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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

Memorandum

SUBJECT: Transmittal of Meeting Minutes and Final Report for the TSCA Science Advisory Committee on Chemicals Meeting Held July 29 to August 2, 2019

TO: Jeff Morris, PhD
Director
Office of Pollution Prevention and Toxics

FROM: Todd Peterson, PhD, [redacted] 10/31/19
Designated Federal Official
TSCA Science Advisory Committee on Chemicals
Office of Science Coordination and Policy

THRU: Steven M. Knott, MS, [redacted] 10/31/19
Executive Secretary
TSCA Science Advisory Committee on Chemicals
Office of Science Coordination and Policy

Hayley Hughes, DrPH, MPH, CSP [redacted] 10/31/19
Director
Office of Science Coordination and Policy

Attached, please find the meeting minutes and final report for the TSCA Science Advisory Committee on Chemicals open meeting held in Arlington, Virginia on July 29 to August 2, 2019. This report addresses a set of scientific issues being considered by the Environmental Protection Agency regarding the Peer Review for the Draft Risk Evaluations for 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD).

Attachment

cc:

Alexandra Dunn
David Fischer
Jeff Morris
Tala Henry
Mark Hartman
Cathy Fehrenbacher
Stan Barone
Nhan Nguyen
Yvette Selby-Mohamadu

OPPT Docket

TSCA Scientific Advisory Committee on Chemicals

Kenneth Portier, PhD
Henry Anderson, MD
Charles Barton, PhD
Steven Bennett, PhD
Sheri Blystone, PhD
Deborah Cory-Slechta, PhD
Holly Davies, PhD
Kathleen Gilbert, PhD
Concepcion Jimenez-Gonzalez, PhD
Mark Johnson, PhD
Alan Kaufman
John Kissel, PhD
Daniel Schlenk, PhD
Catherine Willett, PhD

TSCA SACC ad hoc Peer Reviewers

Udayan Apte, PhD
George P. Cobb, PhD
David A. Eastmond, PhD
Stephen G. Grant
Robert C. Hale, PhD
Yue-Wern Huang, PhD
Michael A. Jayjock
Lawrence H. Lash, PhD
Maria T. Morandi, PhD
John B. Morris, PhD
Isaac N. Pessah, PhD
Thomas J. Rosol, DVM, PhD, MBA
Charles V. Vorhees, PhD
Calvin C. Willhite, PhD
Yiliang Zhu, PhD

TSCA Science Advisory Committee on Chemicals
Meeting Minutes and Final Report
No. 2019-02

Peer Review for EPA Draft Risk Evaluations for
1,4-Dioxane and
Cyclic Aliphatic Bromide Cluster (HBCD)

July 29 – August 2, 2019

TSCA Science Advisory Committee on Chemicals Meeting,

Held at the Holiday Inn Rosslyn at Key Bridge, 1900 Fort Myer Drive, Arlington, Virginia

NOTICE

The Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals (SACC) is an advisory Committee operating in accordance with the Federal Advisory Committee Act and established under the provisions of TSCA as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act of 2016. The TSCA SACC provides independent advice and recommendations to the U.S. Environmental Protection Agency (EPA or Agency) on the scientific basis for risk assessments, methodologies, and pollution prevention measures and approaches for chemicals regulated under TSCA. The SACC serves as a primary scientific peer review mechanism of the EPA, Office of Pollution Prevention and Toxics (OPPT), and is structured to provide balanced expert assessment of chemicals and chemical-related matters facing the Agency. Additional peer reviewers are considered and from time-to-time added on an *ad hoc* basis to assist in reviews conducted by the TSCA SACC. This document constitutes the meeting minutes and final report and is provided as part of the activities of the TSCA SACC.

The TSCA SACC carefully considered all information provided and presented by the Agency, as well as information presented by the public. The minutes represent the views and recommendations of the TSCA SACC and do not necessarily represent the views and policies of the Agency, nor 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 and final report do not create or confer legal rights or impose any legally binding requirements on the Agency or any party. The meeting minutes and final report of the July 29 – August 2, 2019, TSCA SACC meeting represent the SACC's consideration and review of scientific issues associated with Peer Review for EPA Draft Risk Evaluations of 1,4-Dioxane, and Cyclic Aliphatic Bromide Cluster (HBCD). Steven Knott, MS, TSCA SACC Executive Secretary, reviewed the minutes and final report. Kenneth Portier, PhD, TSCA SACC Chair, and Todd Peterson, PhD, TSCA SACC Designated Federal Official, certified the minutes and final report. The report is publicly available on the SACC website (https://www.epa.gov/tsca-peer-review) under the heading of "Meetings" and in the public e-docket, Docket No. EPA-HQ-OPPT-2019-0238 (1,4-Dioxane) and Docket No. EPA-HQ-OPPT-2019-0237 (HBCD), accessible through the docket portal: https://www.regulations.gov. Further information about TSCA SACC reports and activities can be obtained from its website at: https://www.epa.gov/tsca-peer-review. Interested persons are invited to contact Todd Peterson, PhD, SACC Designated Federal Official, via e-mail at peterson.todd@epa.gov.

CONTENTS

TSCA Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2019-02

Peer Review for EPA Draft Risk Evaluations for 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD)

July 29 – August 2, 2019

TSCA Science Advisory Committee on Chemicals Meeting,

Held at the Holiday Inn Rosslyn at Key Bridge, 1900 Fort Myer Drive, Arlington, Virginia

[redacted]

Kenneth Portier, PhD
TSCA SACC, Chair
TSCA Science Advisory Committee on Chemicals

Date: OCT 3 1 2019

[redacted]

Todd Peterson, PhD
Designated Federal Official
TSCA Science Advisory Committee on Chemicals

Date: OCT 3 1 2019

Toxic Substance Control Act
Science Advisory Committee on Chemicals Meeting
July 29 - August 2, 2019

Peer Review for EPA Draft Risk Evaluation of
1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD)

PARTICIPANTS

TSCA SACC, Chair
Kenneth Portier, PhD Consulting Biostatistician
Athens, Georgia (formerly National Cancer Society)

