Ph.D., Formerly Acting Deputy Director (Retired), Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA

Michael Pennell, Ph.D., Associate Professor of Biostatistics, College of Public Health, Ohio State University, Columbus, OH

Lesliam Quiros-Alcala, Ph.D., Assistant Professor, Maryland Institute of Applied Environmental Health, School of Public Health, University of Maryland, College Park, MD

3. INTRODUCTION

On May 24-25, 2016 the US EPA Chemical Safety Advisory Committee (CSAC) met in an open public meeting in Arlington, VA to consider and review scientific issues associated with the draft document entitled, “TSCA Work Plan Chemical Risk Assessment 1-bromopropane (n-Propyl Bromide): Spray adhesives, dry cleaning, and degreasing uses (CASRN: 106-94-5).” The assessment focuses on uses of 1-bromopropane in commercial applications (i.e., vapor degreasing, spray adhesives, and dry cleaning) and consumer applications (i.e., aerosol solvent cleaners and spray adhesives). Given the range of endpoints (i.e., cancer and non-cancer; the latter includes potential effects on the developing fetus and adults of both sexes), susceptible populations are expected to include adults (including pregnant women) in commercial uses and children (as bystanders) and adults of all ages (including pregnant women) for consumer uses. Thus, the assessment focuses on all humans and life stages. The CSAC was charged with reviewing the scientific and technical merit of the draft 1-bromopropane risk assessment focusing exclusively on the scientifically relevant issues pertinent to the assessment.

The following US EPA presentations were provided during the CSAC meeting (listed in order of presentation):

Welcome and Opening Remarks – Stan Barone Jr., M.S., Ph.D., Acting Director, Office of Science Coordination and Policy and Jeff Morris, Ph.D., Deputy Director, Office of Pollution Prevention and Toxics

Introduction and Background – Tala Henry, Ph.D., Director, Risk Assessment Division, Office of Pollution Prevention and Toxics

Overview of the Draft Risk Assessment for TSCA Work Plan Chemical, 1-Bromopropane (CASRN-106-94-5) – Katherine Anitole, Ph.D., and Greg Macek, Risk Assessment Division, Office of Pollution Prevention and Toxics

4. PUBLIC COMMENTERS

Oral public comments were provided by

Christina Franz and Nancy Beck, Ph.D., on behalf of the American Chemistry Council (ACC)

Written public comments were provided by:

Anonymous

Lee Anderson on behalf of the BlueGreen Alliance

Steve Anderson, D.V.M., Ph.D., D.A.B.T., on behalf of Albemarle Corporation

Steven Bennett, Ph.D, on behalf of the Consumer Specialty Products Association (CSPA)

Department of Defense, Office of the Assistant Secretary of Defense for Energy, Installations, and Environment, Environmental Safety and Occupational Health Directorate, Chemical and Material Risk Management Program

Christina Franz on behalf of the American Chemistry Council (ACC)

Eve Gartner and Emma Cheuse, on behalf of Blue Green Alliance, Earthjustice, Environmental Health Strategy, Natural Resources Defense Council, Safer Chemicals Healthy Families and Sierra Club Toxics Committee

Amy D. Kyle, Ph.D., M.P.H., School of Public Health, University of California, Berkeley

Mariana Lo, on behalf of Earthjustice

Ali Mirzakhilili, P.E., on behalf of the State of Delaware, Department of Natural Resources and Environmental Control, Division of Air Quality

Mark Stelljes, Ph.D., on behalf of EnviroTech International

J. Jared Snyder, on behalf of the New York State Department of Environmental Conservation (DEC)

Tracey J. Woodruff, Ph.D., M.P.H., University of California, San Francisco

Public comments are available in the public e-docket, Docket No. EPA-HQ-OPPT-2015-0805, accessible through the docket portal <https://www.regulations.gov>.

5. TABLE OF ABBREVIATIONS

| | |
|----------------------------|--|
| 1-BP | 1-Bromopropane |
| 2-BP | 2-Bromopropane |
| AC | Acute Concentration |
| ACC | American Chemistry Council |
| AcPrCys | N-acetyl-S-(n-propyl)-l-cysteine |
| ACToR | Aggregated Computational Toxicology Resource |
| ADAF | Age-Dependent-Adjustment Factors |
| ADC | Average Daily Concentration |
| AER | Air Exchange Rate |
| ACGIH | American Conference of Governmental Industrial Hygienists |
| AIC | Akaike Information Criterion |
| AOP | Adverse Outcome Pathway |
| AT | Averaging Time |
| BIC | Bayesian Information Criterion |
| BLS | Bureau of Labor Statistics |
| BMCL | Benchmark Concentration Lower Confidence Limit |
| BMD | Benchmark Dose |
| BMDL _{1SD} | Benchmark Dose Lower Confidence Limit, 1 Standard Deviation Change from the Mean |
| BMDL _{[1 or 5]RD} | Benchmark Dose Lower Confidence Limit, [1% or 5%] Relative Deviation From Control Mean |
| BMDS | Benchmark Dose Software |
| BMR | Benchmark Response |
| BPMA | Bromo Propane Mercapturic Acid or N-acetyl-S-(n-propyl)-l-cysteine |
| BW | Body Weight |
| C | Concentration |
| CARB | California Air Resources Board |
| CASRN | Chemical Abstracts Service Registry Number |
| CDC | Centers for Disease Control and Prevention |
| CEM | Consumer Exposure Model |
| CERHR | Center for the Evaluation of Risks to Human Reproduction |
| CFD | Computational Fluid Dynamics |
| CFF | Far Field Concentration |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CNF | Near Field Concentration |
| CNS | Central Nervous System |
| ConsExpo | Consumer Exposure and Uptake Models |
| CONTAM | Multizone Airflow and Contaminant Transport Analysis Software (NIST) |
| CPCat | Chemical and Product Categories database |
| CSAC | Chemical Safety Advisory Committee |

| | |
|--------------|--|
| CSPA | Consumer Specialty Products Association |
| CYP | Cytochrome P450 |
| DC | Dry Cleaning |
| DEC | New York State Department of Environmental Conservation |
| DNA | Deoxyribonucleic Acid |
| DOI | Digital Object Identifier |
| EC | Engineering Control |
| ECETOC | European Centre for Ecotoxicology and Toxicology of Chemicals |
| ED | Exposure Duration |
| E-FAST | Exposure and Fate Assessment Screening Tool |
| EPA / US EPA | Environmental Protection Agency |
| ETI | Envirotech International |
| FACA | Federal Advisory Committee Act |
| FMO | Flavin-containing Monooxygenase |
| FQPA | Food Quality Protection Act of 1996 |
| GM | Geometric Mean |
| GSH | Glutathione |
| GST | Glutathione S-Transferase |
| HAP | Hazardous Air Pollutant |
| HEC | Human Equivalent Concentration |
| HETAB | Hazard Evaluation and Technical Assistance Branch |
| HHE | Health Hazard Evaluations |
| HPV | High Production Volume |
| IMF | Institute of Metal Finishing |
| IUR | Inhalation Unit Risk |
| LADC | Lifetime Average Daily Concentration |
| LOAEL | Lowest Observed Adverse Effect Level |
| logKow | Logarithm of the Octanol-Water Partition Coefficient |
| MADr-BMD | Model Averaging for Dichotomous Response Benchmark Dose |
| MIE | Molecular Initiating Event |
| MMWR | Morbidity and Mortality Weekly Report |
| MOA | Mode of Action |
| MOE | Margin of Exposure |
| NDERM | Dermal Number, a dimensionless ratio of applied load and absorbable amount |
| NEI | National Emissions Inventory |
| NHANES | National Health and Nutrition Examination Survey |
| NIEHS | National Institute of Environmental Health Sciences |
| NIOSH | National Institute of Occupational Safety and Health |
| NIST | National Institute of Standards and Technology |
| NJDEP | New Jersey Department of Environmental Protection |
| NOAEL | No Observed Adverse Effect Level |
| NTP | National Toxicology Program |
| OMB | Office of Management and Budget |
| OPPT | Office of Pollution Prevention and Toxics |

| | |
|--|---|
| OSHA | Occupational Safety and Health Administration |
| PBPK | Physiologically Based Pharmacokinetics |
| PERC | Perchloroethylene/Tetrachloroethylene |
| personal_care cosmetics prohibited_ASEAN | Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II; substances prohibited in cosmetic products; CPCat description of ACToR list |
| PID | Photo Ionization Detector |
| PNS | Peripheral Nervous System |
| POD | Point of Departure |
| PUMS | Public Use Microdata Sample |
| RAD | Risk Assessment Division |
| REACH | Registration, Evaluation, Authorisation and restriction of Chemicals, EU |
| RF | Reduction Factor |
| RoC | Report on Carcinogens (NTP) |
| TCE | Trichloroethylene |
| TLV | Threshold Limit Value |
| TRI | Toxics Release Inventory |
| TSCA | Toxic Substances Control Act |
| TWA | Time Weighted Average |
| UF | Uncertainty Factor |
| VOC | Volatile Organic Compound |
| WIL | WIL Research Laboratories |
| WOE | Weight of Evidence |

6. EXECUTIVE SUMMARY OF COMMITTEE DISCUSSION AND RECOMMENDATIONS

Overall, the Committee found that EPA/OPPT (hereafter referred to in the Committee’s responses as the Agency) had developed a good risk assessment document for 1-bromopropane (1-BP). The Committee provided a number of recommendations intended to improve the clarity and transparency of the scientific analyses presented in the Agency’s document. In addition, the Committee provided specific recommendations to address or more clearly acknowledge the limitations of the scientific analyses. However, the Committee expressed the view that the Agency should not delay completing the risk assessment because the occupational and consumer use scenarios already evaluated indicate high risks of adverse effects and some Committee members’ comments indicate that these risks might have been under- rather than over-estimated.

Committee members agreed that the 1-BP risk assessment (and other TSCA chemical assessments to be presented in the future) would benefit by adoption of systematic review practices to increase the transparency of how studies were selected and evaluated. For example, the Committee recommended that it should be explicitly stated what criteria were used to determine “the monitoring was adequate and of acceptable quality” (risk assessment document, page 44). The Committee also noted that it would be useful to reference studies that were

evaluated but did not meet baseline criteria to inform the exposure estimates. Inclusion of more details on the literature are recommended throughout the report and in Appendix M.

In addition, the Committee noted that the audience for the risk assessment document is unclear. The stated audience is the Agency's risk managers, but some topics are explained at a much more basic level than others.

The following is a summary of the Committee's key recommendations for each theme provided in the Agency's charge to the CSAC.

General Issues on the Risk Assessment

In general, the Committee found that the information provided in the Background and Scope of the risk assessment is appropriate and fit for its purpose. The Committee found that the conceptual model appropriately considers worker exposures and consumer uses, with the majority of exposure occurring via inhalation. Committee members agreed that inhalation exposure is the most important and that while dermal exposures might be important as a contributor to overall exposure, if data are not available for monitoring or modeling efforts, then it is reasonable not to include this route of exposure. However, the Committee recommended that a quantitative argument would be more persuasive and some Committee members recommended that an estimate for dermal exposure should be included and gaps/limitations clearly stated to address another potential workplace exposure pathway.

Committee members observed that the consumer uses with acute exposures are important to include in this assessment. In addition, several Committee members commented that there should have been more consideration of exposures from co-residence near dry cleaning facilities, community-level exposures in areas nearby industrial or dry cleaning operations, and the general population (a concern raised by the NHANES data and apparent appearance of 1-BP in some consumer product databases). The Committee found that the exposure terminology employed in the report needs to be adjusted; i.e., the report should refer to residential rather than consumer exposure. This distinction is important since residential exposure implies a population with a wider age distribution, and is important to ensure that exposures to children are not under-predicted.

Occupational Exposure Assessment

The Committee found that the Agency's analysis of occupational exposures is necessarily complex, entailing multiple occupational scenarios and utilizing both measured and predicted air concentrations to assess hazard. In addition, the Committee found that for the types of scenarios considered, the Agency has probably collected and adequately "codified" the most pertinent information although data were quite limited for certain scenarios. The Committee observed that many of the charge questions posed by the Agency are requests for additional exposure information. Therefore, the Committee recommended that the Agency further explore various means for obtaining such information for future assessments.

The Committee made several recommendations based on the fact that many dry cleaning facilities are family-owned and operated. For example, the Committee recommended that the

scenarios for worker hours in dry cleaners could be expanded to include a wider range of scenarios (e.g., 4, 6, 8, and 12 hours). The Committee also noted that estimating exposures to children (“workers” and “bystanders”) in dry cleaning facilities could be considered. It is plausible that in family-owned/operated dry cleaning facilities children under 16 could be helping/working (or could be “bystanders” while they wait for their parents to finish their job) and potentially be exposed to 1-bromopropane. In addition, the committee concluded that it was appropriate for the Agency to assume that the machines in the dry-cleaning exposure scenarios were older models as family-owned and operated facilities may not have the resources to purchase newer equipment.

The Committee noted that inclusion of post-EC (Engineering Control) exposure estimates is useful as this provides an estimate of the impact of ECs in different exposure scenarios; however, as noted in the risk assessment report, it is uncertain whether ECs at dry cleaning facilities would reduce levels by the estimated amount of 90%.

The Committee noted that comparison of modeling results and environmental and/or biomarker measurements is useful, if possible. The Committee recommended that the Agency consider the feasibility of adding graphical or tabular comparisons between predicted and observed environmental concentrations when the latter are available. The Committee also noted that comparison of biomarker ranges observed in selected and unselected study populations would be valuable.

The Committee recommended expanding the Monte Carlo simulation of occupational exposures by replacing some of the point estimates of input variables with distributions; an example of such a point estimate that should be replaced by a distribution is the number of working hours. In contrast to the probabilistic approach used for occupational exposure analysis, the Agency has conducted a deterministic analysis of the consumer exposure scenario. While sympathetic to issues of data insufficiency, the Committee encourages the Agency, going forward, to adopt probabilistic approaches and members of the Committee observed that the Agency would be better served by employing a probabilistic approach for the consumer exposure assessment. The Committee noted that discussion of the type the Committee engaged in regarding the validity of individual estimates (e.g., the overspray fraction) would be obviated by use of distributed values.

The Committee concluded that the Agency appropriately uses a high-end estimate for worker exposure and includes the estimate based on monitoring in the risk characterization section.

Consumer Exposure Assessment

The Committee evaluated the approach that was used by the Agency to estimate exposures to 1-BP from use of consumer products in the home, and concluded that, although the basis of the approach is fundamentally reasonable, the scenarios represent a subset of uses of consumer products containing 1-BP. Though these may be the potentially most important scenarios, the Committee noted that it is essential to provide better justification regarding their selection.

Much effort is currently being put into development of consumer exposure models useful in the context of REACH in Europe and for purposes of Life Cycle Analysis in the U.S. Comparability

of consumer exposure modeling within the TSCA Work Plan process and other initiatives is of interest to the Committee. The Committee discussed the utility of comparing a subset of CEM E-FAST calculations with an “external” model of similar sophistication such as those developed for the European REACH program (e.g., ConsExpo or ECETOC).

The Committee suggests that the Agency consider multiple uses on any day of the various aerosol products, and use on multiple days per week. A do-it-yourselfer may have multiple items that need cleaning/degreasing/gluing in a single project and thus may use the product multiple times on a given day or multiple days in a week. One Committee member expressed concerns related to modeling exposure based on a single short use and spreading the exposure out over 24 hours. The Committee member noted the possibility of conflating two concepts (modeling of exposure and time extrapolation from experimental exposure to the human scenario), but expressed a concern about very short high exposures being equated in terms of degree of adverse effect to longer exposures to much lower levels.

The Committee further suggested that the Agency consider that the selected exposure scenarios probably represent episodic pathways in a subset of the population (i.e., users and co-habitants of users). Given the possibility of overlooking a significant exposure scenario, the inclusion of biomarker data could be useful. Along these lines, the measurement of BPMA levels by Boyle et al. (2016) suggests the possibility of low level, but very widespread, non-occupational exposures to 1-BP; however, the Committee recognizes that there are some questions regarding the specificity of the biomarker used. Once BPMA or another metabolite has been validated as a biomarker of 1-BP exposure, this could be used for a more accurate assessment of residential exposure.

Hazard and Dose Response Assessments

The Committee concluded that the available evidence supports using a low-dose linear model to assess dose-response for carcinogenicity. Most Committee members agreed that the existing evidence supports a conclusion of mutagenicity/genotoxicity as the primary mode of action (MOA) for 1-BP and some of its metabolites (i.e., oxide, alpha-bromohydrin, and glycidol). One Committee Member concluded that the evidence for mutagenicity was not convincing. The Committee suggested the Agency consider broadening the terminology used in the report to describe the primary MOA as “mutagenic/genotoxic” or “genotoxic” to better characterize the contribution of the non-mutagenic endpoints that support genotoxicity.

In general, the Committee members observed that the Agency had conducted a thorough review of the literature and adequately explained the multiple lines of evidence supporting the selected non-cancer endpoints. The Committee agreed that the Agency had appropriately considered various non-cancer endpoints, including liver, kidney, reproductive, developmental, and neurotoxicity for assessing human risk associated with acute and chronic inhalation exposures to 1-BP. The Committee found that together, the most sensitive non-cancer endpoints seem to be neurologic, reproductive, and developmental endpoints. In most cases, adverse toxic effects were observed in both humans and animals at the concentration range 100-1000 ppm.

Some Committee members suggested that a POD value for the neurologic endpoints from human data is enough to exclude the 10-fold UF for inter-species considerations. Some committee members suggested that comparing POD values derived for neurotoxicity in humans with the HEC from the animal studies may be a good way to check the inferences being made from the animal studies, recognizing the uncertainties in the human data in terms of exposure assessment. As noted above, the Committee suggested the Agency better clarify the basis for key study selection (e.g., use of the WIL report for liver toxicity). The Committee found the evidence that 1-BP causes neurotoxicity very convincing. In this case, the Agency used 15 years of behavioral, neuropathological, neurochemical, and neurophysiological studies in rodents as well as cross-sectional studies and case reports in humans to establish a causal association with 1-BP and neurotoxicity.

The Committee also found that the choice of multiple reproductive endpoints including decreases in prostate, epididymal, seminal vesical weight and sperm motility in male and prolonged estrous cycle, decrease in number of antral follicles and implantation sites in female were appropriate for the assessment of reproductive toxicity. The Committee further found that the POD values selected seemed appropriate given the dose response of 1-BP in the WIL study.

The Committee noted that the model averaging approach used for cancer endpoints has many advantages over the use of a single parametric dose-response model in determining a POD, including addressing model uncertainty when there isn't strong mechanistic support for a particular dose-response relationship, and producing more stable estimates than individual models. While model averaging used by the Agency has several strengths, the Committee noted it also has several weaknesses. First, since the models the Agency used in computing the average are all monotonic, the average dose-response curve must be monotonic. Since monotonicity is commonly assumed in dose-response assessment of carcinogens, the Committee did not find this particular assumption to be problematic.