Designated Federal Official
Todd Peterson, PhD
TSCA Science Advisory Committee on Chemicals Staff
Office of Science Coordination and Policy, EPA

TSCA Science Advisory Committee on Chemicals Members

Henry Anderson, MD [3]
University of Wisconsin-Madison
Madison Wisconsin

Charles Barton, PhD [3]
Independent Consultant
Alpharetta, Georgia

Steven Bennett, PhD [3]
Household & Commercial Products Association
Washington, District of Columbia

Sheri Blystone, PhD [3]
SNF Holding Company
Riceboro, Georgia

Deborah Cory-Slechta, PhD [3]
Department of Environmental Medicine
University. of Rochester
Sch. of Medicine and Dentistry
Rochester, New York

Holly Davies, PhD [1]
Washington State Department of Health
Tumwater, Washington

Kathleen Gilbert, PhD (Retired) [3]
Department of Microbiology & Immunology
University of Arkansas for Medical Sciences
Arkansas Children's Hospital Research Institute
Little Rock, Arkansas

Concepcion Jimenez-Gonzalez, PhD [1]
GlaxoSmithKline
Research Triangle Park, North Carolina

Mark Johnson, PhD [3]
U.S. Army Public Health Center
Aberdeen Proving Ground, Maryland

Alan Kaufman [3]
Toy Industry Association
New York, New York

John Kissel, PhD (Retired) [3]
Environmental & Occupational Health Sciences
School of Public Health
University of Washington
Seattle, Washington

Daniel Schlenk, PhD [3]
Department of Environmental Sciences
University of California, Riverside
Riverside, California

Catherine Willett, PhD [3]
The Humane Society of the United States
Washington, District of Columbia

TSCA SACC ad hoc Peer Reviewers

Udayan Apte, PhD [3]
Department of Pharmacology, Toxicology, and Therapeutics
University of Kansas Medical Center
Kansas City, Kansas

George P. Cobb, PhD [3]
Department of Environmental Science
Baylor University
Waco, Texas

David A. Eastmond, PhD [1]
Department of Molecular, Cell and Systems Biology
University of California, Riverside
Riverside California

Stephen G. Grant, PhD [3]
Nova Southeastern University
Fort Lauderdale, Florida

Robert C. Hale, PhD [2]
Department of Aquatic Health Sciences
Virginia Institute of Marine Science
College of William & Mary
Williamsburg, Virginia

Yue-Wern Huang, PhD [3]
Missouri University of Science and Technology
Rolla, Missouri

Michael A. Jayjock, PhD [1]
Jayjock Associates, LLC
Langhorne, Pennsylvania

Lawrence H. Lash, PhD [3]
Department of Pharmacology
Wayne State University School of Medicine
Detroit, Michigan

Maria T. Morandi, PhD [3]
Independent Consultant
Houston, Texas

John B. Morris, PhD (Emeritus) [3]
University of Connecticut
Storrs, Connecticut

Isaac N. Pessah, PhD [3]
University of California, Davis
Davis, California

Thomas J. Rosol, DVM, PhD, MBA [3]
Department of Biomedical Sciences
Heritage College of Osteopathic Medicine
Athens, Ohio

Charles V. Vorhees, PhD [3]
University of Cincinnati
College of Medicine and Division of Neurology
Cincinnati Children's Research Foundation
Cincinnati, Ohio

Calvin C. Willhite, PhD [3]
McLaughlin Center for Population Health Risk Assessment and
Risk Sciences International
Novato, California

Yiliang Zhu, PhD [3]
Department of Internal Medicine
School of Medicine
University of New Mexico
Albuquerque, New Mexico

---
[1] Peer reviewer 1,4-Dioxane
[2] Peer reviewer HBCD
[3] Peer reviewer 1,4-Dioxane and HBCD

LIST OF ACRONYMS AND ABBREVIATIONS

ACC	American Chemistry Council
ACI	American Cleaning Institute
ADME	Absorption, Distribution, Metabolism, and Excretion
AF	Adjustment Factors
AIHA	American Industrial Hygiene Association
AMAP	Arctic Monitoring and Assessment Programme
APF	Assigned Protection Factor
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	Bioconcentration Factors
BLS	Bureau of Labor Statistics
BZ	Breathing Zone
C&D	Construction and Demolition
CAA	Clean Air Act
CBI	Confidential Business Information
CDR	Chemical Data Reporting
CEC	Constituents of Emerging Concern
CERHR	Center for the Evaluation of Risks to Human Reproduction
CI	Confidence Intervals
COC	Concentrations of Concern
COU	Conditions of Use
CV	Coefficient of variation
CWA	Clean Water Act
DF	Degrees of Freedom
DHHS	Department of Health and Human Services
DMR	Discharge Monitoring Report
EBFRIP	European Brominated Flame Retardant Industry Panel
ECHA	European Chemicals Agency
EPS	Expanded Polystyrene
ER	Extra Risk
ESD	Emissions Scenario Documents
EU	European Union
GLP	Good Laboratory Practice
GS	Generic Scenarios
HAP	Hazardous Air Pollutant
HHE	Health Hazard Evaluation
HI	Hazard Index
HIPS	High Impact Polystyrene
HSDB	Hazardous Substances Data Base
IARC	International Agency for Research on Cancer
IH	Industrial Hygiene
IIOAC	Integrated Indoor-Outdoor Air Calculator