The second major assumption involved in model averaging is that an appropriate model space has been chosen. The model space chosen by the Agency included the log-probit model. The Committee found that there are conceptual objections and empirical evidence for not using the log-probit model to generate an average dose-response curve. Therefore, the Committee recommends removing the log-probit model from the model averaging due to its instability when applied to the three cancer data sets and its disagreement with standard mechanistic assumptions for carcinogens.

The Committee also recommended that the Agency clearly explain the rationale for using an approach for determining the POD which differs from standard Agency practice as described in the Agency's cancer risk assessment guidelines.

Risk Characterization

The Committee observed that dose-response assessment always involves uncertainty; hence the use of uncertainty factors in the non-cancer risk assessment. For cancer risk assessment, choice of model to determine the cancer slope factor introduces model uncertainty, and extrapolation from animals to humans always involves some unquantifiable uncertainty. Nonetheless, overall,

the Committee agrees with the Agency that the uses of 1-BP containing materials present high risks of adverse non-cancer and cancer outcomes to workers and consumers. The Committee noted that the focus on the high-end acute exposure for occupational (95th percentile) and consumer (90th percentile) populations seems appropriate. The Agency notes that the MOEs indicate that workplace exposures are mostly unacceptable in terms of non-cancer health risk; even with exposures measured after engineering controls were put into place, many of the MOEs were smaller than the benchmark MOE. The Committee agrees with the Agency's conclusion. In addition, the Committee agreed, for the most part, that the estimate of consumer exposure from spray adhesives, cleaning products, spot removers, etc. (Tables ApxL-2, L-3) seemed logical. Since the MOEs calculated for consumer exposure scenarios were below the benchmark MOE of 100, there is a legitimate reason to believe that risk to consumers exists as well.

A few Committee members expressed concern about the selection of only a total uncertainty factor of 100 to form the basis of the benchmark MOE for the developmental and reproductive endpoints selected. While some Committee members were comfortable with a benchmark MOE of 100 when using the animal-based POD, one member notes that the Agency could think about a larger uncertainty factor for intra-species variability resulting in a benchmark MOE up to 300 for this chemical. Further, another Committee member observed that for developmental toxicity, the Agency should consider an additional uncertainty factor, analogous to the Food Quality Protection Act factor applied for assessing pesticide tolerances. It is not clear whether there are short windows of exposure for neurotoxicity in children relevant to an acute exposure scenario as there are for the fetus, but some Committee members noted this should be considered in the choice of the uncertainty factor and discussed in the document.

The Committee found that, based on the dose-response assessment, the Agency appropriately chose the lowest PODs and associated HECs for each of the non-cancer endpoints from among the datasets amenable to dose-response assessment (with the possible exception described below, in Section 7). The Agency chose to use developmental toxicity based on animal studies as a basis for acute exposure risk assessment for occupational scenarios. The Committee concluded this was an appropriate endpoint to choose for assessing acute exposures to consumers using 1-BP containing products. The Committee noted that this endpoint is appropriate for an acute exposure scenario given that developmental toxicity may occur from a brief exposure during a critical window of susceptibility. The Committee found that, overall, using the lowest human equivalent concentrations as the point of departure for the developmental and reproductive toxicity for acute inhalation exposures is appropriate (and is standard risk assessment practice).

The Committee found that the choice to use the Inhalation Unit Risk (IUR) from the lung tumor data presented in the NTP report is appropriate. One Committee member suggested using a range of values for the IUR, to include the rat model as well as the mouse, but other Committee members considered selection of the most sensitive site in the most sensitive species appropriate. The Committee also discussed the observation that each of the 3 tumor types occurs in one sex and within one animal species (keratoacanthoma/squamous cell carcinoma in male F344 rats; large intestine adenoma in female F344 rats; and alveolar/bronchiolar adenoma or carcinoma in female B6C3F1 mice). However, the Committee noted during the discussion that this pattern is

not uncommon and site concordance is not necessary to conclude there is a risk. Thus, the Committee found that it is appropriate to use the most sensitive site, gender, and species in cancer risk assessment, as is the standard risk assessment procedure.

The Committee also recommended that the Agency should consider incorporating any of the suggestions raised during the dose-response modeling discussion into the IUR analysis, i.e., excluding the log-probit model, only including models that fit the data and are linear at low doses, and expanding the analysis to key non-cancer endpoints. A number of Committee members asked for a comparison of the modeling analysis used in 1-BP with more typical analysis as outlined in the U.S.EPA Risk Assessment Guidelines for carcinogens (US EPA, 2005a). This seems to be included in an appendix but the Agency should consider whether it needs to be referenced in the main body of the report. The Committee agreed that it is not appropriate to try to quantitate cancer risk from acute exposures, for all the reasons given by the Agency.

Most Committee members agreed that, overall, the available data and assumptions used by the Agency represented a fair and logical approach to estimating the parameters that determine exposure, but a few Committee members noted that there could be residual concerns between events or there could be relevant exposure mixtures from other chemicals in the consumer products. In addition, a number of Committee members were concerned that the risk assessment did not take into account the possibility that bystanders could be in the same room as the user for the consumer scenarios.

Several Committee members noted that the exposure calculations in the MOE determination are based on 8-hour time weighted averages (TWA). Committee members noted that there may be scenarios where workers may be exposed during a 12-hour rather than 8-hour shift (e.g., dry cleaners) and, if such scenarios cannot be estimated, the limitations of excluding them should be discussed in the risk characterization.

7. DETAILED COMMITTEE DELIBERATIONS AND RESPONSE TO CHARGE QUESTIONS

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 with most consumer products contents ranging between 60-100%.

Based on the physical-chemical properties and use scenarios described in the 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.

Committee Response

Comments on Background and Scope

In general, the Committee found that the information is appropriate and fit for its purpose. The summary should provide more explanation regarding what authority the Agency has under TSCA, what are TSCA products, what are unacceptable risks, and what risk management options are available under TSCA.

TSCA uses the term “unreasonable risk.” However, Section 1.1 of the risk assessment indicates that the purpose of this document/assessment is to identify “unacceptable risks” to humans or the environment and to inform risk managers and the broader risk community of any unacceptable risks so identified. In addition, the questions on page 31 of the risk assessment refer to “risks of concern,” which seems to be a different standard without any explanation. Are these different phrases regarding risks supposed to be meaningfully different?

Several Committee members commented that there should have been more consideration of exposures from co-residence near dry cleaning facilities, community-level exposures in areas nearby industrial or dry cleaning operations, and the general population (a concern raised by the NHANES data and apparent appearance of 1-BP in some consumer product databases). These topics came up repeatedly during the meeting and they should be discussed here and either included in the scope, or more explanation should be provided including the rationale for not including these scenarios.

Another comment on scope is the possibility that products containing 1-BP might also contain 2-BP as an impurity and that the levels of this isomer might be significant. In Blando et al. (2010) the potential for 2-BP to be present was described, but the authors did not report their analysis of 2-BP in the air samples. They found a range of non-detectable to trace quantities of 2-BP in the air samples, orders of magnitude lower than the 1-BP detected.

The Committee members agreed with the assessment that while dermal exposures might be important as a contributor to overall exposure, if data are not available for monitoring or modeling efforts, then it is okay not to include this route of exposure. However, the Committee recommended that a quantitative argument would be more persuasive and some Committee members recommended that an estimate for dermal exposure should be included and gaps/limitations clearly stated to address another potential workplace exposure pathway.

The Committee commented that in the assessment and regulatory history section it is important to note that this chemical has been marketed as a “green chemical” and this has presented significant challenges in risk communication because many users or customers may assume this means the chemical is non-toxic.

The Committee also recommended that the risk assessment would be more useful if it included conclusions on potential uses of 1-BP, especially since 1-BP is a potential substitute for perchloroethylene (PERC). This would inform choices of substitutes for other substances, including Work Plan chemicals, and help avoid regrettable substitutes. It is important to note that 40 CFR Part 63 Subpart M - National Perchloroethylene Air Emissions Standards for Dry Cleaning Facilities will require the phase out of PERC machines by 2020. If the only option for dry cleaners to comply with this action is to switch to 1-BP as a drain and drop solution, many will be pushed to convert their machines to 1-BP, resulting in an increase in use. Coordination with the air program will be helpful.

In section 1.2, “Uses and Production Volume,” the Committee recommended it might be worth noting and clearly stating that many factors impact the risk and hazard presented to a community. It might not be production volume that is most predictive of risk because exposure can be driven by many factors beyond just volume of use.

The Committee found that the limitations section is very detailed and well done. However, it might also be worth noting a few other points in the limitations section that affect every risk assessment. While it is not practical to consider or even be aware of every potential use or misuse of a chemical product, it might be worth noting that it is not uncommon for products to be used in a manner inconsistent with label instructions and for work practices to differ from best practices. For example, in occupational settings many times work practices are not ideal because they occur within the context of worker knowledge, time pressures, budget pressures, resource pressures, and both management and worker appreciation for safety and health. As such, there can be extreme variability in exposures, especially when assessing exposure among multiple workers in multiple workplaces. As with every risk assessment, it might also be worth explicitly stating that many communities and workers are exposed to multiple chemicals and hazards concurrently and that this assessment focuses on the effects of one chemical and does not account for any agonist or antagonistic behavior that might occur with exposures to multiple chemicals, whether community, worker, or lifestyle exposures (e.g., alcohol). A useful reason to explicitly mention these types of general limitations of any assessment, which are perhaps obvious to risk assessors, is that professionals beyond risk assessment staff may refer to this document as they carry on their public health duties.

The Committee found that the description of the MOE approach in section 1.55 is generally correct. However, the language on pages 26 and 27 of the executive summary is incorrect and confusing. In three places, language appears that is of the form “Risks were ... below the benchmark MOE.” First, MOE is not risk. MOE benchmarks are safety standards, not risk standards. This is a technical distinction, but the Agency’s personnel should be familiar with it. Risks and MOEs are not similarly scaled and cannot be directly compared. The language should have been along the lines of “Estimated MOEs were below the benchmark MOE.” Second,

estimated MOEs below the benchmark MOE indicate hazard, not low risk. The statement implies low risk, which reverses the meaning of the MOE calculation (potential presence of risk).

Several Committee members commented on whether or not biomarkers of exposure have been identified. For example, N-acetyl-S-(n-propyl)-L-cysteine is now measured in NHANES and appears to be a metabolite of 1-BP. How specific is this biomarker and can it be inferred to be a biomarker indicative of exposure? This metabolite can also be formed from any halogenated propane through glutathione conjugation and subsequent conversion to that N-acetyl derivative which is a common pathway for glutathione conjugates. That type of information also belongs in the Introduction. If N-acetyl-S-(n-propyl)-L-cysteine is a specific marker of exposure, then perhaps it may suggest broader exposure than was considered in this report.

The Agency explained where the information comes from, but it would be helpful to describe the literature search process that identified the relevant literature sources that appear in this section (and in all other sections as well) and it is not clear if the Agency weights different sources differently. Appendix G suggests a variety of sources are treated equally and they should be weighted differently.

Editorial Comments

The Committee recommended that the first two paragraphs in Section 1.1 be reviewed with the goal of clarifying these ideas for readers. The purpose of this document/assessment could be stated more clearly to leave little doubt in the minds of the readers as to what the Agency proposes to accomplish in this assessment. The first two paragraphs have a little about purpose, a little about history, a little about “how we got here” – the latter two topics are covered more extensively and better in subsequent sections. The third paragraph is a transitional one and could more directly outline what follows in the rest of this section.

The Committee observed that there has to be some redundancy in a document like this that is not read in its entirety by most users. However much of the redundancy could be eliminated. For example, although the audience is unclear, based on the level of technical detail, it is not necessary to explain that 10^{-4} is 1 in 10,000, etc., repeatedly in the document. In section 1.4 on Scope, there is a list of nine occupational and consumer uses at the top of the page and then at the bottom of the page starts a list of seven questions that restate the selected uses. There is no need to repeat something that close together within the document. In addition, there is no reason given for combining all three consumer uses into one question (thus making it seven questions instead of nine).

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.

Committee Response

The Conceptual Model and Human Health Risks

The Committee found that the conceptual model appropriately considers worker exposures and consumer uses, with the majority of exposure occurring via inhalation. The Committee members observed that the consumer uses with acute exposures are important to include in this assessment. The exposure scenarios are generally conservative and appropriately assume exposure may occur at a critical developmental window. Additional context might be worth noting in Section 1, especially for the broader public health community who may reference this document. Currently, it is mentioned only within the details of the assessment.

The conceptual model depicted on pg. 35 shows potential pathways and routes of exposure to occupational workers (users and non-users in facilities where 1-bromopropane is being used) and to consumers who directly apply products containing 1-bromopropane. This conceptual model fails to account for other potential sources/pathways of exposures to the general population (e.g., emissions from dry cleaning facilities exposing other building occupants or populations in close proximity) and assumes that exposures occur only in the workplace or in homes where there is direct use of spray adhesives, degreasers, and/or cleaners. 1-BP is a high production volume chemical and very volatile. Clearly because 1-BP is highly volatile, like perchloroethylene, it will escape from dry cleaning, degreasing, and other emissive operations. Many of the engineering controls described in the document involve venting 1-BP vapors to the outside air. Further, the Agency has been petitioned to add 1-BP as a hazardous air pollutant (HAP) because of concern about toxicity and emissions into the ambient air. Thus, the Committee found that exclusion of chronic exposure of the general public near facilities using 1-BP is a major limitation of this risk assessment.

Although environmental persistence is very low, it is possible for people who live in close proximity to an emissions source to be exposed to 1-BP releases. People live and work in apartments or offices co-located with dry cleaners using 1-BP. In Blando et al. (2010), two of the dry cleaners had people living or working on the second floor of the building right above the dry cleaning machines. It is, thus, highly likely that exposures to 1-bromopropane occur in populations living or working in close proximity to facilities using 1-BP. This has been demonstrated previously with perchloroethylene (PERC) (Schreiber, House et al., 1993, Garetano and Gochfeld, 2000, and Storm, Mazor et al., 2013). In addition, perchloroethylene was identified as a common toxic pollutant in the Agency's urban air toxics strategy (US EPA, 1998); if 1-BP were to replace perchloroethylene in dry cleaning it is possible that 1-BP could become a common toxic air contaminant in urban areas.

In addition, exposures occurring in close proximity to facilities using 1-BP could result in a disproportionate health risk in low-income communities and communities of color, as has been documented with perchloroethylene emissions from dry cleaning facilities (Storm, Mazor et al., 2013).

The Committee noted that the problem formulation and scope should be expanded to include chronic exposures and risk to the general population, including infants and children, from

operations that use 1-BP for degreasing or dry-cleaning, or other emissive sources. However, the Committee also did not want the Agency to delay completing the assessment because the occupational and consumer use scenarios already evaluated indicate high risk of adverse non-cancer health effects and cancer risk in workers and non-cancer risks for consumer uses.

The assessment indicates (page 36) that data were not available for emissions from facilities using 1-BP. However, the Committee noted that it is possible to model a hypothetical drycleaner in a community using generic parameters, which are available, for emissions from a typical dry cleaner to assess routine chronic exposures to the general population. The California Air Resources Board (CARB) has done this for perchloroethylene emissions from a "typical" dry cleaner. CARB also had emissions estimates from degreasers used by the Agency in the worker exposure model in this assessment (CARB, 2011, cited in the Agency's draft assessment). The CARB report was conducted to update their emissions inventory for volatile organic compounds; however, the information in the CARB report could be used to estimate emissions from a facility and apply air dispersion modeling to estimate exposures to residential receptors nearby. The NTP (2013) monograph on 1-BP also noted that "EPA has estimated 1-bromopropane concentrations in ambient air at a distance of 100 meters from average-adhesive use model facilities via air dispersion modeling to be 0.138 mg/m³ [0.0274 ppm] and 1.38 mg/m³ [0.274 ppm] for high-adhesive use facilities (Wolf et al., 2003; also cited as Morris and Wolf, 2003 in NTP's 13th Report on Carcinogens)."

At a minimum, and to prevent delaying completion of the risk assessment, the Agency could use results of air dispersion modeling already conducted or apply air dispersion modeling to emissions estimates from facilities using 1-BP (e.g., Wolf et al., 2003, as cited in NTP, 2013 page 12; or the CARB emissions estimates from degreasers) and estimate risk to residential receptors near such a source. The results of such a cancer risk assessment approach for chronic exposure to the general public based on existing air dispersion modeling or emissions estimates, could be appended to the existing draft report. The uncertainties in estimating emissions from a dry cleaner (or a degreasing operation or foam factory using 1-BP containing adhesive sprays) are no greater than in estimating exposure to consumers.

Given that the Agency has determined that the mode of action likely involves genotoxicity, then the Committee understands that an assessment of the cancer risk from chronic exposure to residents near dry cleaning and degreasing operations would evaluate early-in-life exposures by applying the Age-Dependent-Adjustment Factors (ADAF), as described in the Agency's Supplemental Guidance for assessing cancer risk from early life exposure (US EPA, 2005b), to the risk estimate. Since infants and children breathe more per pound of body weight, the age-appropriate inhalation rates would also be applied in the risk estimate. While occupational and consumer use scenarios may indicate high risk for a relatively smaller population, assessment of risks to the general public living near facilities emitting 1-BP would likely involve lower risks but to potentially rather large populations.

Supporting information for inclusion of chronic exposures to the general public includes biomonitoring studies evaluating the presence of a metabolite of 1-BP. The Committee noted that at least two recent studies have documented the presence of N-acetyl-S-(n-propyl)-1-

cysteine, a urinary biomarker of exposure for 1-bromopropane in pregnant mothers ((Boyle, Viet et al., 2016), data from the National Children’s Study) and in children 6-11 years from the general U.S. population (Jain, 2015). The authors reported detection frequencies of 99% and 60.8% in pregnant mothers and children, respectively. Additionally, 2011-2012 data from the National Health and Nutrition Examination Survey (NHANES) released by the Centers for Disease Control and Prevention (CDC, 2015) also provide supporting evidence that there is widespread exposure in the general U.S. population. Although the Committee realizes these reports came out after the draft was written, some consideration of these data would benefit the revised report. In particular, it would be helpful to understand what other compounds may be metabolized to N-acetyl-S-(n-propyl)-l-cysteine in order to help understand whether these biomonitoring data are indicative of widespread general population exposure to 1-BP or a combination of 1-BP and other small chain organohalogenes.

Other Comments on the Human Health Conceptual Model

The Committee found that the use of the term “consumers” may be misleading as exposures may also occur in non-occupational populations, including infants and children, that do not directly use any of the aforementioned products (e.g., those that reside in the same building or near facilities like dry cleaners using 1-BP). Several Committee members suggested that the Agency should consider replacing the term “consumers” with “general population” or “residential users,” and the term “non-users” in the residential and occupational settings with “bystanders” (depending on the final scope and “consumer” scenarios included in the risk assessment).