IRIS	Integrated Risk Information System
IUR	Inhalation Unit Cancer Risk
KABAM	Kow Based Aquatic Bio Accumulation Model
LADC	Lifetime Average Daily Concentrations
LOD	Limits of Detection
MC	Monte Carlo
MCL	Maximum Contaminant Level
MEC	Measured Environmental Concentrations
MOA	Mode of Action
MSDS	Material Safety Data Sheet
NAICS	North American Industrial Classification System
NAS	National Academy of Sciences
NIOSH	National Institute for Occupational Safety and Health
NMAM	NIOSH Manual of Analytical Methods
NS	Not Significant
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation
ONU	Occupational Non-User
OSH	Occupational Safety & Health
OSHA	Occupational Safety and Health Administration
PBT	Persistent, Bioaccumulative, and Toxic
PBZ	Personal Breathing Zone
PEC	Predicted Environmental Concentrations
PECO	Population, Exposure, Comparisons, Outcome
PEL	Permissible Exposure Limits
PF	Protection Factor
PM	Particulate Matter
PNEC	Predicted No-Effect Concentration
PNOR	Particulates Not Otherwise Regulated
POD	Points of Departure
POP	Persistent Organic Pollutants
PPE	Personal Protective Equipment
QSAR	Quantitative Structure Activity Relationship
RAGS	Risk Assessment Guidance for Superfund
RCRA	Resource Conservation and Recovery Act
REL	Recommended Exposure Limit
RQ	Risk Quotients
SACC	Science Advisory Committee on Chemicals
SDWA	Safe Drinking Water Act
SNUR	Significant new Use Regulation
SOC	Standard Occupational Classification
SOT	Society of Toxicology
SR	Systematic Review
STEL	Short-Term Exposure Limit

TH	Thyroid Hormone
TRI	Toxics Release Inventories
TRV	Toxicity Reference Value
TSCA	Toxic Substances Control Act
TSH	Thyroid Stimulating Hormone
TSS	Total suspended solids
TWA	Time Weighted Averages
UCMR	Unregulated Contaminant Monitoring Rule
UCSF	University of California, San Francisco
UF	Uncertainty Factors
VCCEP	Voluntary Children's Chemical Evaluation Program
WOE	Weight of Evidence

INTRODUCTION

The Toxic Substances Control Act (TSCA) of 1976, as amended by The Frank R. Lautenberg Chemical Safety for the 21st Century Act in 2016, Science Advisory Committee on Chemicals (SACC or Committee) completed its review of the set of scientific issues being considered by the Environmental Protection Agency (EPA) regarding the Draft Risk Evaluation for 1,4-Dioxane and the Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster (HBCD)." The Draft Risk Evaluations, supplemental files, and related documents in support of the SACC peer review meeting are posted in the public e-docket at https://regulations.gov (ID: EPA-HQ-OPPT-2019-0238 for 1,4-Dioxane and EPA-HQ-OPPT-2019-0237 for HBCD). The initial notice of availability of the Draft Risk Evaluations, opening the docket for comments, and notice of meeting was published in the *Federal Register* on July 1, 2019 (84 FR 31315). The review was conducted in an open Committee meeting held in Arlington, Virginia, on July 29 – August 2, 2019. Dr. Kenneth Portier chaired the meeting. Dr. Todd Peterson served as the Designated Federal Official.

In preparing these meeting minutes and final report, the Committee carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. These meeting minutes and final report address the information provided and presented at the meeting, especially the Committee response to the Agency charge.

The first two days of the five-day meeting the Committee conducted deliberations in relation to the charge questions for 1,4-Dioxane (Session 1). The remaining three days the Committee conducted deliberations in relation to the charge questions for HBCD (Session 2).

Session 1 – TSCA SACC Peer Review – 1,4-Dioxane

July 29 to 30, 2019:

Opening of Meeting – Todd Peterson, PhD, Designated Federal Official, EPA/Office of Science Coordination and Policy (OSCP)

Introduction and Identification of SACC Members – Kenneth Portier, PhD, TSCA Science Advisory Committee on Chemicals (SACC), Chair

Introduction and Welcome – Mark Hartman, EPA/Office of Pollution Prevention and Toxics (OPPT), Immediate Office

Welcome and Introductory Comments - Alexandra Dapolito Dunn, Esq, Assistant Administrator, EPA/OCSPP

OPPT Technical Presentation – Overview of 1,4-Dioxane Risk Evaluation - Nikki Bass, MS, EPA/OPPT/Risk Assessment Division (RAD)

Public Comments

Oral statements were presented as follows:

Bob Budinsky, Science Leader, Toxicology, Environmental Research and Consulting, The Dow Chemical Company

Fred Corey, Vice Chair, National Tribal Toxics Council

Richard A. Denison, PhD, Lead Senior Scientist, Environmental Defense Fund

Penelope Fenner-Crisp, PhD, DABT, Environmental Protection Network

Brett Howard, American Chemistry Council

Jonathan Kalmuss-Katz, JD, Staff Attorney, Earthjustice Northeast Office

Mark Lafranconi, PhD, DABT, Principal Toxicologist, ERM

Lindsay McCormick, Program Manager, Chemicals and Health, Health Program, Environmental Defense Fund

Stephen P. Risotto, MS, American Chemistry Council

Stephanie A. Schwarz, Legal Fellow, Environmental Defense Fund

Tyler Smith, Staff Scientist, Earthjustice

Bob Sussman, Safer Chemicals Healthy Families

Tracey Woodruff, PhD, Professor and Director, Program on Reproductive Health and the Environment, Department of Obstetrics/GYN, University of California, San Francisco

Written statements were provided to docket as follows:

Stephen Risotto, MS, Senior Director, American Chemistry Council

Richard Denison, PhD, Lead Senior Scientist, Environmental Defense Fund

Suzanne Hartigan, PhD, Senior Director, Regulatory and Technical Affairs, American Chemistry Council

Johnathan Kalmuss-Katz, JD, Staff Attorney, Earthjustice, and **Randy Rabinowitz**, Executive Director, Occupational Safety & Health (OSH) Law Project

Douglas M. Troutman, JD, Sr. Vice President, Government Affairs, American Cleaning Institute (ACI) and **Michael R. Grube**r, Vice President, Government Affairs, Grocery Manufacturers Association (GMA)

Liz Hitchcock, Acting Director, Safer Chemicals Healthy Families et al.

Gary A. Buchanan, PhD, Director, New Jersey Department of Environmental Protection (NJDEP)

Ben Gann, MPS, Director, Chemical Products & Technology Division, American Chemistry Council's (ACC) North American Flame Retardant Alliance (NAFRA)

Environmental Protection Network (EPN)

Charge to Committee

Session 2 - TSCA SACC Peer Review — Cyclic Aliphatic Bromide Cluster (HBCD)

July 31 to August 2, 2019:

Opening of Meeting – Todd Peterson, PhD, Designated Federal Official, EPA/OSCP

Introduction and Identification of Committee Members - Kenneth Portier, PhD, TSCA Science Advisory Committee on Chemicals (SACC) Chair

Introduction and Welcome - Mark Hartman, EPA/OPPT Immediate Office

OPPT Technical Presentation – Overview of HBCD Risk Evaluation - Eva Wong, PhD, EPA/OPPT/RAD

Public Comments

Oral statements were presented as follows:

Fred Corey, Vice Chair, National Tribal Toxics Council

Holly Davies, PhD, Washington State Department of Health

Penny Fenner-Crisp, PhD, DABT, Environmental Protection Network

Ben Gann, Director**,** CPT, American Chemistry Council

Suzanne Hartigan, PhD, Senior Director, Regulatory and Technical Affairs, American

Chemistry Council

Jonathan Kalmuss-Katz, JD, Staff Attorney, Earthjustice Northeast Office

Patrick MacRoy, Deputy Director, Environmental Health Strategy Center / Prevent Harm

Pamela Miller, MS, Alaska Community Action on Toxics

Veena Singla, PhD, Associate Director, Science & Policy Program on Reproductive Health and the Environment, University of California, San Francisco

Maureen Swanson, Project TENDR (Targeting Environmental Neuro-Developmental Risks)

Bob Sussman, Safer Chemicals Healthy Families

Written statements were provided to docket as follows:

Penelope Fenner-Crisp, **PhD, DABT,** Environmental Protection Network (EPN)

Suzanne Hartigan, PhD, Senior Director, Regulatory and Technical Affairs, American Chemistry Council (ACC)

Liz Hitchcock, Acting Director, Safer Chemicals Healthy Families et al.

Jonathan Kalmuss-Katz, JD, Staff Attorney, Earthjustice, and **Randy Rabinowitz**, Executive Director, Occupational Safety & Health (OSH) Law Project LLC

Environmental Protection Network (EPN)

Lindsay McCormick, MPH, Chemicals and Health Program Manager, Environmental Defense Fund (EDF)

Charge to Committee

SESSION 1: Peer Review for EPA Draft Risk Evaluation for 1,4-Dioxane

EXECUTIVE SUMMARY OF SACC REVIEW – 1,4-DIOXANE

The EPA requested input and advice from the Science Advisory Committee on Chemicals (SACC or Committee) on issues posed as questions for the Draft Risk Evaluation (Evaluation) topics, including: content and organization, systematic review, and estimated risks to human health and the environment.

The Committee commended the front-line scientists and career professionals in the Agency for taking on the mammoth task of assessing chemical safety under TSCA. Their diligent work in the face of time, budgetary, and policy constraints is laudable. The Committee's comments are provided in the spirit of assisting the Agency in conducting the highest quality assessment for 1,4-Dioxane.

In general, the Committee indicated the 1,4-Dioxane Evaluation **content and organization** was much improved from that of the Evaluation for PV 29, however a careful editing of the document is required. The 1,4-Dioxane Evaluation provides key information in the main body, with detailed information described in appendices that are linked to the main narrative. The content of the Evaluation is comprehensive within the boundaries of the problem formulation and scope of the Evaluation. The Evaluation provides the expected level of information in terms of physical properties, production, uses, fate and transport, exposed populations (as delineated in the Scope), estimated human and ecological exposures, health and environmental effects, and risk characterization and determination. The document organizes the content in the areas that are clearly relevant to conducting a risk assessment. The Committee appreciated inclusion of additional graphics beyond that in the previous PV 29 risk assessment, but additional graphics could be included to improve the clarity and presentation of the risk evaluation.

The Committee brought up specific examples requiring more explanation and that were more fully addressed later in other charge question responses, including the extrapolation of inhalation risk to dermal risk, definition of excess cancer risk, and the mechanism of action for cancer. The Committee noted that EPA should provide definitions for all specific terms early in the main document, not just by giving a citation to another document. The Committee also indicated a concern for a significant shortcoming in that the scientific basis for certain findings is inadequately described in the Evaluation and recommended that EPA more fully describe the scientific bases especially with respect to consumer and general population exposures that are not addressed in the Evaluation.

EPA sought to modify existing **systematic review** practices to meet its unique regulatory and timeline needs for risk evaluation under TSCA. Committee members did not find the systematic review to be a transparent and objective method for gathering the relevant scientific information, scoring its quality, and integrating the information. Committee members noted consistent problems with both the design and implementation of the systematic review. The Committee found it difficult to determine whether the relevant information was properly evaluated and considered in the Evaluation because key references that were relied on in the risk evaluation were not in the systematic review bibliography and/or the Data Quality evaluation. Committee members consistently found mistakes and inconsistencies in the systematic review and disagreed

with some of the data quality ratings. The Committee made recommendations to improve this report and the systematic review process and agreed with EPA's plan to submit their process to the National Academy of Sciences for review.

The Committee generally agreed that the **environmental fate, exposure, and effects** assessment was inadequate. The dearth of measured data to inform a robust risk assessment of 1,4-Dioxane is an artifact of any approach to eliminate uses that may influence determination of environmental concentrations, frequency of occurrence, or spatial distribution. Much more information is required to inform a robust risk assessment. Some Committee members stated that omission of consumers and the general United States (U.S.) population is inappropriate, unless risk assessments *have been* completed at this point in time. Exposure scenarios that include consumers are important given the known presence of 1,4-Dioxane in plastics, other commercially available products, surface water, drinking water, groundwater, and in sediments. The Committee also had concerns that the omission of these multiple routes of exposure puts workers who inhale or ingest 1,4-Dioxane outside the workplace at even greater risk.

Even for the exposure routes that were considered, inadequate data are included. Some Committee members noted that TSCA does not call for use of voluntary data, rather the law "requires that EPA operate in a manner that is consistent with the best available science and make decisions based on the weight of the scientific evidence." Note this statute does not say best available data, but best available science.

The Committee discussed that if each program office of the EPA says others are assessing the risks and thus not including them in their assessment, the U.S. public will be left with no overall assessment of risks. If risks have been assessed by other program offices of EPA then the Agency should present them as part of the underlying data to support this TSCA Evaluation—if not, the Agency must gather the data for an assessment or include an assessment based on the assumption of near-worst-case exposures.