A few Committee members noted other potential sources that could potentially explain widespread exposure, and could be discussed in the document. These include:

- 1-bromopropane is used as a spray adhesive in the foam manufacturing industry. A few members observed that the 1-BP solvent may get trapped between layers of foam which slows off-gassing. It is possible that foam furniture represents a common source of exposure as the 1-BP slowly diffuses out between layers of adhered foam comprising the furniture cushions.
- 1-bromopropane has been used as an intermediate in the synthesis of pharmaceuticals, insecticides, quaternary ammonium compounds, flavors and fragrances. The risk assessment document stated that in the past 1-BP was used for these applications, but it is not clear whether use as an intermediate in synthesis of other chemicals could still pose an exposure risk. The document should include information on whether 1-BP is still used in synthesizing these compounds or is present in these products and indicate that inability to estimate exposure from these sources (if they exist) is a limitation of the assessment.

One Committee member noted, and others agreed, that the 1-BP (and more to the point other TSCA chemical assessments to be presented in the future) would benefit by adoption of systematic review practices. The assessment could have a methods section which describes the problem formulation work, strategies used to identify key literature (exposure or health outcome), study inclusion/exclusion criteria, etc.

One Committee member suggested three additional areas to discuss in the draft assessment as follows:

1. Environmental releases should be included, even if there are no readily available national sources of information like TRI and NEI. These could be estimated from local sources, such as state hazardous waste documentation. King County, Washington, which includes Seattle, has worked with dry cleaners for years and has a lot of information on use. According to the King Co. survey, 69% of dry cleaners are in buildings that house a business that sells or provides food. (see *Additional References*)
2. Worker exposure during waste disposal should be estimated.
3. The Agency should include exposure from reducing dry cleaning solvents to remove water before disposing of the remaining solvent as hazardous waste.

Comments on the Conceptual Model and Ecological Risk

The Agency concluded that 1-BP does not present a potential hazard ecologically. This decision was based on the Conceptual Model assumption that exposure is likely primarily via inhalation and that 1-BP is not likely to persist in the environment and undergo bioaccumulation. One Committee member agreed with the Agency that the data on lack of persistence and bioaccumulation argue for not including an environmental risk assessment.

However, another member pointed out that while 1-BP does not have physico-chemical properties that would indicate persistence in the environment (i.e., logarithm of the octanol-water partition coefficient or logKow, $t-1/2$), the fugacity model used by the Agency suggests tendencies of movement into water in concentrations that would be equivalent to concentrations in air. Given the categorization of 1-BP as a High Production Volume (HPV) chemical and a use pattern within textile and industrial parts cleansing, one could postulate aqueous discharge into wastewater from industrial and potentially consumer locations. While logKow are relatively low, by definition a logKow of >1 suggests movement into lipid phase 10 times that of water. If a washing facility perpetually discharges waste from cleansed materials, the phenomenon of “pseudo-persistence” may occur particularly in facilities with only primary wastewater treatment. While there have been no reports of 1-BP within surface waters or wastewater, it is likely that the compound has not been a typical target for monitoring. Given its reproductive and developmental toxicity in mammals and the potential for aqueous discharge, equivalent testing should be done in aquatic vertebrates (i.e., fish). Although there does not appear to be data for either exposure, or sub-lethal chronic effects in aquatic organisms, the conceptual model should at least include these possibilities. As was done with regard to the inability to include dermal exposure and PBPK predictions, ecological data gaps should also be identified and discussed at some point in the assessment.

Editorial Comments (Including Comments on Clarity)

- Several members commented that the transparency of the document, including the scope and conceptual model, could be improved. Given that there are many appendices, it is difficult to jump back and forth between the text and appendices to fully understand what is being

presented. Further, there was much repetition because issues were discussed in multiple locations within the document.

- In Section 1.4, the document lists 9 uses but ends by stating that the assessment will provide answers to 7 questions. It would be clearer to focus on the 7 questions you intend to answer in this assessment. The questions clearly identify the scope of the work done. Implied in the questions are the uses. Focusing on the questions gives the reader a clear target for determining at the end of the report whether the Agency achieved what it set out to do.

- Section 1.5, paragraph 1 begins by discussing the “selected scenarios.” It seems that the terms “scenarios” and “uses” are used interchangeably throughout the document. Scenario is defined as “a postulated sequence or development of events”, whereas a use is defined as “the action of using something or the state of being used for some purpose.” Uses in general are identified in the 7 questions of the previous section.

1. Occupational use of 1-BP in spray adhesives

2. Occupational use of 1-BP in dry cleaning machines

3. Occupational use of 1-BP for spot cleaning during dry cleaning

4. Occupational use of 1-BP in vapor degreasing

5. Occupational use of 1-BP in cold cleaning degreasing

6. Occupational use of 1-BP in aerosol degreasing

7. Consumer use of 1-BP in aerosol consumer products – question 7 could be rewritten to follow the format of the previous 6 questions to say “Do risks of concern exist (i.e., acute) for consumer users and non-users during consumer use of 1-BP in aerosol consumer products (i.e., aerosol spray adhesives, aerosol spot removers, aerosol cleaners, and aerosol degreasers).” Also, as an aside, it is not clear whether there are two types of consumer products of concern: aerosol cleaners and aerosol degreasers or whether these are combined as aerosol cleaners/degreasers as shown at the bottom of Figure 1.2. This needs to be clarified.

Scenarios under which monitoring data were collected and/or models were run are described in sections 2.1.2 to 2.1.7.

- One Committee member noted that the fact that a quantitative assessment of environmental risks is not considered (Section 1.5, paragraph 2) seems to be better described in Section 1.4 where the scope of the assessment is discussed. This member realized that the decision to not include this is an outcome of the problem formulation step.

- In Section 1.5.4.1 the terms “exposure” and “exposure pathways” seem to be used synonymously. This section could be better organized by discussing first what exposures are included in this risk assessment and then discussing which exposures are not included, with justifications, if needed. Also, it is not always clear when the exclusion is due to lack of data and when it is due to lack of concern for risk. A case in point seems to be the general population exposure from 1-BP vapor releases from manufacturing facilities. The assessment points to

concern for risk but also the lack of data. Since ecological assessment was deemed not in scope in the previous section, why is it brought up again here?

Additional References

Public Health Seattle and King Co. (2011). A Profile of the Dry Cleaning Industry in King County, Washington. 146 pages.

NIOSH. (2015). Health Hazard Evaluation Report: Evaluation of Occupational Exposures at Drycleaning Shops Using SolvonK4 and DF-2000. Report No. 2012-0084-3227.

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).

Committee Response

General Comments

Risk Assessment requires both toxicity testing and exposure science. The Committee observed that many of the questions posed by the Agency are requests for additional exposure information. This reflects a general underinvestment in exposure science. The Committee recommended that

the Agency might want to explore this issue. One Committee member asked, rhetorically, why there isn't a National Exposure Program analogous to the National Toxicology Program.

Some of the missing exposure information is most likely to be known by industry (product sales, number of employees in a given sector, etc.). The Committee recommended that the Agency explore means for obtaining such information.

Comments on work hours and estimates of population exposed

The Committee found that the scenario for worker hours in dry cleaners (8 hours per day only) that starts on page 49 of the risk assessment did not consider that small facilities are likely to have the owner-operator working longer than 8 hours, and no basis for this assumption was provided. For example, in King County, WA 26% of dry cleaners were owner/operators and had no employees; so in those businesses, the owner would have longer work hours and higher exposures than in the Agency's assumptions.

In addition, the estimated number of affected employees in the dry cleaning industry seems low based on the data provided in the document and there seems to be a discrepancy between values stated in the report and in the Appendix:

On page 46, the report states that, "A more recent survey conducted by AmericanDrycleaner.com in 2012 indicated that 1.1% of respondents used DrySolv, but did not specify the number of respondents participating in the survey (Beggs, 2012, as cited in US EPA, 2013c). EPA/OPPT conservatively assumed a 1-BP market penetration of 1.1 percent."

vs.

On page 184 (Appendix A-6), the report states that: "Findings from a survey conducted about dry cleaning solvent systems in 2009 by AmericanDrycleaner.com revealed that 2.0 percent of respondents use DrySolv® (Murphy, 2009)."

Is the AmericanDrycleaner.com survey referenced above on Pg.46 and Pg. 184 the same? If so, different references have been cited. Further, if it is the same survey, shouldn't the value reported in the body of the text be 2% rather than 1.1%? According to the information provided in the Murphy 2009 reference provided in Appendix A-6, pages 184-185, 2% of respondents indicated that they currently use DrySolv as their solvent system, not 1.1% (Source: <https://americandrycleaner.com/articles/only-half-drycleaners-now-use-perc-survey-says>). The Beggs 2012 reference indicated in the body of the text (page 46) could not be located.

The Agency uses the 1.1% value to estimate the number of workers (1,088) potentially exposed, particularly since it is based on a survey where recall bias may have been present and the total number of respondents was not provided. Given the absence of more reliable data to arrive at the number of workers potentially exposed in dry cleaning facilities and the fact that 1-BP is an alternative as a PERC replacement, it is not clear to the Committee why 4.1% (vs. "1.1%" or "2%") was not used, especially since this survey took place around 2009 when respondents

indicated that “in the future” they would use 1-BP (pages 184-185, Appendix A-6 Cleaning section):

“Only 4.1 percent of respondents indicated that the next solvent system they plan to use is DrySolv® compared to 27.6 percent for high-flash point hydrocarbons, 16.3 percent for perchloroethylene, 14.3 percent for GreenEarth, 11.2 percent for Solvair, 5.1 percent for low- flash petroleum, and 4.1 percent for liquid CO₂ (Murphy, 2009). . .”

The survey was conducted in 2009 when 4.1% of respondents indicated that they would use DrySolv “in the future.”

However, according to the public comment submitted by Dr. Mark Stelljes, on behalf of EnviroTech International:

“Dry cleaning use was only ever espoused by one company (EnviroTech International; ETI) and this use is being phased out. Currently there are fewer than 25 establishments using 1-BP as a dry cleaning solvent, and fewer than 100 employees that could be exposed. ETI is no longer marketing 1-BP as a dry cleaning solvent to new customers. Therefore, the analysis provided in this appendix for dry cleaning greatly overestimates the current and potential future population of potentially exposed individuals.”

There are no current 1-BP dry cleaning applications indicated on EnviroTech International’s website. Therefore, the Committee recommended that the Agency confirm the source of Dr. Stelljes’ comment and consider the information in this risk assessment accordingly.

Conversely, the Committee recommends that on page 47 of the risk assessment it should be stated that although the conversion of a PERC machine to a 1-BP machine is no longer recommended by the manufacturer, conversion to a 1-BP solvent is the only “drain and drop” solution that does not require buying a new machine. In many cases, the costs of having a professional company do the conversion are too high for many dry cleaners and thus this cost avoidance behavior by dry cleaning shop owners provides a motivation to attempt this conversion themselves. Therefore, dry cleaners may attempt to convert their machines to 1-BP, regardless of whether conversion to 1-BP is recommended or not recommended.

In addition, the Committee recommended that when assessing the number of workers in dry cleaning operations, it might be useful to get an estimate of the number of facilities with a cleaning machine and the number that are just “drop shops” where clothes are picked up and dropped off but the actual dry cleaning is done elsewhere. This may impact the total number of those potentially exposed.

The Committee also noted that estimating exposures to children (“workers” and “bystanders”) in dry cleaning facilities could be considered. It is plausible that in family-owned/operated dry cleaning facilities children under 16 could be helping/working (or could be “bystanders” while they wait for their parents to finish their job) and potentially be exposed to 1-bromopropane; however, exposures to children in dry cleaning facilities were not considered in the risk assessment. While the Agency states that they focused on exposures to pregnant women and that this may be protective of other populations, it should NOT be assumed that estimates based on

pregnant women would also be protective of young children (children are still developing, have higher inhalation rates, larger skin surface area, different body weights, etc. compared to adults which would impact exposure doses estimated). In addition, as indicated by the Agency, there are “postnatal exposure studies showing adverse developmental effects that manifest at various stages of development, and span multiple generations (WIL 2001).” Thus, at the very least the Agency should report this as a limitation of this risk assessment and indicate that exposures to children in these facilities could be higher than those estimated for the reasons stated above.

Exposure routes

The dermal exposure route was not assessed. Some Committee members recommended that an estimate for dermal exposure should be included and gaps/limitations clearly stated to address another potential workplace exposure pathway. The Agency states that “because of limited toxicological data and the lack of toxicokinetic information needed to develop physiologically-based pharmacokinetic (PBPK) models for route-to-route extrapolations, the Agency did not evaluate dermal exposures.” Some Committee members recommended that the lack of PBPK modeling and limited toxicological data should not preclude including dermal exposure estimates in this risk assessment. Several sources have indicated that the dermal route is important after the inhalation route (Source: NTP Technical report on the Toxicology and Carcinogenesis Studies of 1-bromopropane (CAS No. 106-94-5); Available at: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr564.pdf ; <http://www.cdc.gov/niosh/docket/review/docket153c/pdfs/eid-tr-sk-1-bromopropane-03242015.pdf>), including a study by Hanley et al. (2006) which reported that “1-BP may be absorbed via the skin, thus contributing to the systemic dose.” Although the NTP report, “Skin Notation (SK) Profile, 1-Bromopropane [CAS No. 106-94-5],” cannot be quoted or cited at this time, it is included in this response to raise awareness that this is under current review and for the Agency to see if this document is finalized and may be cited by the time this risk assessment is completed. The Committee understands that there is a lack of PBPK data available and that, due to the volatility of 1-BP, dermal exposure is not of high concern; however, as indicated by committee members during their discussions at the meeting there may still be considerable dermal exposures in cases where the material has spilled on someone’s clothing, for example, and this type of exposure would be at least partly occluded resulting in higher dermal penetration. In addition, the fact that it has been marketed as a “green alternative” may change exposure-behavior patterns when using the product, as people using 1-BP would think it was safe or not toxic.

Some Committee members noted that the exclusion of dermal exposures may be an important limitation of the assessment of certain occupational exposures. The rationale for excluding them is logical, especially in light of the data limitations. However, there are possible occupational exposures where dermal contact may be occluded (e.g., when wearing gloves that do not protect from the solvent) and therefore dermal absorption may have been an important contributor to total dose. For example, the dry cleaner (case #2) reported in CDC (2008) included the use of rags soaked in 1-BP to clean the machine and this likely resulted in occluded exposures that may have been an important contribution to total dose. The vapor degreaser (Case#1) also reported

frequently having to reach into the solvent bath area while degreasing was taking place and due to a broken cooling coil would get significant condensation on his body. In addition, if improper gloves are used (e.g., rubber) such that the solvent penetrates the glove, you would also potentially have occluded exposures.

The Committee recommended that it might prove useful if it were possible to use data from Frasch et al. (2011) to estimate potential dermal contribution to dose for certain specific occupational scenarios. Alternatively, the report should just note that this is a significant data gap needing additional research.

Exposure time

While the Agency acknowledges that some personnel may work for 12 hours in dry cleaning facilities and assumed a 12 hour operating time for small facilities, which is reasonable, exposure estimates assumed 8 hour work days (i.e., the facility is open for 12 hours, with two- 8hours shifts and a four hour overlap between shifts). The Committee noted that it is highly plausible that many establishments, particularly those that are family-owned and operated, have people working 12-hour shifts. For small places, there is likely at least one person there (the owner/operator) the entire operating time. It may be useful to assume at least one person (the owner/operator) is present at the facility for 12 hours of operation and estimate their exposures. It is also possible that a worker could be at the facility part time. Thus, rather than having working hours be a constant parameter (i.e., 8 hours) in the exposure models, the Committee recommended that this parameter be allowed to vary (e.g., 4, 6, 8, and 12 hours) to cover a range of scenarios.

Exposure Scenarios

The committee concluded that it was appropriate for the Agency to assume that the machines in the dry-cleaning exposure scenarios were older models as many dry cleaning facilities are family-owned and operated and may not have the resources to purchase newer equipment. However, exposure calculations could be conducted separately for 3rd and 4th generation machines rather than lumping these machines into 1 scenario.

During the meeting, the Committee also had some questions about the potential for shops to have more than one machine and a question arose whether it was appropriate for the scenarios modeled to assume only one machine is present in the shop. One Committee member observed that many of the smaller operations do have only one machine, but the member has been to larger facilities that have 2 machines. Although this member did not have any specific data on the distribution of the number of machines by shops, the member would expect the trade associations representing dry cleaners to have an estimate. In Blando et al. (2010), the sampling results reported were from shops that had only one machine operating using 1-BP. Of the four shops included, three had only one machine and one had two machines. The facility with two machines was operating by using 1-BP in only one machine while the other was not in use during the study but was configured to run on PERC. Therefore, this Committee member concluded that modeling with the assumption of one machine is appropriate but it is worth explicitly noting this assumption in the model.

The Committee noted that inclusion of post-EC (Engineering Control) exposure estimates is good practice as this provides an estimate of the impact of ECs in different exposure scenarios; however, as noted in the risk assessment report, it is uncertain whether ECs at dry cleaning facilities would reduce levels by the Agency's estimated amount of 90%. Also, in family-owned/operated establishments ECs may be less likely to be implemented. It appeared that the Agency's assumption of 90% removal efficiency for ECs is based on a degreasing operation with slot hoods, which is a ventilation configuration that may or may not be appropriate for other industrial processes. The NIOSH Health Hazard Evaluations (HHEs) for spray applications (NIOSH, 2002) did not appear to attain this removal efficiency but found an efficiency on the order of 60%. The Committee recommended that it might be more appropriate for there to be a better match of industrial process to the applicable ventilation configuration and an assessment of realistic control efficiencies that can be obtained to estimate the post-EC air levels.

Engineering controls are not likely feasible for most dry cleaners, and if they were they would not likely be implemented. Most shops just simply run fans and open windows when possible, because there isn't enough room in these shops and not likely enough money or motivation for these small business owners to pay for engineering controls. Most had trouble buying a new machine because of the \$40K capital required. Therefore, the Committee noted that the post-EC discussion may not be realistic and consideration should be given as to the real possibility that engineering controls might not be implemented.

The risk assessment assumption for the removal efficiency is based on the Wadden, et al. (1989) paper, which showed that slot hoods could control to 90% removal for TCE vapor degreasers. However, if the solvent is much more volatile (as 1-BP is compared to TCE), then it is possible there could be some deviation from this control efficiency. However, one Committee member noted that they were not aware of any other papers that specifically looked at 1-BP in degreasers and the associated control efficiencies, so this estimate might be the only data and the best estimate available. If that is the case, then the Committee recommended that the potential deviation should just be mentioned as a limitation in the assessment of engineering controls.

Further, it might be worth noting that engineering controls for degreasers such as local exhaust ventilation might not be in use in all facilities. In some cases, facilities might only have condensing coils (if hot) and general ventilation on their batch degreasers.

From the NIOSH 2002a and b reports, it is clear that the ventilation engineering controls made a big difference when they were operational. However, in NIOSH 2002a, the authors note that the ventilation systems were clogged with adhesive and in some cases not functioning at all. While the pre-EC exposure estimates in the Agency's assessment obviously included this consideration, the post-EC measurements would estimate exposure when everything is working properly. Therefore, the Committee observed that the Agency appropriately estimated MOEs for both pre-EC and post-EC scenarios. This would presumably bracket the range of exposures. Exposures to workers where engineering controls are in place could increase over time if the ventilation is not properly maintained. Hopefully, this is considered in the risk management phase.