General human population and biota exposure must be assessed for inhalation, ingestion, and dermal routes. Different sub-populations may have different extents of exposure, but each route must be assessed. After beginning the work to assess these exposure scenarios there is a need to include actual measured environmental data where available. The Committee concurred with the public comments of Dr. Fenner-Crisp that the current process does not follow EPA guidance for risk assessment. The Committee agreed with the National Tribal Toxics Council and the Environmental Defense Fund in the call for the Agency to consider all exposure routes for the broader populations.

Unfortunately, many of the inadequacies of the draft Evaluation have their genesis in a faulty problem formulation. There are several areas where the problem formulation strayed from basic risk assessment principles by omitting well known exposure routes such as water consumption by all occupationally and non-occupationally-exposed humans as well as similar exposures to other biological receptors. The Committee noted that it is inappropriate to use optimistic inhalation estimates rather than realistic or near-worst-case conditions.

The Committee considered that procedures refined in these first TSCA assessments will be important to improving future assessments, and as such they must protect the environment and

human health. Recognizing that *haste* is incompatible with robust, protective, and reliable risk assessments, the Committee recommended that a comprehensive risk assessment, including all routes to non-occupational routes of exposure include currently available data or in the absence of data near-worst-case estimates of release and exposure scenarios along with safety factors.

EPA's characterization of **occupational inhalation exposure** which lead to the Agency finding that 1,4-Dioxane, as used in manufacturing (import), processing (repackaging), and distribution in other considered downstream uses, **does not present an unreasonable risk** of injury to health is **not** adequately supported in this draft Evaluation. The information used to evaluate worker exposure was generally lacking in its ability to present a coherent picture of this critical element of risk. Reliance on meager air monitoring data that were presented without context failed to provide the needed confidence that exposures were being reasonably evaluated. As such, the method and hierarchy used for exposure assessment significantly missed providing an appropriate and confident assessment.

The Committee agreed with the EPA's characterization that 1,4-Dioxane **represents an unreasonable risk to workers** on the specified conditions of use: manufacturing (domestic), processing, industrial use (intermediates, processing aids, laboratory chemicals, adhesives and sealants, professional film cement, printing and printing compositions), and disposal, is adequate, and unlikely to change with the recommendations provided by this peer review. The Agency would do well to increase the industrial hygiene and dermal exposure expertise extant within the team doing this assessment. This is especially true in the realm of dermal and inhalation exposure modeling.

In the context of a tiered and rational risk assessment, the estimation of exposure should begin with the best information readily available to the team, but when lacking information, the Agency should default to reasonable worse case assumptions to fill in the determinants in a detailed exposure scenario. If the assumptions do not support a conclusion of relative safety, then information could be solicited from on-site inspections or from stakeholders to provide certified facts that would allow for the confident altering of these assumptions.

The Committee was asked to assess the information identified by the EPA in their evaluation of 1,4-Dioxane toxicity, and to assess the methodology that used this information to estimate **human health risks**. The assessment focused on **occupational user and occupational non-user exposure**. The decision by the EPA to defer concerns of consumer exposure, or exposure of the general public, through ambient water or air because "other environmental statutes administered by EPA adequately assess and effectively manage these exposures" was not deemed acceptable by many of the Committee members. It was not clear that other statutes are being used to evaluate the health risks of 1,4-Dioxane exposure in the general public.

In general, the Committee found the identification of the **cancer and non-cancer endpoints** to be mostly appropriate. However, there was some concern expressed by one Committee member that the **nasal toxicity** identified as a port of entry hazard was actually caused by 1,4-Dioxane or its metabolites in blood, rather than direct exposure through inhalation. The characterization of the mode of action (MOA) generated the most discussion. The mostly negative results regarding 1,4-Dioxane mutagenicity and genotoxicity led to consideration of a MOA of hepatic

regenerative hyperplasia. However, the Committee concluded that there was not sufficient evidence for this, or indeed, any other MOA. The Committee, in general, agreed that a default linear extrapolation for cancer risk was appropriate.

Regarding **risk characterization**, the Committee agreed that there is a lack of quantitative uncertainty analyses in the Evaluation and some Committee members noted there was qualitative discussion on the impact of specific assumptions on the final conclusion. Committee members noted EPA was striving for objectivity and transparency and to identify the key uncertainties for the underlying data used to identify potential biases in the data and in describing the key sources of data gaps. The Committee recognizes that uncertainties throughout a risk assessment impact the final risk estimates and recommend EPA make it more transparent where uncertainties are quantified and provide justification where they are not. Several Committee members requested more uncertainty and sensitivity analyses to ascertain whether the underlying data is sufficient for the risk characterization.

Individual Committee members had a wide array of responses to the question on whether the information presented supports the findings outlined in the risk characterization section. The responses ranged from the conclusions being reasonable and supported by the data to the conclusions being unsupported by the data or based on over-interpreted data. The Committee had concerns about the dermal risk characterization due to an error in the dermal risk estimates. Many Committee members requested additional explanation in specific areas. Three issues that were noted by several members were the use of PPE to reduce risk to levels below exposure limits, which may be an unreasonable assumption, the lack of inclusion of pregnant women, and the lack of inclusion of the general population exposure via pathways such as drinking water.

DETAILED COMMITTEE DISCUSSION AND RECOMMENDATIONS – 1,4-DIOXANE

As amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act on June 22, 2016, the Toxic Substances Control Act (TSCA), requires the U.S. Environmental Protection Agency (EPA or Agency) to conduct risk evaluations on existing chemicals. 1,4-Dioxane is one of the first ten chemical substances and the second of ten to undergo a peer review by the Science Advisory Committee on Chemicals (SACC). In response to this requirement, EPA has prepared and published a Draft Risk Evaluation for 1,4-Dioxane. The Risk Evaluation process is the second step, following Prioritization and before Risk Management, in EPA's existing chemical process under TSCA. The purpose of risk evaluation is to determine whether a chemical substance presents an unreasonable risk to health or the environment, under the conditions of use, including an unreasonable risk to a relevant potentially exposed or susceptible subpopulation. As part of this process, EPA must evaluate both hazard and exposure, exclude consideration of costs or other non-risk factors, use scientific information and approaches in a manner that is consistent with the requirements in TSCA for the best available science, and ensure decisions are based on the weight-of-scientific-evidence.

The Committee commended the front-line scientists and career professionals in the Agency for taking on the mammoth task of assessing chemical safety under TSCA. Their diligent work in the face of time, budgetary, and policy constraints is laudable. The Committee asked that EPA take their comments in the spirit of assisting the Agency in conducting the highest quality assessment.

The SACC was requested to provide advice and recommendations on the following questions.

Question 1: **Content and Organization (Draft Risk Evaluation & Supplemental File Set):**

EPA's Final Rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726) stipulates the process by which EPA is to complete risk evaluations under the Frank R. Lautenberg Chemical Safety for the 21st Century Act. To that end, EPA has completed an Evaluation for 1,4-Dioxane.

As part of this risk evaluation for 1,4-Dioxane, EPA conducted an assessment of potential environmental and occupational exposures. The evaluation considered reasonably available information, including import, processing, distribution in commerce, use, and disposal information. It is important that the information presented in the risk evaluation and accompanying documents are clear and concise and describe the process in a scientifically credible manner.

Q 1.1	**Please comment on the overall content, organization, and presentation of the draft risk evaluation of 1,4-Dioxane.**

Response:

In general, the SACC (the Committee) found that the Draft Risk Evaluation (the Evaluation) document for 1,4-Dioxane was much improved from the first Evaluation (i.e., the Risk Evaluation document for C.I. Pigment Violet 29 (PV29)) but also suggested that a careful editing of the document is required. The Committee concluded that the organization is generally appropriate for this type of document. Following what is rapidly becoming established practice, the Evaluation provides key information in the main body of the document, with detailed information described in appendices that are linked to the main narrative. The content of the Evaluation is comprehensive within the boundaries of the scope and problem formulation of the evaluation. The Evaluation provides the expected level of information in terms of physical properties, production, uses, fate and transport, exposed populations (as delineated in the Scope), estimated human and ecological exposures, health and environmental effects, and risk characterization and determination. The document organizes the content in the areas that are clearly relevant to conducting a risk assessment. The Committee appreciated inclusion of additional graphics compared to the previous PV29 Evaluation, but still more graphics could be included to improve the clarity and presentation of this risk evaluation.

The Committee expressed concerns that the same information/data discussed in different section are interpreted differently leading to logical inconsistencies, reduced argument clarity, and confusion. Some dermal exposure extrapolations rely on the assumption of no volatilization from the skin, whereas in other cases volatilization is assumed. The Committee recommended EPA ensure internal consistency and more adequately justify differing interpretations of the same information/data.

The Committee expressed concern that EPA does not provide adequate justification for why consumer and general population exposures are not addressed in the Evaluation. For example, many hazardous air pollutant (HAP) standards are regulated on the basis of best available control technology which is not a health-based standard and hence does not necessarily ensure human health protection. Significant health residual risks can remain even when best available control technologies are used, and these human health risks can go unappreciated without thorough evaluation of potential risks. EPA addresses this question in its initial discussion, but the explanation can be significantly improved. For example, EPA provides the following explanation in the second bullet on page 156:

> "As part of the problem formulation for 1,4-Dioxane, EPA identified exposure pathways under other environmental statutes, administered by EPA, which adequately assess and effectively manage exposures and for which long-standing regulatory and analytical processes already exist, i.e., the Clean Air Act (CAA), the Safe Drinking Water Act

(SDWA), the Clean Water Act (CWA) and the Resource Conservation and Recovery Act (RCRA). OCSPP works closely with the offices within EPA that administer and implement the regulatory programs under these statutes. In some cases, EPA has determined that chemicals present in various media pathways (i.e., air, water, land) fall under the jurisdiction of existing regulatory programs and associated analytical processes carried out under other EPA-administered statutes and have been assessed and effectively managed under those programs. EPA believes that the TSCA risk evaluation should focus on those exposure pathways associated with TSCA uses that are not subject to the regulatory regimes discussed above because these pathways are likely to represent the greatest areas of concern to EPA. Exposures to 1,4-Dioxane to receptors (i.e., general population) may occur from industrial and/or commercial uses; industrial releases to air, water or land; and other conditions of use. As described above, other environmental statutes administered by EPA adequately assess and effectively manage these exposures. Therefore, EPA did not evaluate hazards or exposures to the general population in this risk evaluation, and there is no risk determination for the general population. [Problem Formulation of the Risk Evaluation for 1,4-Dioxane, (U.S. EPA 2018)]"

The Committee recommended incorporating similar language into Section 2.3 with references to the specific Agency assessments that are already mentioned within that section. The Committee also recommended that EPA provide additional scientific basis for how consumer and general population exposures will be or are assessed and effectively managed under other regulatory authorities.

The Committee noted several portions of later sections in the Evaluation that should be incorporated in the Introduction or Preamble to better describe the scope and boundaries of the risk evaluation. For example, Section 2.3 (Regulatory and Assessment History) and 2.4 (Scope of the Evaluation) set the regulatory boundaries of the Evaluation; Section 6.1.1 (Unreasonable Risk) describes what the Agency defines as unreasonable risk; this is the only place in the main body of the document where unreasonable risk is clearly addressed/defined and is relevant to all other compounds subject to TSCA review. Similarly, it would be useful to have the descriptions contained within sections 6.1.2.1 (Determining Non-Cancer Risks) and 6.1.2.2 (Determining Cancer Risks) included and/or repeated in Section 5.

The Committee noted that the Evaluation assumes a reasonable excess cancer risk of 10^{-4} without adequate explanation and justification, which, perhaps can be found in the single reference to the National Institute for Occupational Safety and Health (NIOSH). The Committee recommended that choice of this value be better explained and justified.