In the risk assessment, in-line degreasers are described as having lower exposures than batch degreasers. However, the Committee observed that it is important to note that this is the case for those that are vented with emission capture systems.

In the Agency's assessment for the dry cleaning scenario, the modeling assumptions based on spot cleaning at the Bridal shop assumed 8 dresses were cleaned per day. One Committee member observed that many dry cleaners would likely use spot cleaning more frequently. Based on observations from one of the shops in the Blando et al. (2010) study, the spot cleaning of two or three garments with each load may be typical. One Committee member noted that it is not clear how representative the data from David's Bridal is for spot cleaning at dry cleaning facilities. However, at this time this Committee member does not know of any other sources that could be used to inform spot cleaning estimates.

The Committee also noted that in the NIOSH HHE (NIOSH, 2001) which assessed a cold degreasing operation, a note was made about the importance of allowing parts removed from the bath to "drip dry" while still in the ventilated room so as to reduce off-gassing to the workspace. This work practice should be noted as an assumption of the modeling process because exposures would be higher if this work practice is not followed.

Exposure Data

For spray adhesives, the Agency's assessment states that sprayers have the highest exposures but the data in Table 2-2 shows that the sprayers and non-sprayers occupational groups are essentially the same. Although some of the non-sprayer data is lower, there are also less than half the number of non-sprayers compared to sprayers, which may have impacted the distribution of the sampling results. The committee noted that it is unlikely that the differences noted here are meaningful and these two groups likely have the same exposures. In addition, as indicated in NIOSH HHE reports (e.g., NIOSH, 2002) and in the Agency's limitations section, many workers in these factories may not be discretely assigned as a sprayer or non-sprayer as they are in such close proximity that they likely switch or share work tasks. As such, the characterization or "ranking" of sprayers as more highly exposed than non-sprayers may be misleading without the appropriate caveats.

However, one Committee member does not agree that the two groups should be collapsed into one occupational group for their description in the document. Rather, this member recommends a statement describing them as very similar or essentially the same exposure for the reasons cited above would be appropriate.

Comparison of modeling and biomarker results is always useful, if possible. On page 43 of the peer review draft risk assessment, prior biomonitoring studies (Hanley et al., 2006, 2009; Ichihara et al., 2002; Majersik et al., 2007) are explicitly discarded due to inadequate job descriptions or lack of individual data. The Committee noted that even if these studies are not amenable to full analysis, they do include biomarker data that can serve as a point of reference. If the Agency predicts a range of exposures for tasks for which they have a description, do the biomarker results from these undefined tasks fall inside or outside the predicted exposure range? At the very least answering that question might result in identification of a higher risk group. The

Committee further noted that comparison of biomarker ranges observed in selected and unselected study populations would be valuable. Examination of ratios of biomarker levels to air levels for uniformity could also provide some information about potential for non-inhalation exposures and/or heterogeneity across job classifications.

The Committee also noted that comparison of modeling results and environmental measurements is always useful, if possible. The Committee recommended that the Agency consider the feasibility of adding graphical or tabular comparisons between predicted and observed environmental concentrations when the latter are available.

Modeling & Validation

At least 2 Committee members recommended that the Agency should, going forward, adopt use of 2-dimensional (D) Monte Carlo (i.e., explicit separation of variability from uncertainty due to ignorance) as the default in TSCA Work Plan chemical exposure assessments. The full distribution of predicted outcomes should be presented in graphical form, instead of just the 50th and 95th percentiles in tabular form.

For modeling dry cleaning worker exposures, it appears that the Agency used relatively conservative models that allow for dissipation of solvent into the far-field zones to estimate exposures. The Committee noted that it is appropriate to assume the machines were third-generation converted PERC machines. The dry cleaning machines are costly and the majority of dry cleaning operations are small shops. It is not very likely that these small shop owners have invested in fourth or fifth generation machines.

In the assessment of dry cleaning inhalation exposures and the modeling of these exposures, the Agency assumed that the releases were from the front door of the machine or during spot cleaning and finishing. Blando et al. (2010) and CDC (2008) found that leaks from the machine were also important and contributed to the background concentrations. This was especially problematic because 1-BP frequently damaged typical gasket materials (e.g., rubber) and also seemed to corrode the machine parts and pipes. In the reports cited above, a Photo Ionization Detector (PID) was used to trace emissions leaking from gaskets. However, permeation tubes for PID calibration were not available for 1-BP at the time sampling was done in these studies; as such calibration curves could not be made with the PID, and relative concentrations were made using iso-butylene as the calibration gas for the real time PID leak testing. Therefore, only the relative measurements have value and are not actual levels of 1-BP. It was found that in the leak tracing the PID showed the following relative readings: for rubber gaskets, 64 ppm at lint trap gasket, 35 ppm at gasket on top elbow, and greater than 30 ppm at the condenser gasket. For newly reinstalled Teflon gaskets all readings were less than 10 ppm on the PID.

Charging of the dry cleaning machine was not included in the Agency's modeling. However, the Committee noted that this produces a very significant spike in concentration that seemed to persist for a period of time. Several dry cleaners in the study by Blando et al. (2010) indicated this was done typically one time per week, often by dumping a 5-gallon drum through the front door of the machine (Blando et al., 2010; CDC, 2008). Blando et al. (2010) provides an estimate of the time course of concentration spikes in figure 1 of this cited paper.

The 1-BP exposure concentration modeling results for an operator of a dry cleaning machine using 1-BP indicate a 50th percentile around 7 ppm. This value is considerably lower than the 8hr average (full-shift) exposure measured by NIOSH (2010) of 40 ppm for a facility operator in one facility using 1-BP as a dry cleaning agent. Partial-shift 1-BP concentrations ranged from 7.2 to 160 ppm for operators of three facilities measured by NIOSH (2010). Therefore, the Committee concluded that the Agency appropriately uses a high-end estimate for worker exposure and includes the estimate based on monitoring in the risk characterization section.

For the modeling of dry cleaners, the modeling approach appeared to assume that the occupational non-user does not ever enter the near field. One Committee member had observed occupational non-users occasionally going into the near field once or twice per shift to help out when things got busy. This is noted in the risk assessment uncertainties and probably partially explains some of the differences in the modeled results and the monitoring results as noted. The Committee member recommended that the Agency consider whether it is feasible for the model to incorporate this likely behavior.

In the 5-step process described in section 2.1.1 of the risk assessment, there is no discussion of model validation. The Committee noted that if there are monitoring data for some use scenarios, there is the opportunity to compare model-derived estimates against monitoring data-based estimates and gain insight on the validity of the modeling process in general. Note that there is some model validation described in the document. See, for example page 62, where the exposure estimates from the vapor degreasing models are compared to published estimates.

The risk assessment mentions that there are short-term and partial-shift exposure monitoring data that cannot be translated into 8-hr TWA values. The Committee noted that while it is not clear how much of these data there are, if there are a lot of these kinds of measurements, it might be possible to use these data to help validate the models used.

Where data were available for model parameters (e.g., see tables in Appendix K), the Agency used these data and applied a distributional approach, with an assumed distribution shape, that allowed inclusion of variability/uncertainty in the model parameter. However, the Committee noted that it is not clear from the text what drove decisions to use either a uniform or triangular distribution for model parameters when data were lacking to describe an empirical distribution.

California Air Resources Board (CARB) emissions factors for degreasing operations are based on 11 different types of equipment and 38 different solvents and linked to employment data at the time of the survey to produce an emissions factor. If the distribution of cold versus hot processes is different for solvents in general versus those that use 1-BP, this could skew your emissions factors.

Emissions modeling for degreasers using AP-42 also may have some deviation in the emissions factor for cold cleaning because AP-42 was based on a different suite of solvents that have different properties and volatilities. However, it was clarified at the meeting that in fact the emissions factors were specifically for 1-BP and this should be more clearly stated in the risk assessment document.

Quality control

On page 44 (section 2.1.2.4), the Agency states that “EPA/OPPT determined the monitoring was adequate and of acceptable quality.” The Committee recommended that it should be explicitly stated, for transparency, what criteria were used to determine that “the monitoring was adequate and of acceptable quality.” Again, was a ranking system used? If a ranking system was used, details need to be provided so that it is clear to the audience why select studies/data were or were not considered in this risk assessment.

Editorial Comments

One Committee member found the term “foam manufacturing” confusing. This member thought this term represented workers manufacturing foam; instead it is workers manufacturing other articles with foam.

On page 50, the Monte Carlo simulation is described as having 5,000 iterations, while everywhere else in the document it is described as having 1 million iterations. There was no explanation for this difference and one Committee member asked if it is a typo.

In section 1.5 the Agency listed “uses” that would be examined in this assessment. The first paragraph of Section 2.1 parallels this previous listing and includes further specification/description for three of the six “uses.” Is there a reason for not providing a clarifying statement for all six uses?

Sections 2.1.2 through 2.1.7 really describe the ‘scenarios’ used to answer the seven questions. This should be clarified in the text.

On page 208, Appendix G, the Agency states that it searched “Standard engineering sources used by OPPT/RAD for occupational exposure assessments.” For transparency, please provide more information including examples of such sources.

On page 211, Table _ApXH-1, the table indicates that the averaging time for an acute exposure (AT_{acute}) is 24 hours/day while the formula below the table $AC=(C \times ED)/AT$ indicates 8 hours for AT. These values need to be verified and revised accordingly.

In Tables _ApxK-2 thru K-8 under the comments column for some parameters, a distribution was assumed and noted (e.g., triangular, lognormal, etc.). The Agency should provide a brief explanation on why they selected the stated distribution or at the very least provide a reference.

In Table ApxK-2 (vapor degreasing), on page 232, it is not clear why the upper-bound for number of employees at dry cleaning facilities would be set to infinity. Is there a reason this number was not set to an upper-bound of 14 as this was the number indicated by the reference?

One member found that in the Tables on pages 236-239 it was not clear whether the number of loads were assumed to be 14 rather than allowing this parameter to vary; however, other members found the tables to be clear.

On page 147, there is a reference that seems to be improperly cited: von Grote et al., 2003 should be von Grote et al., 2006.

It was not clear from reading the section on inhalation exposure for adhesive sprayers in the foam furniture industry how the data from the NIOSH and OSHA studies were incorporated into Table 2-2. There were at least three sources and one value is presented for the mean and 95th percentile. It would be helpful to bring forward some of the information from the appendices to provide a brief explanation. For example, on page 215, under Table ApxI-4, there is the following text which provides some explanation: "For each employee category (sprayer, non-sprayer, and occupational non-user) and exposure scenario (pre-EC or post-EC), EPA/OPPT calculated the 95th and 50th percentile exposure levels from the observed data set. The 95th percentile exposure concentration represents high-end exposure to 1-BP across the distribution of exposure data. The 50th percentile exposure concentration represents a typical exposure level."

Table ApxH-1 (Parameter Values for Calculating Exposure Estimates) has an incorrect parameter value entry. The table indicates the averaging time for acute exposures for occupational settings is 24 hours. The equation below the table indicates this value is 8 hours, which is what was used for the occupational acute exposure.

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.

Committee Response

Additional Occupational Exposure Scenarios

The Agency has dismissed dermal exposure due to rapid volatilization of 1-BP from skin. This is reasonable under non-occluded conditions. Occlusion of exposed skin by clothing, use of 1-BP soaked rags without gloves, naïve glove use, or by adhesive could potentially result in non-trivial dermal exposure. The Committee recommended that the Agency should at least provide screening level calculations to justify exclusion of the dermal pathway. *In vitro* absorption data published by Frasch et al. (2011) are germane.

Actual examples of likely important dermal exposure include the dry cleaner (case #2) reported in CDC (2008) who used rags soaked in 1-BP to clean the machine and the vapor degreaser operator (case #1) who reported frequently having to reach into the solvent bath area while degreasing was taking place. Due to a broken cooling coil he got significant condensation on his body.

Other scenarios mentioned by the Committee included poorly documented but potentially high exposure activities in the dry-cleaning industry such as cleaning filters or pouring 1-BP into the machine.

Editorial and Other Comments

The Committee found that the Agency's analysis is necessarily complex, entailing multiple occupational scenarios and utilizing both measured and predicted air concentrations to assess hazard. Agency personnel have invested much time in the document and understand its internal logic. However, Committee members and interested members of the public must typically make

judgments within a relatively short time frame. Multiple Committee members reported having difficulty following arguments, and in particular spending much time flipping between the text and Appendices J and K. The table below shows section headers in those parts of the document. They do not follow a logical or consistent pattern.

Table 1: Inconsistencies in Section Headers across the Main Text and Appendices J and K.

| Main Text | Appendix J | Appendix K |
|-------------------------------|--|-----------------------------|
| Spray Adhesives | Vapor Degreasing, Cold Cleaning, and Spot Cleaning | Degreasing |
| Dry Cleaning | Aerosol Degreasing | Vapor Degreasing |
| Spot Cleaning at Dry Cleaners | Dry Cleaning | Aerosol Degreasing |
| Vapor Degreasing | | Dry Cleaning |
| Cold Cleaning Degreasing | | Unloading Dry Cleaning |
| Aerosol Degreasing | | Finishing |
| | | Spot Cleaning (multizone) |
| | | Spot Cleaning (stand alone) |

This suggests that some consideration should be given to organization of the document before it is finalized. At a minimum, an explanatory matrix of the following type would be helpful:

Table 2: Example Matrix Explaining the Organization of the Risk Assessment Document.

| Occupational scenario | Pathways considered | Approach | Governing Eqs. | Exposure Factors |
|-----------------------|---------------------|-----------------------------|----------------|------------------|
| Spray Adhesives | inhalation only | measured air concentrations | N/A | N/A |
| Dry cleaning | inhalation only | modeled air concentrations | Eq_ApxJ-XX | Table_ApxK-X |

Section 2.1.2.3. On page 43, second to last paragraph, mention is made of the threshold limit value (TLV) of 0.1 ppm set by the American Conference of Governmental Industrial Hygienist (ACGIH) for spray adhesive sprayer and non-sprayer exposure levels. For perspective, the Committee noted that it would be useful to report the risk level the Agency assigns to exposure at the TLV.

Section 2.1.3.3. The Committee noted that the description of the exposure monitoring data for dry cleaning machine operators is unclear with respect to which scenario the resulting 95th and 50th percentile exposure estimates of 50.2 and 29.8 ppm 8-hr TWA actually represent. For example, are all of these shops assumed to use third generation machines (non-vented, dry-to-dry

machines with refrigerated condensers), even though there is mention of general building ventilation without specific controls to reduce exposure to the dry cleaning solvent. What are the ranges of number of loads cleaned, number of solvent cooking cycles, amount of make-up solvent added, and how often is solvent added? The fact that many of these questions likely cannot be answered is the reason for the models.

Section 2.1.3.4. The Dry Cleaning Exposure Post-EC scenario is only described by a footnote on Table 2-5. The Post-EC refers to “engineering controls with an assumed 90% efficiency.” The Committee noted that it took a lot of digging and reading to figure out that this refers to a parameter called EC in Table ApxK-4. The comments for this parameter refer to a study on open top vapor degreasers. In Table ApxK-1, Degreasing Facilities, it is stated that the EC of 90% is based on local exhaust ventilation to reduce workplace emissions – lateral exhaust hoods installed on two sides of an open top vapor degreaser. It appears that achievement of an EC of 90% efficiency requires the air exchange rate (AER) to increase, which in turn impacts the far-field ventilation rate (Qff). From this, the Committee noted that it is not clear if the 90% reduction is applied to the far-field ventilation rate, Qff, or the far-field concentration level, CFF.

Another approach to engineering control might be changing from 3rd generation to 4th generation DC machines. From Table ApxK-5, unloading DC machines we see a difference in cylinder concentration of 8600 ppm for 3rd generation versus 300 ppm for 4th generation machines. It would seem reasonable to run scenarios for 3rd generation facilities with and without workplace ventilation efficiencies, and then additional scenarios for 4th generation facilities. Instead each Monte Carlo simulation used a cylinder concentration that was chosen from a uniform distribution between 300 and 8600 ppm. The Committee observed that this confounds variability across machine type with variability in cylinder concentration within each machine type.

Section 2.1.4.4. The Spot Treating scenario used the same EC parameter as the dry cleaning scenario. In Table 2-7 the AC, ADC and LADC estimates change by exactly a factor of 10 from Pre EC to Post EC for both the 50th and 95th percentiles. The Committee recommended that further explanation of this outcome in a Monte Carlo simulation would be helpful. For example, is the 90% reduction just imposed deterministically after the fact?

Section 2.1.5.4. For clarity, the sentence beginning with “The post-EC scenarios reference” on page 62 should mention Table 2-10 as the original reference is on the preceding page.

Section 2.1.6.4. Per the cold cleaning degreasing scenario (page 66): “To model exposures during 1-BP cold cleaning, an exposure reduction factor, RF, with uniform distribution from 0.032 to 0.571 is applied to the vapor degreasing model.” The Committee noted that Appendix J does not indicate which model parameters the RF impacts. The discussion on page 55 refers to emissions from cold cleaning ranging from 3.2 to 57.1 percent of emissions from traditional open-top vapor degreasers. From figure 2-11, it appears that the RF would apply to G, the average vapor generation rate. It could also conceivably be applied to the near-field concentration, CNF.

The Committee noted that Tables 2-10 (**Section 2.1.5.4**, vapor degreasing) and 2-12 (**Section 2.1.6.4**, cold cleaning) show the same 10 fold reductions in AC, ADC and LADC estimates as did Table 2-7 (**Section 2.1.4.4**, spot cleaning).

Section 2.1.7.3. The Committee noted that modeling of the “what-if” scenario of a vented booth discussed on page 69 would be helpful.

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.

Committee Response

Additional References

A search on PubMed led to the following references which document workplace exposures to 1-BP. Access to most of these references was not possible and some articles are in Chinese; however, the Committee recommends they may still be worth evaluating/translating as they might contain data to help refine the risk assessment with regards to occupational exposures/monitoring data.

1. Fang, Z., Miao, R., Yang, D., Ji, J., Wu, W., Zhang, Y., Ji, Z., Shi, Y., and Zhu, B. (2015). "[Effects of 1-bromopropane on liver and kidney functions of exposed workers]." *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi*. [Chinese Journal of Industrial Hygiene and Occupational Diseases]. 33(5): 357-358.

Exposures seem to have resulted from working in a 1-BP manufacturing plant (article in Chinese).

2. Miao, R., Fang, Z., Yang, D., Zhang, Y., Wang, Y., Zhy, Y., Zhu, B., and Zhang, M. (2015). "[Effects of 1-bromopropane on hematological changes of exposed workers]." *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi*. 33(5): 350-351.

Abstract not available so cannot verify exposure source in workers (article in Chinese).

3. Miao, R., Fang, Z., Zhu, B., Yang, D., Qian, G., Chen, Y., and Zhang, Y. (2015). "[Cardiac effects of 1-bromopropane on exposed workers]." *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi*. 33(5): 352-353.

Abstract not available so cannot verify exposure source in workers (article in Chinese).

4. Miao, R., Shi, Y., Zhu, B., Ding, P., Yang, D., Fu, Z., Zhang, Y., Wang, Y., and Zhang, M. (2015). "[Electrophysiological effects of 1-bromopropane on exposed workers]." *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi*. 33(5): 355-357.

Abstract not available so cannot verify exposure source in workers (article in Chinese).

5. Wang, T. H., Wu, M. L., Wu, Y. H., Tsai, W. J., Lin, K. P., Wand, C. L., Yang, C. C., and Deng, J. F. (2015). "Neurotoxicity associated with exposure to 1-bromopropane in golf-club cleansing workers." *Clin Toxicol (Phila)* 53(8): 823-826.

A case report on 6 patients.

6. Moon, H., Shin, S., and Byeon, S. (2015). "Exposure Monitoring and Health Risk Assessment of 1-Bromopropane as a Cleaning Solvent in the Workplace." *Human and Ecological Risk Assessment: An International Journal*. 21:3, 744-752. DOI: 10.1080/10807039.2014.926203.

Available at: <http://www.tandfonline.com/doi/pdf/10.1080/10807039.2014.926203>.

The Committee observed that this study was of particular note. This study performed a 1-BP exposure assessment in 10 workplaces that used the chemical as a cleaning solvent. However, it seems this study may not have been considered in the Agency's risk assessment. The study authors note that most of the workplaces sampled were equipped with local exhaust ventilation facilities, but most of the workers were not wearing any protective gear. Table 3, page 749 in the article, provides summary statistics and concentration ranges for the 10 workplaces sampled (5 samples/facility).

7. SLR International Corporation – data on dry cleaning facilities available upon request.

In addition, SLR International Corporation has conducted some exposure monitoring of 1-BP in dry cleaning facilities as indicated in public comments submitted by Dr. Mark Stelljes (Comment #19). Dr. Stelljes has indicated that these data may be made available upon request. The Committee recommends that the data should be requested to determine its relevance and appropriateness for informing the risk assessment.

8. Public Health Seattle and King Co. (2011). *A Profile of the Dry Cleaning Industry in King County, Washington*. 146 pages
And
NIOSH. (2015). *Health Hazard Evaluation Report: Evaluation of Occupational Exposures at Drycleaning Shops Using SolvonK4 and DF-2000*. Report No. 2012-0084-3227.

The Committee recommended that the Agency should also include studies on dry cleaners by Public Health Seattle and King County, Washington. Even though relatively few dry cleaners are currently using 1-BP, information on work practices (e.g., spot cleaning and number of dry cleaning machines per facility) is useful for this risk assessment.

9. Ichihara, G. (2005). Neuro-reproductive toxicities of 1-bromopropane and 2-bromopropane. *Int Arch Occup Environ Health* 78: 79–96; DOI 10.1007/s00420-004-0547-9 and
CDC (CDC Research Inc.). (2008). *Neurologic Illness Associated with Occupational Exposure to the Solvent 1-Bromopropane--New Jersey and Pennsylvania, 2007-2008*. *Morb Mortal Wkly (MMWR)*. Rep 57: 1300-1302.

The Committee noted the above, two additional articles in peer-reviewed literature that may be helpful. In addition, the Committee noted that the CDC, 2008 article cited in the Agency's assessment has some clinical data and biomarker information that might be useful in the exposure assessment.

Additional Data Sources

- 1) The Committee noted that if the assessment were to attempt to estimate the number of undocumented workers in various industries the Agency might be able to abstract data that could be used to gain an estimate with the US Census Bureau Data Ferret tool at:
<http://dataferrett.census.gov/>

In addition, some researchers have used Public Use Microdata Sample (PUMS) data from the American Community Survey to also attempt to produce estimates of undocumented persons in the US. These data can be found at:

<https://www.census.gov/programs-surveys/acs/data/pums.html>.

Worker population estimates cited from the Bureau of Labor Statistics (BLS) may not include undocumented workers who may be an important component of the workforce in many of these industries.

- 2) The Committee has also found Dun & Bradstreet products helpful in identifying and assessing facilities, locations, revenue, and workforce in specific industries.

<http://www.dnb.com/products/all-products.html>.

General Comments on Literature

As stated earlier in this report, the Committee noted that on page 43 of the Peer Review Draft Risk Assessment, prior biomonitoring studies (Hanley et al., 2006, 2009; Ichihara et al., 2002; Majersik et al., 2007) are explicitly discarded due to inadequate job descriptions or lack of individual data. Even if these studies are not amenable to full analysis, they do include biomarker data that can serve as a point of reference. For example, if the Agency predicts a range of exposures for tasks for which they have a description, do the biomarker results from these undefined tasks fall inside or outside the predicted exposure range? At the very least answering this question might result in identification of a higher risk group. The Committee noted that comparison of modeling results and environmental and/or biomarker measurements is always useful, if possible. The Committee recommended that the Agency consider the feasibility of adding graphical or tabular comparisons between predicted and observed environmental concentrations when the latter are available. The Committee also noted that comparison of biomarker ranges observed in selected and unselected study populations would be valuable. Examination of ratios of biomarker levels to air levels for uniformity could also provide some information about potential for non-inhalation exposures and/or heterogeneity across job classifications.

While the Agency indicates that the literature was thoroughly reviewed for robustness, adequacy, etc., the Committee found that it is not clear what exact methodology was used to systematically

rate, rank, and select studies to inform sections of the risk assessment. For example, was a quantitative ranking system developed for study quality? Pages 261-262 provide some information, but more details are needed (e.g., is a positive response to at least one of the questions in each of the features listed in the table sufficient to deem a study of “adequate quality”; what selection criteria were used to ensure consistency).

As indicated previously, the Committee noted that it would be good to reference studies that were evaluated but did not meet baseline criteria to inform the exposure estimates. More details on the hazard literature are also recommended in the report text and Appendix M and throughout the report, for greater transparency. The Committee noted that this is key as the Agency based selection of HECs for MOEs on the studies selected.

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.

Committee Response

Additional Data and Comments on the Occupational Exposure Assessment

The Committee found that for the types of scenarios considered, the Agency has probably collected and adequately “codified” the most pertinent, though very limited, available information. The Committee recommendations that follow focus more on the optimal use of the information obtained by the Agency rather than with new data.

- A recent article by Hillborne and Averill (2016) provides updated information on the variability of parameters affecting VOC vapor dispersion in the workplace but it is doubtful that this information can significantly affect the outcomes of the risk assessment calculations. The Committee noted that it is more important however, and probably more straightforward, to improve the definition of the distributions that were derived from the available data.
- There are substantial concerns with the definition of the distributions of input variables and parameters described in Appendix K. The Committee members agreed that it would be a preferable recommendation to use truncated lognormal distributions instead of accepting zero to infinity ranges and to provide references, if available, on the selection of other distributions.
- The Committee recommended expanding the Monte Carlo simulation of occupational exposures by replacing some of the point estimates of input variables with distributions; an example of such a point estimate that should be replaced by a distribution is the number of working hours.
- At least 2 Committee members agreed that, going forward, a useful and informative task in subsequent Work Plan chemical exposure assessments would be to separate variability from uncertainty and perform a 2-dimensional (2-D) Monte Carlo analysis.
- The Committee recommended that it is very important to explicitly identify the rules - assuming that such rules have been used - ensuring the consistency and “proper matching” of

parameter/ input selection for each individual Monte Carlo run. Neither the main body of the report or the appendices appear to address this point.

- The Monte Carlo runs, if outputs are properly selected, also can provide substantial insight into the sensitivity and uncertainty aspects of the system. However, it is not clear that this has been considered in the document under review.
- The available input information and the probabilistic/distributional (Monte Carlo) approach for occupational exposure modeling calculations precludes the use of substantially more comprehensive models such as Computational Fluid Dynamics (CFD) packages or even multi-zonal formulations such as CONTAM by NIST. However, it would be useful (though not a top priority at this point) to compare and “benchmark” a selected (and limited) subset of calculations with such a comprehensive model. This type of “benchmarking” can identify and help eliminate weaknesses in the formulation of the simpler model and thus increase confidence in its application.
- The Agency dismissed dermal exposures based upon the argument of rapid evaporation of 1-BP from the skin. This is reasonable under many circumstances. Nevertheless, the Committee recommended that a quantitative argument would be more persuasive. Kissel (2011) introduced the concept of NDERM, a dimensionless ratio of skin load (potential supply) to rate of loss (due to absorption or volatilization) times experimental or exposure duration. This concept could be helpful in evaluating the likelihood of dermal exposure negligibility. Frasch et al. (2014), which is referenced in the document under review, is a relevant follow-up paper.

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.

Committee Response

Comments on the Approach Used

The Committee evaluated the approach that was used by the Agency to estimate exposures (characterized “consumer exposures” in the document under review) to 1-BP from use of consumer products in the home, and concluded that, although the basis of the approach is fundamentally reasonable, there are concerns that need to be addressed. These concerns, as well as related recommendations by the Committee, are summarized below:

- The Committee found that the exposure terminology employed in the report under review needs to be adjusted and clarified. Indeed, the modeling analysis performed by the Agency involves residential exposures from usage of consumer products, such as sprays containing 1-BP: such exposures would in fact be experienced not only by consumers per se, but also by other members of the household where the products are used, especially children. Therefore, the Committee noted that it is important that a distinction is made in the analyses between occupational and residential exposures. It is also important to take into account that residential exposures involve the general population, which has a wider distribution of ages, activity patterns, and physiological/biological characteristics such as inhalation rates (which in turn affect intakes and uptakes associated with exposures of the airborne chemical) than the population experiencing occupational exposures.

Another, related issue is that residential exposures may also be associated with usage of 1-BP in “occupational settings”, either for residences co-located or in the immediate vicinity of dry cleaner facilities, or through the usage of the chemical by professionals for on-site residential carpet cleaning. The scenarios modeled by the Agency represent a subset of the actual possible (and plausible) exposures. In these scenarios, the consumers were assumed to be adults and bystander exposures including children were assumed to occur in another part of the house and not in the room where the activity was occurring. While this might be true in the majority of cases, it is also possible to have children, particularly older children and adolescents, in the same room as the adult using the product. The Committee noted that it would be useful to evaluate assumptions like this, so as to ensure that real-world exposures are not overlooked and exposures to children are not under-predicted.

- The residential/consumer exposure modeling analysis performed by the Agency, employing the Consumer Exposure module (CEM) of E-FAST (a screening level model) is based on a limited number of (deterministic) scenarios; this analysis was supplemented by sensitivity testing, described in Appendix L. Members of the Committee noted that, going forward, the Agency would be better served by employing a probabilistic approach for the consumer exposure assessment. Three arguments support this position. First, use of a probabilistic approach for the occupational case and a deterministic approach for the consumer case is inconsistent. Second, presenting output values that are not anchored to distributions as being estimates of 50th and 95th percentiles is problematic from a mathematical perspective.

Third, an implicit assertion that “guesstimates” of this type can be multiplied in strings to give aggregate 50th or 95th percentiles is also erroneous. In addition, concerns regarding the validity of individual estimates of modeling parameters (e.g., the overspray fraction) would be obviated by use of distributed values for these parameters. A distributional/probabilistic approach could also (partially) address the uncertainties associated with a lack of current information on household uses of products containing 1-BP. The Agency used a 1987 Westat survey of household solvent use to develop the exposure scenarios and the use patterns may have changed in the past 30 years. Though a new survey should eventually be conducted to address these data gaps, a probabilistic approach can characterize the effects of uncertainties in such data.

- The scenarios modeled by the Agency in the document under review consider a specific subset of uses of consumer products containing 1-BP. Though these may potentially be the most important scenarios, the Committee observed that it is essential to provide justification regarding their selection. In particular, the Agency should discuss the relevance (or not) of publicly and readily available information from its own sources. As an example the chart in Figure 1 (next page), produced by querying the Agency’s ACToR (Aggregated Computational Toxicology Resource) database, depicts the “Top 10 Chemical and Product Categories” for 1-BP, but it is far from clear, how this information may relate to the magnitude and frequency of consumer/residential exposures to 1-BP.
- The Committee discussed the utility of comparing a subset of CEM E-FAST calculations with an “external” model of similar sophistication such as those developed for the European REACH program (e.g., ConsExpo or ECETOC). At a minimum the use of alternative parameterizations could provide insight and concurrence of models supports robustness of their outcomes.
- The Committee strongly recommends that recent biomarker data published by Boyle et al. (2016) should be incorporated into the report. That paper suggests the possibility of low level, but widespread, non-occupational exposures to 1-BP. The Committee recognizes that there are some questions regarding the specificity of the biomarker used. With that caveat, comparison of predicted exposures with possible biomarker levels in the general population would still be useful and should be considered by the Agency.

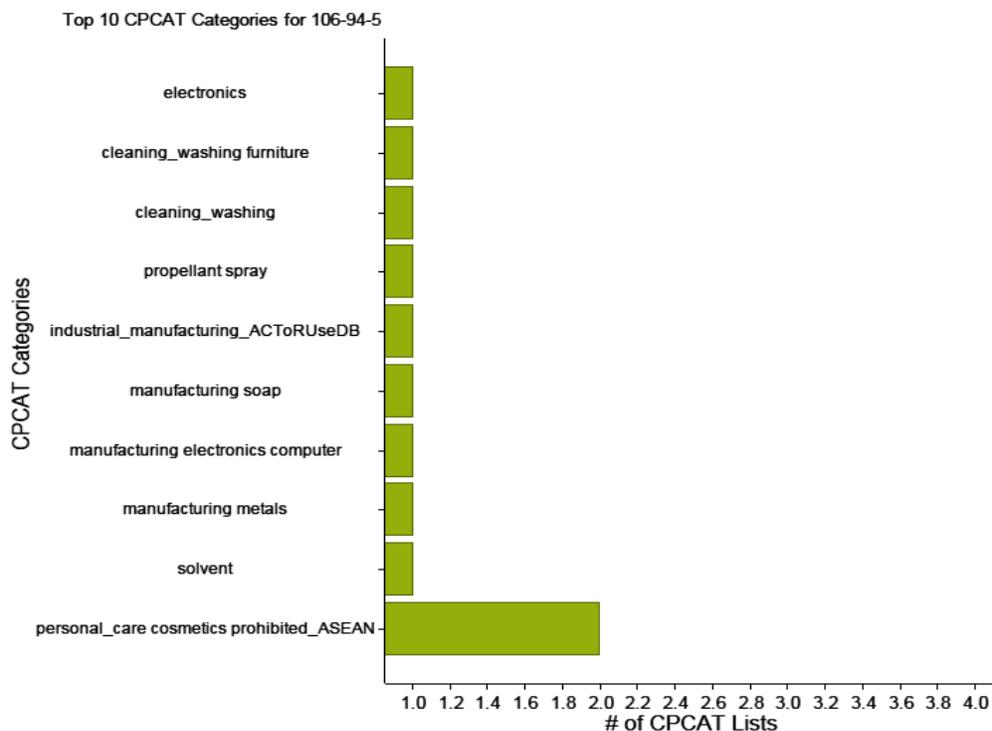


Figure 1: EPA ACToR (Aggregated Computational Toxicology Resource) database, “Top 10 Chemical and Product Categories” for 1-Bromopropane

- One Committee member expressed concerns related to modeling exposure based on a single short use and spreading the exposure out over 24 hours. The basic assumption behind time extrapolation, at least when extrapolating the toxicological results from an experimental exposure to a longer or shorter human exposure scenario, is that Haber's Law applies. This invokes the concept that concentration X time is a constant, meaning a shorter higher exposure is equal to a longer lower exposure in terms of degree of adverse health effect. This might be true for relatively small extrapolations for acute exposures, such as a few minutes to a few hours. However, in this case, on the exposure front at least, peak concentration from less than a minute of use is being extrapolated over time to estimate exposure concentration for a 24 hour time period. It seems to be a big leap in terms of assuming the same effect would occur. There may be dose rate issues (e.g., depletion of GSH from high brief exposures) that get buried in such an extrapolation. The Committee member encourages the Agency to discuss this problem further and see if there is a different way to approach this. The Agency notes that we do not know when the window of susceptibility is for a developmental effect. We also don't know how wide the window is in terms of timing. Perhaps assuming an 8 hour acute exposure in the residential setting, as is done for a workplace, may be more reasonable in terms of estimating exposure from a single short term use. The Committee member noted the possibility of conflating two concepts here (modeling of exposure and time extrapolation from experimental exposure to the human scenario), but, even so, maintained a concern about very short high exposures being equated in terms of degree of adverse effect to long duration low-level exposures.

Editorial Comments

- One issue identified by the Committee members has been the presentation of information relevant to the modeling analysis that appears to be scattered at different locations in the main body of report and the various appendices. For example, on page 74 the reader finds the statement “One percent (1%) of the product was assumed to become instantly aerosolized (i.e., product overspray) and was available for inhalation” with no reference or justification for this important assumption. The reader has to go to Appendix L and look in Table ApxL-1 to actually find a justification and source for this assumption, and then even further in Section L-4 to find an extensive discussion of this parameter. As another example, Table 2-17 is supposed to describe the model scenarios but falls far short of doing this. Actually, Table 2-18 begins this process by describing all the common input parameters and their settings but in Section 2.2.1.4 the reader finds that she/he needs to go to Appendix L to see settings for the remaining parameters (Table ApxL-1). Reading the eight paragraphs of Section 2.2.1.3 helps a little, but even after reading this, it is not clear that the reader has sufficient information to duplicate the simulations performed with E-FAST. It is awkward having to flip between the main body of the report and Appendix L to get an understanding of what was done. Another demonstration of the need for a more coherent presentation involves Section 2.2.1.4. A number of paragraphs tell the reader what was not used, but fail to describe clearly what was used in the analysis. For example, the last paragraph on Page 79 talks about how the model (the Consumer Exposure Module of E-FAST) outputs peak concentration and how this was not used in the risk assessment. But nowhere in the main report is it explained what was used. The reader has to go to page 254 and Appendix L to learn that “Values (ppm) in Table ApxL-4 were the only values used in the risk assessment.” These are “24-hr time averaged indoor air concentrations for 1-BP (ppm) that were not sensitive to user specific characteristics such as body weight or respiration rate.” The Committee recommends that, in order to improve the readability of the document, essential material of the Appendices should be summarized in the main body of the report, if possible with references to the specific locations in those Appendices where this material is presented in detail.

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.

Committee Response

Consumer Uses

In contrast to the probabilistic approach used for occupational exposure analysis, the Agency has conducted a deterministic analysis of the consumer exposure scenario. While sympathetic to issues of data insufficiency, the Committee encourages the Agency, going forward, to adopt probabilistic approaches. Such a strategy would greatly aid evaluation of exposure predictions by

facilitating quantitative comparison to biomarker data, where available, and/or to results of modeling exercises conducted by other parties. The latter point raises another issue. Much effort is currently being put into development of consumer exposure models useful in the context of REACH in Europe and for purposes of Life Cycle Analysis in the U.S. Comparability of consumer exposure modeling within the TSCA Work Plan process and other initiatives is of interest to the Committee. The Agency should consider how systematic comparisons across modeling platforms might be made going forward.