The Committee expressed concerns as to whether there are sufficient data to model cancer risk using a model that incorporates a threshold effect instead of the default linear low-dose extrapolation model. In addition, EPA does not provide sufficient explanation for the departure from Integrated Risk Information System (IRIS) findings. At least one Committee member suggested that the American Chemistry Council (ACC) comment letter presents a number of good reasons for using a threshold model, and hence this model should at least be discussed in

the Evaluation[1]. Note that this Committee member also urged caution since the scientific basis for the ACC comments was not evaluated by the Committee. The Committee recommended that EPA improve its explanation for the models used and incorporate scientifically valid and evidence-supported models that may be identified through public comments. The Committee provided more feedback on the scientific issues of the MOA in response to question 5 on human health hazards

The Committee appreciated the application of Monte Carlo (MC) methods in the Evaluation for 1,4-Dioxane. This is an improvement over the strictly deterministic approach in the previous PV29 Evaluation. However, the Committee is concerned that MC was selectively applied and a rationale for its use/non-use in different scenarios and for some but not all parameters is not evident. Many of the exposure pathways discarded might demonstrate non-negligible risk in upper tails if MC were applied to associated scenarios. If estimates for these scenarios are considered too speculative, then perhaps a value-of-information question is forced (to the benefit of the overall Evaluation). The Committee recommended a more detailed explanation for use or non-use of MC within the Evaluation.

Q1.2	**Please provide suggestions for improving the clarity of the information presented in the documents.**

Response:

The Committee noted that EPA created two other documents, the 58-page Scope of the Risk Evaluation for 1,4-Dioxane (EPA Document EPA-740-R1-7003, June 2017, OCSPP (U.S. EPA 2017)) and the 90 page Problem Formulation of the Risk Evaluation for 1,4-Dioxane, (EPA Document EPA-740-R1-7012, May, 2018, OCSPP (U.S. EPA 2018)), that address scope and problem formulation in detail. However, the Committee found Section 2.4, Scope of the Evaluation, inadequate in a number of ways. The summary of the Scope in Section 2.4 seems to jump right into the middle of a discussion rather than provide an opportunity for readers, who have not read the other two documents, to be brought up to speed on what decisions were made leading up to this Evaluation. There is a very important statement made in this section (page 28) that could be missed without some additional highlighting and/or clarifying text, namely:

> "Consumer uses were not considered within scope of this risk evaluation per the problem formulation, which states that such activities will be considered in the scope of the risk evaluation for ethoxylated chemicals. EPA believes that its regulatory tools under TSCA section 6(a) are better suited to addressing any unreasonable risks that might arise from these activities through regulation of the activities that generate 1,4-Dioxane as an impurity or cause it to be present as a contaminant than addressing them through direct regulation of 1,4-Dioxane (U.S. EPA 2018)."

1 https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0022

To make this statement more understandable the contents of Section 2.3.5.3 General Population Exposures of the Problem Formulation document should be summarized in Section 2.4 of the Evaluation. The general population is exposed to parts per billion (ppb) levels of 1,4-Dioxane in contaminated waters and as consumers of many cleaning and personal care products that may include 1,4-Dioxane as an impurity. These exposures are of concern to the general population. The summary should also address the fact that the general population exposures exclusion also excludes potentially exposed or susceptible subpopulations, such as infants, children, pregnant women, the immune-suppressed, or the elderly. This summary would also help to reinforce the modifier provided to the general population risk determination presented on page 156 of the Evaluation:

> "Therefore, EPA did not evaluate hazards or exposures to the general population in this risk evaluation, and there is no risk determination for the general population."

The scientific basis for these policy decisions is inadequately described in the Evaluation and Committee members were concerned that this is a significant shortcoming. One Committee member suggested that the EPA could describe byproduct and impurity levels below a threshold level as one way of addressing the risk considerations to the general population and susceptible subpopulations. This would also provide manufacturers and stakeholders with a better description of which ethoxylated chemicals should be evaluated for risk. The Committee recommended that EPA expand Section 2.4 to better articulate the decisions described in the Scope and Problem Formulation documents to better inform the reader.

The Committee noted that Section 2.4.2, Conceptual Models, suggests that the category of occupational non-users (ONUs) includes (page 32-33):

> "…bystanders and certain other groups of individuals who may experience greater exposures than the general population due to proximity to conditions of use to be potentially exposed or susceptible subpopulations."

However, non-occupational bystanders do not seem to be discussed or considered. These are individuals who, due to proximity to conditions of use (manufacturing facilities, water treatment and/or waste treatment facilities) may be potentially exposed, and especially individuals who are members of susceptible subpopulations who live in close proximity to these facilities. The Committee recommended that EPA include a discussion of why the category of non-occupational bystanders was not considered.

The Committee noted that in Section 5.3.1. (page 46), which states:

> "EPA assumes that these exposures are expected to be lower than worker exposures, since ONUs do not typically directly handle the 1,4-Dioxane nor are in the immediate proximity of 1,4-Dioxane. Only inhalation exposures to vapors are expected, which will likely be less than worker exposures"

workers are a class of expected "healthy individuals" who may be more likely to tolerate higher

exposures and for which exposures are limited to an 8-hour work shift. Apparently, the Evaluation does not consider bystanders who are also members of susceptible subpopulations, that is, individuals who live in close proximity to occupational sites, who may be exposed 24 hours a day, and who are more likely to respond adversely at lower acute or chronic inhalation exposures. Additionally, the discussion in Appendix E suggests that there are 1,4-Dioxane releases to the environment from manufacturing facilities that may increase the likelihood of exposures to non-occupational bystanders. The Committee recommended that the general population risk determination presented on page 156 of the Evaluation needs to be extended to stress that EPA did not evaluate hazards or exposures to non-occupational bystanders, who may live in close proximity to facilities manufacturing 1,4-Dioxane, using 1,4-Dioxane and/or processing the waste from such facilities, and in particular non-occupational bystanders who are members of susceptible subpopulations. EPA should provide a rationale for this exclusion. Additionally, Figure 2-2 may also need to be modified to accommodate this exclusion.