The Agency has limited its analysis of non-occupational exposures to three active uses involving aerosol spray products. These are plausible exposure pathways, but may or may not provide adequate coverage. First, the Committee suggests that the Agency consider multiple uses on any day of the various aerosol products, and use on multiple days per week. A do-it-yourselfer may have multiple items that need cleaning/degreasing/gluing in a single project and thus may use the product multiple times on a given day or multiple days in a week.

Second, the Committee further suggested that the Agency consider that the selected exposure scenarios probably represent episodic pathways in a subset of the population (i.e., users and co-habitants of users). Production of 1-BP is increasing and other products containing 1-BP are presumably obtainable. Given the possibility of overlooking a significant exposure scenario, the Committee recommended that evaluation of biomarker data should be considered within the consumer exposure analysis. Boyle et al. (2016) (in a publication not currently cited in the TSCA Work Plan Chemical Risk Assessment) report 99% detection and a median of 2.6 ng/ml of the ostensible 1-BP metabolite BPMA (aka N-acetyl-S-(n-propyl)-l-cysteine, aka AcPrCys) in a large sample of pregnant women participating in the National Children's Study. Jain (2015) has reported similar median urinary levels in children aged 6-11 sampled for NHANES (although lower overall prevalence of detection). This suggests common exposure.

However, BPMA is a non-specific metabolite and the aforementioned results could reflect exposure to other halopropanes. BPMA is well correlated with urinary bromide ion (Hanley et al., 2009; Mattias et al., 2012) in occupationally exposed populations (but appears to give lower yield). Whether it is a valid biomarker at lower non-occupational exposures is unclear. Nevertheless, ubiquitous exposure to low-level 1-BP is not impossible. Earlier sections reveal that furniture assembly (foam block gluing) is an important potential source of occupational exposure. That activity involves spraying adhesive containing 1-BP onto large surfaces of foam which are then pressed together to build thickness for use in cushions. This process could lead to trapping of 1-BP in the interior of the assembled cushions which could be released into indoor air over extended periods. The Committee recommended that the Agency predict urinary BPMA levels expected in light of the presumed scenarios and compare to the available biomarker data. It would also be useful to survey the literature for 1-BP (and other halopropane) levels in indoor air. If 1-BP can't be found, urinary BPMA levels in the general public are likely to have another explanation (and Bromo Propane Mercapturic Acid may be a misnomer). Boyle et al. (2016) also reported a maximum BPMA value of 4260 µg/L in their population. That number is similar to persons in non-spraying jobs in Hanley et al. (2009).

Editorial Comments

At least one committee member observed that flipping back and forth from Section 2.2 to Appendix L was cumbersome. In Section 2.2.1.5 on pages 80 and 81, there are four references to Appendix K that should be references to Appendix L.

In Appendix L, Table ApxL-2, on page 247, the Comparison of the Westat Survey Data and Simulation Values for 1-BP indicates that for spray adhesives the mean amount of spray adhesive product used per event (2.98 oz) based on the survey data is larger than the 90th percentile amount (2.0 oz).

In Appendix L, Table ApxL-2, on page 248, the time spent in a room after use for engine degreasers indicates a mean of 5 minutes and a 90th percentile of 0 minutes.

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 feasible 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.

Committee Response

Weight of Evidence Regarding Mutagenic/Genotoxic and Additional Modes of Action

Most Committee members agreed the existing evidence supports a conclusion of mutagenicity/genotoxicity as the primary mode of action (MOA) for 1-BP and some of its

metabolites (i.e., oxide, alpha-bromohydrin, and glycidol). One Committee Member concluded that the evidence for mutagenicity was not convincing. The document appropriately notes the potential contribution of additional MOAs, such as oxidative stress, immunosuppression, and cell proliferation, glutathione depletion, and inflammation. Although not considered completely convincing, the results from cultured mammalian cells in which 1-BP caused mutations and the fact that 1-BP can be metabolized by CYP2E1 into at least five mutagenic intermediates favors a primary MOA of mutagenicity versus some other mode of action such as increased oxidative stress or immune suppression. The Committee recommended that the document should be reviewed for consistency in describing the primary MOA, i.e., on page 95 the phrase “Besides mutagenicity/genotoxicity...” is used and on page 112 the phrase “Although data suggest a probable genotoxic mode of action (MOA)...” is used. The Agency should consider broadening the terminology used to describe the primary MOA to “mutagenic/genotoxic” or “genotoxic” for consistency and to better characterize the contribution of the non-mutagenic endpoints that support genotoxicity. Mutagenicity refers to a chemical or physical agent’s capacity to cause mutations (genetic alterations). Agents that damage DNA causing lesions that result in cell death or mutations are genotoxicants. All mutagens are genotoxic, but not all genotoxicants are mutagens as they may not cause retained alterations in DNA sequence.

Despite some inconsistencies in the evidence for mutagenicity (e.g., results from the 2011 NTP report) and the inherent challenges of understanding the scope and relative contribution of all possible MOAs underlying a carcinogenic phenotype, the Committee concluded that the available evidence supports using a low-dose linear model to assess dose-response. This is consistent with the Agency’s Guidelines for Carcinogen Risk Assessment practice of using a linear model for dose-response assessment unless there is compelling evidence that there is a threshold mechanism responsible for carcinogenesis.

The Committee had an overarching comment on chapter 3, “Human Health Hazard Assessment,” that the document could better clarify the strategy used to identify studies considered relevant; Figure 3-1 of the risk assessment document does not provide an appropriate level of detail. Databases searched, example search strategy, process used to screen studies for relevance, and a study flow diagram should be described, at least in the appendix materials. With respect to MOA, the document describes the limitations in the evidence, but the Committee suggested it could provide more explanation using study details to bolster the case for genotoxicity of 1-BP, including:

- There were positive and negative genotoxicity studies in bacterial test systems, and that there are complications trying to assess genotoxicity of a volatile compound. It is worth noting that the 1981 publication by Barber indicates that while only a few of the 10 tested VOCs were positive in *S typhimurium* test strains when using an unenclosed system, 7 of 10 were positive when using a system that traps the VOCs.
- Base-pair mutations were observed in the mouse lymphoma assay (with and without metabolic activation).

- 1-BP and structurally similar compounds are alkylating agents. This reactivity would allow formation of DNA-adducts and DNA damage, for which there was some evidence in workers, albeit relatively weak. DNA adducts have also been observed with *in vitro* incubation (Lee et al., 2007).
- The NTP Report on Carcinogens (2013) notes the formation of globin adducts in workers exposed to 1-BP, and this was observed in exposed rats as well by Valentine et al. (2007). This didn't appear to be referenced in the Agency's document. The NTP report also describes a study by Toraasson et al. (2006) evaluating DNA damage by the Comet assay. This study found associations between 1-BP exposures assessed/measured at the individual level and DNA damage in leukocytes, some of which were statistically significant, and all of which were in the positive direction.
- Besides being a direct-acting alkylating agent, 1-BP can also be metabolically activated to the epoxide intermediate via hydroxylation at the 2-position followed by dehydrobromination.
- If possible, consider including a relatively recent paper by Zhang et al. (2013; written in Chinese) showing the impact of 2-BP on DNA methyltransferases and histone acetylation in the testis of exposed rats. It is possible that 1-BP may act similarly, such that epigenetic regulation of oncogenes represents another potential mechanism.
- Consider explaining why the new Bioreliance study does not provide strong data in support of a non-genotoxic MOA, i.e., issues related to positive control.

In moving forward, the Committee recommended that the Agency should consider using the NTP Report on Carcinogens (RoC) or similar documents as the primary basis of a conclusion rather than conduct a *de novo* mode of action or other health hazard analysis. For 1-BP, the RoC monograph is recent (2013), was constructed in adherence with OMB peer-review guidelines, and reached a similar conclusion to the Agency's ("reasonably anticipated" versus "likely human carcinogen"). In the future, the Agency could focus on literature published subsequent to a rigorous analysis done by another agency or organization and consider whether any new data changes the nature of a main conclusion rather than summarize and evaluate every new study, at least for endpoints that are relatively non-controversial.

Editorial comments

- Given the Committee support for a conclusion of mutagenic/genotoxic as the primary MOA, the Agency should consider deleting or replacing the words "the major" with "an uncertainty" in the following sentence (page 151): "For cancer hazard assessment, the major uncertainty is whether the mechanism/mode of action of 1-BP carcinogenesis should be considered mutagenic/genotoxic or non-genotoxic."
- It would be helpful to present the doses and responses from the animal studies of cancer that form the basis of the cancer risk assessment in the body of the report. Sections 3.2.2, 3.3.3, and 3.4.2 do not show these data, and while they are found in Appendix O.5, it would be helpful to have a summary table in the text (e.g., Appendix Table O-3) and to describe the quality of

these data, and their relevance for human inference, because they form the basis of the cancer risk assessment.

- As noted above, the Committee recommended that the document should be reviewed for consistency in describing the primary MOA.

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.

Committee Response

Choice of Endpoints and PODs

In general, the Committee concluded that the Agency appropriately considered various non-cancer endpoints, including liver, kidney, reproductive, developmental, and neurotoxicity for assessing human risk associated with acute and chronic inhalation exposures to 1-BP. In most cases, adverse toxic effects were observed in both humans and animals at the concentration range 100-1000 ppm.

The Committee found that the database overwhelmingly supports use of neurotoxicity as the key endpoint of concern for human exposure. There are both animal toxicology studies demonstrating neurotoxicity from 1-BP exposure and human epidemiological and case reports demonstrating neurotoxicity in occupational settings. Neurobehavioral deficits including decreased motor function and cognitive deficits in laboratory animals along with neurochemical and structural changes in the brain can be used as chronic neurotoxic endpoints to predict the neurological impairment in humans following long-term low-level occupational exposure. Several case studies indicated that humans exposed to 1-BP inhalation experienced severe peripheral neuropathy, muscle weakness, headache, gait disturbances, and cognitive deficits. Furthermore, the developing brain is sensitive to environmental neurotoxicants at levels far below those that are known to harm adults (Amir Miodovnik, 2011). Likewise, high bromine concentration and reduced brain weight was observed in rodent pups following gestational exposure (Ishida et al., 2016). The Committee also found that the POD values for the neurotoxic effects seemed logical based on NOAEL or BMDL_{1SD}. Thus, concern for developmental neurotoxicity could be an important consideration in the assessment of human risk from 1-BP exposure, although, the data are still very limited. Some Committee members also suggested that a POD value for the neurologic endpoints from human data are enough to exclude the 10-fold UF for inter-species considerations and comparing the neuro POD value for humans with the HEC from the animal studies may be a good way to check the inferences being made from the animal studies.

Based on literature, liver and kidney toxicities are important endpoints of 1-BP toxicity but appear to be less sensitive for determination of human risk. The Committee members found that the inhalation endpoint of increased incidence of vacuolization of centrilobular hepatocytes (Table 3-1) selected based on the WIL report was understandable if not particularly compelling. The WIL report noted that the liver changes were probably reversible. On the other hand, most of the rats in that study were sacrificed relatively early in life, and it is possible that liver changes would become more robust over time. Hepatocyte vacuolization can represent an early sign of liver toxicity. The Committee noted that Liu et al. (2010) described more robust liver pathology in the form of necrosis in some of the mouse strains tested. Thus, the Committee observed that it would have been useful to know why the WIL paper was used instead for the POD determination.

The Committee also found that the choice of multiple reproductive endpoints including decreases in prostate, epididymal, seminal vesical weight, and sperm motility in male and prolonged estrous cycle, decrease in number of antral follicles, and implantation sites in female seemed well chosen for the assessment of reproductive toxicity. Furthermore, infertility endpoints are preferred to litter size because of direct human relevance if there are adequate data to characterize risk. The Committee further found that the POD values selected seemed appropriate given the dose response of 1-BP in the WIL study. This is also true for the developmental effects noted and the associated POD values. However, one Committee member noted that in the BMDS analysis of decreased BW in F1 male pups in the WIL Research study (page 366, Table Apx P-36), there were several models with close fit statistics, but one Model (Hill) came up with a lower BMDL_{5RD} than the one that was chosen as the POD. The Hill model had a slightly higher AIC, but had a better p value than the model chosen to determine the POD for this endpoint. Thus, if the Hill model result had been chosen for body weight in pups, the BMDL, and thus the POD would have been 23 ppm, lower than the decreased litter size POD, a BMDL of 41 ppm, used for the acute exposure scenario. It is not clear from the document why this lower BMDL was not chosen as the POD.

Based on the data provided in appendix O, the Committee found that both hematological effects and immunotoxicity could be added to the list of endpoints for which the Agency could evaluate dose-response. Decreased blood cell counts appeared in a number of studies, although the NOAELS indicate this may be a less sensitive effect. These other endpoints might be relevant for exposures at the workplace, particularly for repeated high exposures to people using 1-BP.

The Committee found that together, the most sensitive non-cancer endpoints seem to be neurologic, reproductive, and developmental endpoints. Thus, the majority of the work should be focused on these endpoints for the determination of human risk from 1-BP exposure.

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.

Committee Response

WOE and Choice of Non-Cancer Endpoints

In general, the Committee members concluded that the Agency had conducted a thorough review of the literature and adequately explained the multiple lines of evidence supporting the chosen non-cancer endpoints described below. Some additional, recent human studies were noted by the Committee members, and are referenced below.

Developmental/reproductive toxicity: The WOE for developmental/reproductive toxicity was based on numerous studies in mice and rats. The Committee found especially convincing the 2001 report “An Inhalation Two-Generation Reproductive Toxicity Study of 1-bromopropane in Rats” conducted by WIL Laboratories on behalf of The Bromine Solvent Consortium. This report examined both genders, exposed to four different concentrations of 1-BP. The groups consisted of 25 rats/generation/gender/treatment group and examined a multitude of reproductive and developmental parameters. Exposure to 1-BP as F0 or F1 rats generated many significant differences in infertility, pup body weight, and weights of several reproductive and growth-related organs. In addition, the reported decreases in the number of implantation sites and increases in “unaccounted” implants for corresponding ovulatory events, reported as the difference between the total number of implantation sites counted and the number of pups born, were interpreted as an indication of post-implantation loss. Similar effects were observed in other studies with increased implantation loss in rats and in mice. In another two-generation inhalation study, exposure of rats to 250 ppm or more altered numerous reproductive endpoints in both females and males. The strength of the WIL report in conjunction with similar findings by several other studies suggested that developmental/reproductive toxicity due to 1-BP exposure was likely.

According to the NTP-CERHR expert panel report on the reproductive and developmental toxicity of 1-bromopropane, occupational use of 1-BP in a glue spray gun generated TWA of air concentrations ranging from 60-261 ppm (Ichihara et al., 2002). Three women in the occupational study experienced serious neurological and reproductive effects. There is minimal concern for reproductive or developmental effects when humans are exposed at the lower end of the human occupational exposure range (0.04-0.63 ppm). However, the extent of 1-BP exposure among a particularly sensitive population is reported as high. A metabolite of 1-BP (N-acetyl-S-(n-propyl)-l-cysteine) indicative of exposure was found in 99% of pregnant women based on samples collected between 2009 and 2010 for the National Children’s Vanguard Study (Boyle et al., 2016). However, one Committee member suggested that this metabolite may not be specific for 1-BP exposure and can be a metabolite of any 1 or 2-halopropane; this point needs to be investigated to appreciate the significance of these findings.

Neurotoxicity: The Committee found the evidence that 1-BP causes neurotoxicity was also very convincing. In this case, the Agency used 15 years of behavioral, neuropathological, neurochemical, and neurophysiological studies in rodents as well as cross-sectional studies and case reports in humans to establish a causal association with 1-BP and neurotoxicity. The studies appear to link electrophysiological impairment with behavioral modification in animals.

Mechanistically, these studies appear to be consistent with human symptoms observed after high dose exposures to 1-BP and confirm peripheral neurotoxicity as an endpoint of excessive 1-BP exposure. A study of Chinese workers reported 1-BP TWAs between 0.35 and 535 ppm (Li et al., 2010; article in Chinese). The authors also reported neurological effects in these workers. Multiple and consistent adverse neurotoxic manifestations have been described including peripheral weakness, numbness, and ataxia.

Hepatotoxicity: The Committee concluded that the WOE for 1-BP-induced hepatotoxicity in animal models was adequate, even though one study in humans (exposure to 23 ppm for 40 months; Li et al., 2010) did not indicate liver toxicity. The WOE data for liver toxicity was more convincing if the AOP paradigm is utilized. For example, if 1-BP undergoes bio-activation via CYP2E1 or CYP2F1 and subsequent conjugation with GSH (or conjugation via GST, or non-enzymatically), GSH depletion should lead to oxidative stress and lipid peroxidation which is mechanistically linked to hepatocyte vacuolization which was observed in previous studies.

Kidney toxicity: The fourth non-cancer endpoint described was kidney toxicity based on animal studies showing changes in kidney epithelia hyperplasia, pelvic mineralization, and blood urea nitrogen. However, two studies in humans exposed to 1-BP failed to demonstrate renal effects and, therefore, the Committee found that the WOE for this endpoint is less compelling than neurotoxicity and reproductive/developmental toxicity.

Immunotoxicity: Although not selected as a non-cancer endpoint, some studies did demonstrate immune suppression in rodents exposed to 1-BP. The Committee found that the lack of transparency as to how studies were selected to arrive at potential endpoints makes it hard to ascertain why this endpoint was dismissed even though the Agency also mentions that immunosuppression may be a potential MOA for cancer. One of the Committee members noted that GSH depletion was observed in spleen from 1-BP treated animals which was associated with decreases in T cells in the spleen. Other effects reported in mice included reduced splenic cellularity and decreased absolute spleen weight (Lee et al., 2007). However, another Committee member was not convinced that the decrease in splenic GSH would necessarily lead to immune suppression.

Adverse Outcome Pathway Approach

Several Committee members suggested that the Agency may use the Adverse Outcome Pathway (AOP) to qualitatively assess causality and use the AOP wiki as a public forum for any proposed pathway. The Agency can get external as well as internal review through this tool. Use of the AOP approach will not only aid the Agency in showing causality with endpoints selected for threshold development, but also allow the Agency to identify data gaps and potential biomarkers. An example AOP approach is shown below in figure 2.

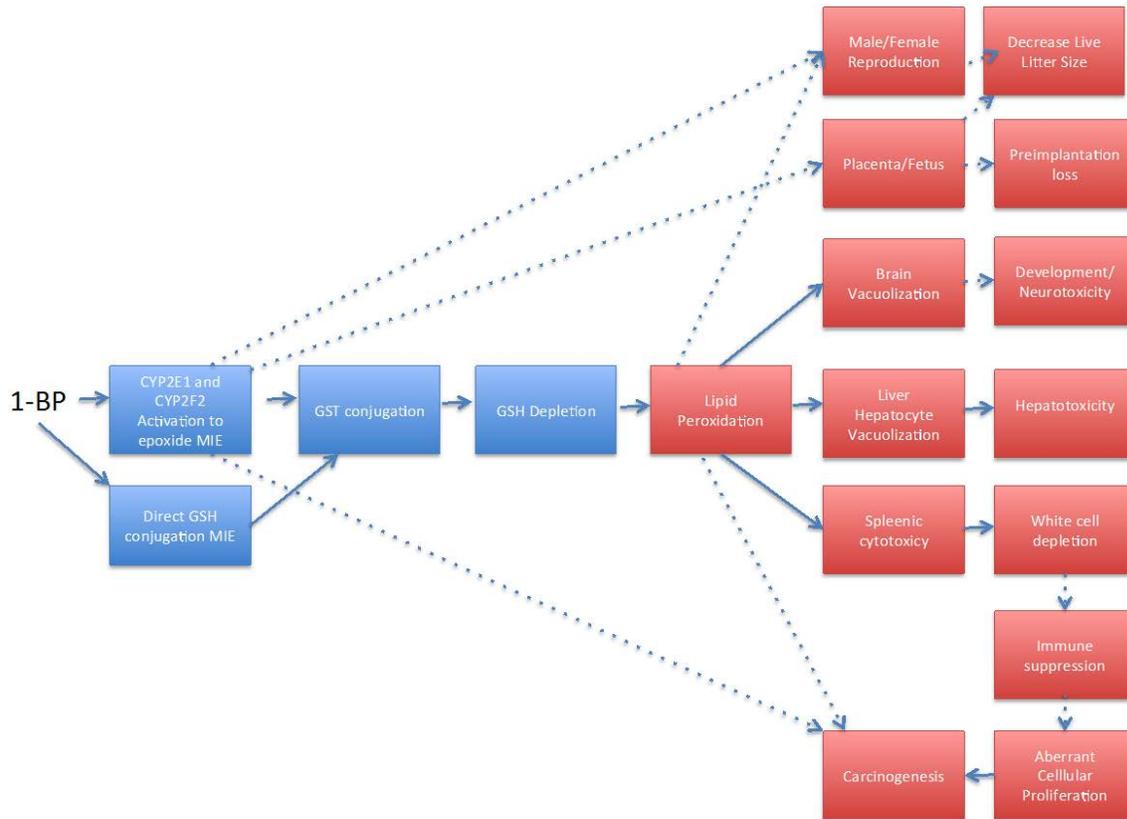


Figure 2: Example AOP Approach - Red box color represents adverse outcomes. Solid lines represent literature support for linkage. Dashed lines represent hypothetical relationships. MIE= Molecular Initiating Event (s) (CYP activation with subsequent GSH conjugation).

Conclusions

The Committee concluded that the selected endpoints of neurotoxicity and developmental/reproductive toxicity caused by 1-BP exposure seem especially well justified based on numerous animal studies, and in many cases, human case-control studies and case reports. Risks for adverse neurological and developmental effects were apparent regardless of the type of 1-BP exposure (50th percentile/central tendency or 95th percentile/high-end) pre-EC for all the uses evaluated. Occupational non-users showed risks for adverse neurological and developmental effects with high-end exposures (95th percentile) regardless of the availability of engineering controls for most use scenarios.

The large number of papers documenting reproductive toxicity and neurotoxicity associated with exposure to 1-BP is compelling, and underlines the decision to use these as non-cancer endpoints. Because of the reproducibility of the results generated by different laboratories, the endpoints should be considered appropriate even though each individual study has not been evaluated for its own merits.

The GSH depletion caused by 1-BP exposure may also play a role in its neurotoxicity since CYP2E1 is also present in brain, particularly human fetal brain (Brzezinski et al., 1999). CYP2E1 is also present in placenta, which may also be linked to reproductive/developmental toxicity through this molecular initiating event.

Although there were studies in rodents demonstrating at least early signs of 1-BP-induced hepatotoxicity and kidney toxicity, the Committee found that the lack of human data demonstrating comparable effects made these two endpoints less compelling than neurotoxicity and reproductive/developmental toxicity.

Editorial Comments

The Committee commented that details concerning inclusion/exclusion criteria for the different studies would have been useful. Along these lines, the Agency should clarify what is meant by “adequate.”

The POD for reproductive toxicity referred to in Table 3-4 (page 114) does not coincide with what is provided in Table 3-1 (page 105). Table 3-4 references WIL 2001; while Table 3-1 references Ichihara 2000.

Additional References

The Committee recommended the following additional references that should be included in the risk assessment:

1. Miao, R., Shi, Y., Zhu, B., Ding, P., Yang, D., Fu, Z., Zhang, Y., Wang, Y., and Zhang, M. (2015). "[Electrophysiological effects of 1-bromopropane on exposed workers]." *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi*. 33(5): 355-357.
2. Wang, T. H., Wu, M. L., Wu, Y. H., Tsai, W. J., Lin, K. P., Wang, C. L., Yang, C. C., and Deng, J. F. (2015). "Neurotoxicity associated with exposure to 1-bromopropane in golf-club cleansing workers." *Clin Toxicol (Phila)*. 53(8): 823-826.
3. Fang, Z., Miao, R., Yang, D., Ji, J., Wu, W., Zhang, Y., Ji, Z., Shi, Y., and Zhu, B. (2015). "[Effects of 1-bromopropane on liver and kidney functions of exposed workers]." *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi*. 33(5): 357-358.
4. Lee, S.K., Jeon, T.W., Kim, Y.B., Lee, E.S., Jeong, H.G., and Jeong, T.C. (2007). Role of Glutathione Conjugation in the Hepatotoxicity and Immunotoxicity Induced by 1-Bromopropane in Female Balb/C Mice. *J Appl Toxicol*. 27: 358-367.
5. Brzezinski M.R., Boutelet-Bochan H., Person R.E., Fantel A.G., Juchau M.R. (1999). Catalytic activity and quantitation of cytochrome P-450 2E1 in prenatal human brain. *J Pharmacol Exp Ther*. 1999 Jun; 289: 1648-53.

Question 4-4: Typically, EPA uses the benchmark dose modeling software (BMDS) with a benchmark response (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.

Committee Response

Model Averaging Approach

The Agency used an approach proposed by Wheeler and Bailer (2007) to derive a BMD and benchmark dose lower confidence limit (BMDL) based on a dose-response curve averaged across multiple parametric dose response models available in BMDS. A weighted average was computed with individual dose-response curves weighted by a fit statistic, the Akaike Information Criterion (AIC), such that the better fit models had a greater influence on the average curve. The BMDL was estimated using the 5th percentile of the BMD from bootstrapped samples.

The Committee noted that model averaging has many advantages over the use of a single parametric dose-response model in determining a POD. First, model averaging is a valid method for addressing model uncertainty when there isn't strong mechanistic support for a particular dose-response relationship. The method has also been shown to outperform selection of the single best fit model in terms of bias and coverage of the one-sided confidence interval (CI) for the BMD used to calculate the BMDL (Wheeler and Bailer, 2007). These same studies have shown that model averaging exhibits good properties (low bias, acceptable coverage rate of the CI) when the true model is not included in the average, but the suite of models used to perform the averaging is sufficiently diverse. Yet another advantage of model averaging is that it often produces more stable estimates than individual models (see, for example, Yuan and Ghosh, 2009). Furthermore, since bootstrapping is used to generate CIs, the approach is virtually guaranteed to achieve nominal coverage rates while the confidence intervals generated in BMDS for individual models are asymptotic and may not achieve the nominal rates at small sample sizes, even if the correct model is fit. Finally, the software the Agency used (MADr-BMD) has been peer reviewed and published in the statistical literature (Wheeler and Bailer, 2008) and has been extensively tested by the software authors using data previously fit using the Agency's BMDS package.

While model averaging used by the Agency has several strengths, the Committee noted it also has several weaknesses. The approach the Agency used relies on two key assumptions, which if violated, could result in biased estimates of the BMD. First, since the models they used in computing the average are all monotonic, the average dose-response curve must be monotonic. Since monotonicity is commonly assumed in dose-response assessment of carcinogens, the Committee did not find this particular assumption to be problematic. The second major assumption involved in model averaging is that an appropriate model space has been chosen; i.e., the models used to compute the average must be diverse enough to capture the true dose-

response relationship but should not include models that contradict the mechanistic knowledge of a toxicant. If inappropriate models are included, bias can occur even if these models are down-weighted because of poor fit (e.g., if risk estimates are very different from the other models the down-weighting might not be enough).

The Agency averaged across log-probit, Weibull, and multistage models of highest allowable order based on the results of a simulation study performed by Wheeler and Bailer (2007). In the Wheeler and Bailer study, the three model suite chosen by the Agency often performed better than using a larger class of seven models (the three model suite plus a quantal-linear, quantal-quadratic, logistic, and probit model) in terms of bias of the estimated BMD and coverage rate of the one-sided CI used to calculate the BMDL. However, as recommended by Wheeler and Bailer (2007), one should exclude from the averaging models that don't match the mechanistic assumptions of the toxicant. Since low dose linearity is commonly assumed for carcinogens, this would suggest that the log-probit model should be removed from consideration because it is a tolerance distribution model and hence assumes that organisms have an inherent tolerance to a toxicant (cf. Piegorsch and Bailer, 1997, Section 7.2.1). The Weibull model would also fall into this group unless the alpha (α) parameter is close to 1.

Besides the conceptual objections to using the log-probit model, the Committee found that there is empirical evidence for not using the model to generate an average dose-response curve. For two of the three data sets, the Agency was unable to estimate a BMDL using the log-logistic model. When they were able to obtain a BMDL using the log-logistic model, the BMD/BMDL ratio was 7.4×10^{10} (Table P-64), which suggests that the model is very unstable. Furthermore, since the BMD estimates obtained from the log-probit model differed dramatically from the estimates obtained from the Weibull and multi-stage model, its inclusion might have significantly biased the final BMD estimate for each outcome.

A final weakness of the model averaging approach is that for some dose-response relationships, it can result in BMD estimates with questionable accuracy. For instance, in situations where the true dose response is monotonic but very shallow or even flat, the method can produce BMD estimates that are greater than the maximum dose administered, sometimes being infinitely large (10^8) (Wheeler and Bailer, 2007).

In light of the above comments, the Committee provided a few recommendations to the Agency. First, the Committee recommends removing the log-probit model from the model averaging due to its instability when applied to the three cancer data sets and its disagreement with standard mechanistic assumptions for carcinogens. Instead, the Agency should use models which adequately fit the data and are consistent with the mechanistic assumptions for carcinogens (e.g., low-dose linearity). A reasonable approach would be to consider multi-stage models of different degree and the Weibull model assuming the α parameter (exponent of dose) is close to one. However, in 2 of the 3 data sets the Weibull model is equivalent to the linear multistage model (due to α hitting the boundary value of one) and the data could not support a multistage model of power greater than one (linear). Thus, model averaging could only be performed on one data set (large intestine adenomas in females).

The Committee also recommended that the Agency clearly explain the rationale for using an approach for determining the POD which differs from standard Agency practice. This comment applies not only to the use of model averaging but also the use of 0.1% added risk as the BMR instead of the more frequently used 10% extra risk. Furthermore, the Agency should show the difference in results using their model averaging method and the more traditional method of determining the POD.

Finally, the Committee noted some issues in the Agency's implementation of the model averaging method and reporting of results. As mentioned earlier, parameters of the Weibull model and multistage model hit boundary values and hence could not be estimated. In these instances, these parameters should not be included in the penalty terms for the AIC and Bayesian Information Criterion (BIC). The penalties are correct in the AICs reported in Tables P-62, P-64, and P-66 but are incorrect in the MADr-BMD output reported in Appendix P-3; since, the Committee assumes, that the AIC values reported by MADr-BMD were the ones used in the averaging, this would mean that the model averaging would have to be corrected. On a similar note, the "degree" labeling for the multistage models in Appendix P-3 is misleading because in only one of the instances were coefficients beyond the linear term nonzero. Finally, the results pasted from MADr-BMD include many decimal places which imply a greater level of precision than what is realistically supported by the data; thus, the Committee recommends reducing the number of decimal places reported.

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 the 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^{-4} , 10^{-5} , and 10^{-6} (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 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.

Committee Response

MOE Approach

The Committee found that, overall, using the lowest human equivalent concentrations as the point of departure (POD) for the developmental and reproductive toxicity for acute inhalation exposures is appropriate (and is standard risk assessment practice).

The MOE approach is one of the standard approaches for non-cancer risk assessment. It is parallel to the approach for site-specific or regional pollutants where one compares exposure estimates to Reference concentrations (RfCs), which are levels at or below which non-cancer health effects are not expected to occur even in sensitive subpopulations. When developing an RfC for a chemical, the POD is divided by uncertainty factors (UF) to arrive at a concentration that is considered a "safe" exposure level without undue risk of non-cancer health effects. The uncertainty factors are meant to account for toxicokinetic and toxicodynamic differences between experimental animals and humans as well as differences among humans. Uncertainty factors are also applied for other database deficiencies. In the MOE approach, the estimated exposure is divided into the POD to calculate a Margin of Exposure. The calculated MOE is then compared to a benchmark MOE, which is the total UF (product of individual UFs). If the MOE is lower than the benchmark MOE, then the risk is considered unacceptable. The assumptions are the same in both approaches, namely that animal evidence is relevant to humans unless data counter-indicate, and that uncertainty factors account for toxicokinetic and toxicodynamic differences between species and among humans in response to toxicants, and account for other database uncertainties or deficiencies.

One Committee member found the description of the MOE approach to be confusing. The calculation of each MOE should be straightforward from the information provided in the tables, but currently not enough information is provided. The conversion of PODs into HECs should be shown, with each assumption clearly stated.

The Agency derived MOEs for acute inhalation exposures to 1-BP for both occupational and consumer use. The Committee noted that the focus on the high-end acute exposure for occupational (95th percentile) and consumer (90th percentile) populations seems appropriate. Risks were identified for most of the acute occupational exposures scenarios (user and non-user alike), even with use of engineering controls (EC). Similar findings were noted for the 50th percentile exposure estimates. For the 90th percentile exposure estimates, and for many of the 50th percentile exposure estimates, risks were also identified for acute inhalation consumer

exposure scenarios. The MOE values identified were about 1-2 orders of magnitude below the benchmark MOE of 100.

Occupational exposure - The Agency chose to use developmental toxicity based on animal studies as a basis for acute exposure risk assessment for occupational scenarios. The Committee concluded that this was an appropriate endpoint to choose for assessing acute exposures to workers using 1-BP containing products. As noted in the description of studies, "Evidence for 1-BP induced developmental toxicity include dose related adverse effects on live litter size (WIL Research, 2001), postnatal survival (Furuhashi et al., 2006), pup body weight, brain weight and skeletal development (Huntingdon Life Sciences, 1999, 2001; WIL Research, 2001)" (page 92). Thus, there are multiple endpoints related to developmental toxicity, at least some of which had PODs close to the POD for decreased live litter size (e.g., decreased seminal vesicle weight, $BMDL_{1SD} = 38$ ppm; decreased brain weight in F2 females $BMDL_{1RD} = 50$ ppm; others in the 80 to 100 ppm range; Table 3-1, page 104).

Decreased litter size indicates reduced fecundity in rodent models. Litter size reduction can be related to male and female reproductive function or can result from a direct effect on the fetus. It is difficult sometimes to disentangle the cause(s). Litter size is a standard endpoint in reproductive and developmental toxicity studies, as noted in the Agency's guidelines.

The Committee noted that this endpoint is appropriate for an acute exposure scenario given that developmental toxicity may occur from a brief exposure during a critical window of susceptibility. It is unclear in the standard reproductive and developmental toxicity testing paradigms when the precipitating biological event(s) occur. As the Agency notes, "the constellation of both male and female reproductive effects (in the F0 males and females) collectively contributing to the decreases in live litter size, all occurred within a short window of exposure between ovulation and implantation" (page 101).

Note that there are a number of male and female reproductive system toxicity endpoints described in the same studies. These include unaccounted for implantation sites, decreased fertility, and effects on spermatozoa. There is no indication that reproductive and developmental toxicity of 1-BP in the animal studies would not be relevant to humans.

One Committee member was troubled with using decreased live litter size because humans don't have litters so a change in size of litter is not directly relevant to humans. While understanding why the endpoint was selected, this Committee member found it needs to be paired with other reproductive endpoints that are more directly relevant to humans if they are available, e.g., fertility. Also, this member noted that reproductive endpoints are different from developmental endpoints and should be characterized as such. The document does not clearly separate them.

As described in the response to question 4-2, one Committee member noted that if the Hill model result for decreased BW in F1 male pups in the WIL Research Study had been chosen, the POD would have been 23 ppm, lower than the decreased litter size POD of 41 ppm used for the acute exposure scenario. It is not clear from the document why the lower BMDL was not chosen as the POD.

The Agency used the typical default uncertainty factors of 10 for interspecies extrapolation and 10 for intraspecies extrapolation to determine the benchmark Margin of Exposure of 100. While some Committee members were comfortable with a benchmark MOE of 100 when using the animal-based POD, one member notes that the Agency could think about a larger uncertainty factor for intraspecies variability for this chemical. Toxicokinetic studies indicate metabolism of 1-BP is relatively complicated and involves both oxidation (via CYP P450) preceding conjugation with glutathione and possibly FMO mediated following conjugation with glutathione. There are a number of genetic polymorphisms for the glutathione transferases that influence rate of metabolism. It is not clear how these polymorphisms would affect the toxicity of 1-BP in humans. However, there are a number of toxicogenomics studies on other chemicals where GST metabolism is important that indicate a strong influence of GST genotype in the induction of toxicity in humans. Levels of glutathione also vary by diet, medication use, disease state, other pollutant exposures, and other factors that introduce variability in the human population. Variation in the CYP enzymes also exist. Age at exposure is also important in terms of metabolic capability, particularly for infants and toddlers, as well as the developing fetus. The Office of Environmental Health Hazard Assessment in California EPA has increased the default intraspecies UF to 30 in their risk assessments for non-cancer endpoints in recognition of the wide variability in toxicokinetics that exist among people due to genetics, age, gender, disease status, diet, etc. Thus, one Committee member observed that a benchmark MOE up to 300 is justifiable. Further, as noted below, another Committee member commented that for developmental toxicity, the Agency should consider an additional uncertainty factor, analogous to the Food Quality Protection Act factor applied for assessing pesticide tolerances.

Consumer exposure - The Committee also concluded that developmental toxicity is an appropriate endpoint for assessing acute exposure to the consumer from household uses of 1-BP, given that developmental effects can occur from exposures in discrete windows of susceptibility. Since it is widely believed that toxicants can generate developmental/reproductive effects at relatively low concentrations in a short exposure window, it seems likely that this is the risk that would be of greatest concern for consumers following acute exposure. The Committee found that, for the most part, the estimate of consumer exposure from spray adhesives, cleaning products, spot removers, etc. (Table ApXL-2, L-3) seemed logical. Since the MOEs calculated for consumer exposure scenarios were below the benchmark MOE of 100, there is a legitimate reason to believe that risk to consumers exists.

The decisions that went into the acute inhalation consumer exposure scenario seemed appropriate to some Committee members, but a few Committee members noted that there could be residual concerns between events or there could be relevant exposure mixtures from other chemicals in the consumer products. In terms of weakness, variables that might affect risk calculations for the consumer exposure are the size of the house, differences in air exchange rates among houses, possible use by consumers of engineering controls (e.g., ventilation,), and the likelihood that many hobbyists use some of the 1-BP-containing products (i.e., spray adhesive) more than once per day. However, most Committee members concluded that overall the available data and assumptions used by the Agency seem to represent a fair and logical approach to estimating the parameters that determine exposure. In view of the route of exposure most likely to directly

impact consumers (use of 1-BP-containing household products), it seems logical that such exposure would be very episodic rather than chronic. This does not take into account hobbyists who might use a 1-BP-containing product more than once per day, but in general seems to capture the majority of consumer use.

The Agency considered only acute exposures in the consumer use scenario because the half-life of 1-BP is short, and it was assumed that the products containing 1-BP would be used only once in a day and only infrequently. The Committee found that the assumption that even if the products were used more than once there would not be residual 1-BP is reasonable, if exposures occurred days apart. However, several Committee members observed that it may be important to consider multiple-use scenarios. A do-it-yourselfer may have multiple items that need cleaning/degreasing/gluing in a single project and thus may use the product multiple times on a given day and multiple days in a week. Most consumers are unaware of the toxicity of chemicals in consumer products and might not think about using 1-BP containing products multiple times in a day or week, particularly if they are working on a complicated project. Thus, some Committee members noted that multiple uses per day and per week should be considered for the consumer exposure scenario.

Estimating exposure for multiple uses in a day or across several days would necessitate having a POD to compare to those exposures in an MOE analysis. The exposures wouldn't be chronic and wouldn't be acute either, so there would need to be some thought about what to use for a POD and how to consider averaging time for exposure. The developmental toxicity study (WIL Research, 2001) used as a basis for the acute POD could be used for a POD for a longer exposure with multiple uses per day since, as noted earlier, the exact window of susceptibility in pregnancy is unknown. Also, the study which is the basis of the neurotoxicity POD (Honma et al., 2003) was a 3 week study. That study could be considered as providing a POD for an exposure scenario somewhere between acute and sub-chronic in the residential use scenarios.

One Committee member noted that a benchmark MOE of 300 (10 for inter-species and 30 for intraspecies), as described above for the occupational exposure scenarios, is justifiable for the consumer use scenario as well.

A number of Committee members were concerned that bystanders could be in the same room as the user for the consumer scenarios. If the bystander is a child, given that 1-BP is neurotoxic and that a child's CNS and PNS continue to develop into and beyond adolescence, then there is concern about potential developmental neurotoxicity to children from exposure to 1-BP. It is not clear whether there are short windows of exposure for neurotoxicity in children relevant to an acute exposure scenario as there are for the fetus, but some Committee members recommended that this should be considered in the choice of the UF and discussed in the document. Since the exposure assessment assumes that bystanders will be in adjacent portions of the house and not where the consumer product is being used, the exposure estimate for the bystander children is lower than that for the consumer user and is underestimated if the child is in the room where the consumer product is being used.

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.

Committee Response

Additional Comments on MOE Approach

The Committee found that, based on the dose-response assessment, the Agency appropriately chose the lowest PODs and associated HECs for each of the non-cancer endpoints from among the datasets amenable to dose-response assessment (with the possible exception of one developmental endpoint noted in response to questions 4-2 and 5-1 above; pup body weight with the Hill model had a lower POD than that for the decreased live litter from the WIL Research study). Other endpoints that it appears the Agency could have considered are hematological and immune effects (see also response to question 4-2 above).

The Agency appropriately strongly considered neurological endpoints, as workers exposed to 1-BP experienced severe neuropathy, muscle weakness, headache, gait disturbances, and cognitive deficits. Furthermore, residual neurological symptoms, such as disruption of cognitive function, has been reported in individuals who are highly exposed to 1-BP. However, the mechanism by which this occurs is not clear. Since ocular symptoms have been observed following acute exposure to 1-BP, this could be considered for a non-cancer endpoint as well, if the symptoms persist.

As noted above, it is not always entirely clear why the specific studies used for POD were chosen over others; the Committee recommended that the explanation should be expanded in the document. The benchmark MOEs were based on uncertainty factors, which were largely the default factors typically used by the Agency in risk assessment. As discussed above, one Committee member noted that the default for intraspecies uncertainty could arguably be larger than 10.

The Agency chose to base the primary MOEs on the high end exposure estimates. One uncertainty in the consumer exposure is the variability in the duration of exposure (hours/day) and number of exposures. Given the uncertainty in the exposure data (both monitored and modeled), the variability in exposures during the working day/week from different activities, and the desire to protect people who have higher exposures, the committee noted that it is appropriate to focus on high end exposure estimates. Using the “median” exposure would, in essence, only protect half the population.

Several Committee members noted that the exposure calculations in the MOE determination are based on 8-hour time weighted averages (TWA) and the assumption for dry cleaners was that there were two workers who worked 2 overlapping shifts of 8 hours each. However, since many dry cleaner shops are small businesses, it is reasonable to assume that there is only one worker who operates the machine over the entire day, such that this worker operates on an extended

shift. However, if this were assumed it would be important to note that the extended shift guidance on calculation of an 8 hour time-weighted average from OSHA (OSHA, 2014) may not be appropriate to apply here because the computation of an MOE is not a compliance exercise. Therefore, consideration could be given to the computation of a raw time weighted average over the entire shift if the Agency were to consider a total 12 hour shift with one worker rather than 2 workers operating the machine in two overlapping 8 hour shifts. In other words, if the worker exposure is modeled as a 12 hour shift, the TWA should include all exposures (not just exposures for an 8 hour period) and be averaged over the entire shift (not just 8 hours) weighted as appropriate.

Given that neurotoxicity has been observed in the occupational setting, this is an important endpoint to consider for chronic exposure. Of note, the lowest HEC (25 ppm) is derived from a neurotoxicity study in rats. The epidemiological studies reporting neurotoxicity in workers using or manufacturing 1-BP were not readily useable for dose response assessment. However, they do provide some information on exposures of workers with neurological deficits. For example, Ichihara et al. (2004) measured 8-hr TWA 1-BP exposures of individual workers in a 1-BP production factory and found a range of exposures from 0.34 to 49 ppm, with a GM of 2.92 ppm. Fifteen of 27 workers in the 1-BP factory exhibited neurological deficits relative to control workers. While there were limitations to the exposure assessment and design of this paper and it can't be used for quantitative dose-response assessment, the authors reported neurological deficits in these workers relative to age- and education-matched unexposed controls, consistent with other studies. The HEC of 25 ppm is around the midpoint of the reported exposure range but higher than the GM. Some Committee members recommended that the Agency could discuss the animal POD in relation to the exposures measured in human studies to put the animal POD in context, understanding the limitations of the exposure assessments in the human studies.

The UFs that the Agency used to generate the benchmark MOE for neurological endpoints consisted of an UF of 10 to extrapolate from a 3 week exposure in rodents to a chronic exposure in humans, and an UF of 10 for interspecies and 10 for intraspecies extrapolation, for a total UF and benchmark MOE of 1000. The second most sensitive endpoint, based on the HEC, is developmental effects, but the total UF for this endpoint, and thus the benchmark MOE, is 100. This benchmark MOE is smaller than that for nervous system effects. The uncertainty factors utilized in this assessment follows many previous assessments done and in particular follows the developmental assessment examples presented in the Agency's developmental toxicity assessment guidelines (US EPA, 1991) and the Science Policy Council Handbook on Risk Characterization (US EPA, 2000). However, questions about the application of uncertainty factors and their appropriate selection and application have existed for many years (US EPA, 1991). A few Committee members expressed concern about the selection of only a total uncertainty factor of 100 to form the basis of the MOE for the developmental and reproductive endpoints selected. One member discussed the potential use of an additional uncertainty factor of 3 or 10 for impacts that may affect offspring or pregnancy, such as that suggested by the Agency's comments and documents on the pesticide program's consideration of an additional uncertainty factor in tolerance assessment and the Food Quality Protection Act (US EPA, 2002a & 2002b), which suggests that when merited an additional uncertainty factor can be considered

in sensitive populations. Additional consideration may also be merited for the reproductive and developmental endpoints because data exists in human populations of potential similar reproductive effects, not just in animal studies. Blando et al. (2009) presented information related to the cases reported in CDC (2008) regarding a clinical case report of a worker receiving medical treatment before and after an incident with 1-bromopropane showing signs, as measured by his urologist, of decreased sperm counts and motility after significant exposure to 1-bromopropane compared to a reproductive clinical assessment of sperm counts taken before the exposure incident. It should be pointed out that this was a case report and as such is subject to many limitations in interpretation. In addition, in a review by Ichihara (2005) signs of clinical reproductive effects including azoospermia, oligospermia, and amenorrhea, were described in factory workers exposed to a similar isomer, 2-bromopropane. Ichihara (2005) also speculated about the potential for 1-bromopropane to be related to infertility problems reported in a NIOSH health hazard assessment conducted by Reh et al. (2002). As such, these reports may suggest it is reasonable to ask if further consideration should be given to an additional uncertainty factor for developmental and reproductive endpoints.

The MOEs presented in the document based on both monitoring and modeling are mostly well below the benchmark MOEs indicating relatively high risk for non-cancer health effects for almost all the endpoints and exposure scenarios. Note that the MOEs calculated based on exposure monitoring data were even smaller than the MOEs based on exposure modeling. The Agency notes that these MOEs indicate that workplace exposures are mostly unacceptable in terms of non-cancer health risk; even with exposures measured after engineering controls were put into place, many of the MOEs were smaller than the benchmark MOE. The Committee agrees with the Agency's conclusion.

In terms of weaknesses, the uncertainties associated with the exposure assessment and with the dose-response assessment are folded into the risk characterization. This is one of the limitations of risk assessment. It is clear from the epidemiological literature including case reports and animal studies that 1-BP is neurotoxic. It is also clear from the toxicological literature that 1-BP is a reproductive and developmental toxicant; this is supported by some evidence in humans. In this document, there were limited data to use to estimate consumer exposures in particular. Thus, those estimates are fairly uncertain. The data for occupational studies involved both monitoring and modeling and for risk assessment were relatively robust. The dose-response assessment always involves uncertainty; hence the use of uncertainty factors in the non-cancer risk assessment. For cancer risk assessment, choice of model to determine the cancer slope factor introduces model uncertainty, and extrapolation from animals to humans always involves some unquantifiable uncertainty. Nonetheless, overall, the Committee agrees with the Agency that the uses of 1-BP containing materials present high risk of adverse non-cancer and cancer outcomes to workers and consumers.

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.

Committee Response

Cancer Risk Approach

The Committee agreed that it is not appropriate to try to quantitate cancer risk from acute exposures, for all the reasons given by the Agency. In essence, the studies upon which the unit risk factors are based are chronic exposure studies, either from occupational exposures or animal studies (the case with 1-BP). It is not possible to know the effect of an acute exposure on cancer risk given available data. The Agency used its Risk Assessment Guidelines and followed the standard procedure to estimate risk (although not the inhalation unit risk (IUR) factor that goes into the risk estimate). In estimating the risk to workers, the Agency used an appropriate exposure duration and inhalation rate (about 10 m³ during an 8 hour work shift) to estimate dose. The assumptions were adequately laid out, although mostly in footnotes.

The Committee found that the choice to use the IUR from the NTP lung tumor data is appropriate. The female mouse lung was the most sensitive site in the rodent experiments, resulting in the most potent estimate of inhalation unit risk (relative to the other sites where there was a statistically significant increase in tumor incidence). The Agency could have added the potency factors for each site to get a multi-site IUR factor. But, the lung potency estimate is quite a bit larger than the estimates of cancer potency for the two other sites. Thus, it would just be an academic exercise to determine a multi-site IUR in this case. One Committee member suggested using a range of values for the IUR, to include a rat model as well as mouse, but other Committee members considered selection of the most sensitive site in the most sensitive species appropriate.

The Committee also discussed the observation that each of the 3 tumor types occurs in one sex and within one animal species (keratoacanthoma/squamous cell carcinoma in male F344 rats; large intestine adenoma in female F344 rats; and alveolar/bronchiolar adenoma or carcinoma in female B6C3F1 mice). However, the Committee noted during the discussion that this pattern is not uncommon and site concordance is not necessary to conclude there is a risk. Overall, the aggregate of these three tumor types among mice and rats and among males and females is a strength in the carcinogenic observation.

One of the public commenters argued that the mouse lung was not a good model because it is especially sensitive to chemicals activated by CYP2E1. However, human lung also has CYP2E1. Further, the carcinogenic response is not just dependent on the rate of activation but also on the rate of detoxification, in this case conjugation to GSH and glucuronide. There are no epidemiological studies of a sufficiently large cohort of humans exposed chronically to 1-BP to estimate cancer risk from such exposure or to inform as to the sensitivity of humans versus mice. Humans are much more heterogeneous in terms of genetics (including polymorphisms in metabolic enzymes), disease status, age, and other exposures when compared to the laboratory animals on which the cancer bioassays are conducted. Further, human variability exists in many other factors that play a role in the carcinogenic process (e.g., DNA repair, antioxidant levels, and immune surveillance) and these have not been quantified either in animal models or humans.

Thus, the Committee found that it is appropriate to use the most sensitive site, gender, and species in cancer risk assessment, as is the standard risk assessment procedure.

The Committee also recommended that the Agency should consider whether any of the suggestions raised during the dose-response modeling discussion should be incorporated into the IUR analysis, i.e., excluding log-probit model, only including models that fit the data and are linear at low doses, and expanding the analysis to key non-cancer endpoints.

Editorial Comments and Requests for More Explanation in Report

The Committee also provided editorial comments and additional suggestions including:

- Table 4-3 indicates that the cancer risk is described as "Possible cancer effects in the lung from chronic exposure," citing NTP 2011. This sentence should just say "Possible cancer effects." The sentence, as the Agency has written it, assumes site concordance between the rodent model and humans. Although one might expect lung tumors in humans from 1-BP exposure because it is the first site of contact and there is CYP2E1 in the lung, site concordance is not really the norm. Rather, cancer may occur at different sites in humans and among other species than that in the test species. In addition, as reported in the NTP Monograph on 1-bromopropane (NTP, 2013), 1-BP induced tumors distally in the rodent models.
- The use of a BMR of 0.1% added risk (1 in a 1000) has at times been suggested as potentially the lower limit of the sensitivity of cancer assays and frequently 10% has been used (US EPA, 2012 benchmark dose guidance, US EPA, 2005a). This was discussed at the meeting and it was noted that the models were not that sensitive to using different added risk values. However, the Agency should still provide more explicit discussion and justification for using this BMR value.
- The Agency should be more specific about why the NTP carcinogenicity study was considered "good quality" – for example, by adherence to the elements outlined in appendix N (randomization, individual animal data, and rigorous peer-review process).
- The Agency should explain their choice of a BMR based on added risk instead of extra risk (the more commonly used measure). Re-iterating harmonization with the NIOSH analysis could be more explicit and perhaps mentioned in several places.
- A number of Committee members asked for a comparison of the modeling analysis used in 1-BP with more typical analysis as described in the Agency's cancer risk assessment guidelines. This seems to be included in an appendix, but the Agency should consider whether it needs to be explicitly described or referenced in the main body of the report.

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.

Committee Response

Clarity of Risk Characterization

The Committee noted that the audience for the risk assessment is unclear. The stated audience is the Agency's risk managers, but in the risk characterization, as with other sections, some things are explained at a much more basic level than others.

The Committee recommended that the conclusions should match the questions asked in Section 1. If the conclusions are "there are cancer and non-cancer risks for certain users and uses," then the questions should not be "do risks of concern exist..." Further, the risks may be smaller than what is estimated, based on the use of non-human data. This should be addressed in the document.

In addition, going forward the Agency should consider using a probabilistic approach to risk characterization and explain the assessment choices. The Agency should also include discussion of the uncertainties around exposures to people living near dry-cleaners or relevant industrial sites, if these scenarios are not added to the scope of the assessment.

The Committee noted that the benchmark cancer risk should be determined in the risk assessment rather than in the risk management. However, it doesn't matter in this case, since the added cancer risks are so high.

In addition, the Committee noted that Section 4 does not read clearly. There is unnecessary repetitiveness, sometimes on the same page. Other important points are not explained in the main part of the document, but are in the appendices, so one has to flip back and forth to understand what was done. The main document should stand on its own, with appendices for supporting information. Also, important points should be moved out of table footnotes and be included in the text (see for example, Table 4-1).

Other Issues

On the top of page 151, the Agency acknowledges the presence of model uncertainty in estimating PODs but states that the effect is likely minimal as long as the model fits the data well within the range of the data. One committee member pointed out that this statement is not always true because two models can have indistinguishable fit (AICs within 2 units according to the rule of thumb proposed by Burnham and Anderson, 2002) but produce remarkably different PODs. For example, in the analysis of renal pelvic mineralization (Table P-13), the fit of the selected model (probit) was indistinguishable from the fit of all other models considered, most of which provided BMDLs which were less than half the BMDL provided by the probit model. Thus, the committee member recommended that this statement be revised or removed.

Other Comments

One Committee member suggested that the Agency should add a page at the end of each chemical-specific risk assessment listing prior results in the series. This would emphasize the serial nature of the activity and perhaps eventually reveal patterns that might be exploited to speed up the overall process (since the adequacy of the pace of the assessments under the current

plan is a relevant question). At a minimum the table should include the name of the compound(s), the completion date of the risk assessment, and a link to that document. A lot of additional data should be compiled for comparative purposes somewhere, but would be difficult to put in a summary table. A compromise might look like this:

Table 3: Example Table for Listing Results of Prior Risk Assessments for a Chemical.

| Compound | Risk Assessment completion date and link | Toxicity endpoints of concern | Exposure pathways of concern |
|-----------------|---|--------------------------------------|-------------------------------------|
| | | | |
| | | | |

Another Committee member provided the following miscellaneous comments on dose-response modeling:

- The document indicates that BMDS sometimes gave warnings about BMDL calculations (e.g., page 360). The Agency should elaborate on these warnings.
- P-values of goodness-of-fit tests were compared when assessing fit but BMD guidelines specifically discourages this practice. It is hard to compare the p-values because groups are based on estimated risk which differs across models.
- In cases where fit was indistinguishable between models (i.e., AIC within two units), using the model with the smallest AIC was not really defensible. Using a more protective estimate, model average estimate, or estimate of model that provided best fit in the region of the BMR would have been better.
- The Agency should explain why model averaging was not used for non-cancer endpoints.
- On page 365, the Agency should define what they consider a large spread of BMCLs
- Related to the previous point, some models were excluded because of high BMD/BMDL ratios (e.g., relative seminal vesicle weight on page 341). The Agency should define “high.”
- The Agency should provide more details about the methods used to analyze fetal pup weight; in particular they should mention:
 - How the litter effect was accounted for;
 - Whether or not they accounted for the effect of litter size on pup weight.
- In cases where there was poor fit for all models the Agency should:
 - Provide a plot of the “best” fit model to show how bad the fit is;
 - Indicate the multiple comparisons procedure used to identify the LOAEL and provide all of the corrected p-values in the appendix.

Editorial Comments

- Be consistent with the structure of summary statistics tables in Appendix P (dose is in rows in some tables, columns in others).
- On page 331, the multistage model provided the best fit to data on centrilobular hepatocytes in male rats.

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