The Committee noted that EPA should provide definitions for all specific terms early in the main document, not just by giving a citation to another document. For example, "sentinel exposure" is first mentioned in Section 2.5.3 but the definition is provided later in Section 5.5. The term "bystander" (page 32) is not defined. Clarity of the document is significantly reduced by the very frequent use of vague, rather than precise terms. Perhaps some of these terms are defined in other EPA documents, but they should be defined at least once in the Evaluation. It does a disservice to expect a reader to search other EPA documents for key terms. For example, there is a discussion of "reasonable risk" versus "unreasonable risk" at the end of the document but there should be a brief definition at the outset—the Committee noted even in the Executive Summary—and the reader should be directed to that section in early portions of the text.

The material that is provided near the end of the text consists of a lengthy, but totally generic discussion of the factors that may contribute to the determination of unreasonable risk. The discussion is valuable in a general guidance sense, but in no way provides specific information on the actual conclusions that were made relative to 1,4-Dioxane. The text is replete with "may be" and "including, but not limited to…" qualifiers. Thus, it only provides general information, not the level of detail needed to truly understand the precise issues that went into the specific conclusions relative to 1,4-Dioxane. Such information should be provided.

The text often states EPA used "reasonably available information." It is not clear what "reasonable" means in this context. Stating "reasonably" available literature is that which can be "reasonably" accessed is not sufficient. To add further confusion there are instances where the text states the available literature without the descriptor "reasonably." Does this mean that differing levels of search strategies were used?

The text is replete with terms such as "readily" and "rapidly" that are used without definition or qualification. Do these terms mean something occurs in a matter of seconds, minutes, hours? This is all contextual. In the context of respiratory vapor absorption "readily" actually means instantaneously (in seconds, if not less), with respect to renal elimination "readily" often means within hours. The Committee recommended that EPA incorporate a glossary of terms into the

Evaluation to improve the clarity and consistency.

The Committee was unclear whether it is EPA policy to determine that a risk is "reasonable" when this is only true if appropriate protective equipment is used. This definition may be misleading or lead to erroneous conclusions. The Committee recommended EPA include any qualifications upon a condition of use to ensure clarity and transparency when a determination of "reasonable" risk is made.

The Committee expressed concern that Section 2.1 Physical Chemical Properties has several errors or uses vague language that decrease clarity of the Evaluation. For example, the statement "Dioxane has a Log K_{ow} value of -0.27, indicating that this chemical is hydrophilic and readily miscible in water" (page 24) is inaccurate and misleading. The chemical definition of miscibility is that compounds mix in all proportions to form a homogeneous solution. The fact that a compound has a low lipid solubility (Log K_{ow}) does not necessarily indicate that the compound is miscible in water. Solubility/miscibility is a thermodynamic property and is not a kinetic property and the inclusion of "readily miscible" does not make logical sense. Certainly, a Log K_{ow} value in no way imparts information on the rate at which a compound will dissolve/mix in water. Moreover, the meaning of "readily" is obscure. Does this mean seconds, minutes, or hours? The Committee recommended striking "readily" and improving the clarity of this section.

Some Committee members noted that Section 2.1 Table 2.1 provides an estimate of the Henry's Law constant, which reflects the distribution of 1,4-Dioxane vapors between water and air at equilibrium. However, the table does not provide the blood:air partition coefficient, which is the key parameter that an inhalation toxicologist needs to understand respiratory tract absorption. Moreover, the inhalation dosimetry section of the document relies on partition coefficient normalizations to extrapolate animal levels to expectations in humans. The Committee recommended that EPA provide the partition coefficient in this section of the text to improve the clarity of the Evaluation.

- The Committee identified several typographical and grammatical issues that should be corrected:
    - Pg. 25, Section 2.2 – First paragraph appears to have duplicative statements and is confusing as written.
    - Page 43, Paragraph 2 – This is one long run-on sentence that includes reference to "Section (0)".
    - Pg. 47, Section 3.4.1 – "ONUs are workers at the facility who are neither directly perform activities near the 1,4-Dioxane source area not regularly handle 1,4-Dioxane."
    - Pg. 48, Section 3.4.1, third bullet – "CDR data to identify the number of sites where exposure may occur and approximate workers who may be exposed to the chemicals."

- Pg. 53, 2nd paragraph – "The use of a respirator not necessarily would resolve inhalation exposures since it cannot be assumed that employers have or will implement comprehensive respiratory protection programs for their employees."
- Pg. 86, 2nd paragraph – "Controlled human studies have shown that acute exposures to 1,4-Dioxane caused few perceivable signs or symptoms or primarily irritation to the eyes, nose, and throat, depending on the exposure duration and concentration" is confusing as written.
- Pg. 154, 1st line – "Conversely, EPA may make a no unreasonable risk determination for conditions of use where the substance's hazard and exposure potential, or where the risk-related factors described previously, lead EPA to determine that the risks are not unreasonable." is confusing as written.
- Pg. 172, 1st line item, second paragraph – "While risk estimates for other pathways of occupational exposure for this condition of use (such as chronic noncancer inhalation exposures and noncancer dermal exposures) are exceed the Agency's risk benchmarks in the absence of PPE," is confusing as written.

Recommendations to improve the content, organization, presentation, and clarity of information in the Evaluation:

1. **Provide a brief history and basis for why the chemical is under risk evaluation. While much of this information is introduced in the Scope and Problem Formulation, inclusion in the Evaluation would greatly enhance the final product.**
2. **Improve the clarity of the Evaluation with careful review and editing.**
3. **Include additional graphics to improve the clarity and presentation of the Evaluation.**
4. **All section references (including appendices and their subheadings) should be formatted as hyperlinks to support easier review and reading.**
5. **Provide additional scientific basis for how general population, occupational and consumer exposures not currently assessed under TSCA are effectively managed under other regulatory authorities.**
6. **Provide a clear scientific rationale for the determination of "reasonable" risk for conditions of use that require personal protective equipment for such determination to be appropriate.**

Recommendations to improve the 1,4-Dioxane Evaluation:

7. **As noted on page 28. "*EPA believes that its regulatory tools under TSCA section 6(a) are better suited to addressing any unreasonable risks that might arise from***

***these activities through regulation of the activities that generate 1,4-Dioxane as an impurity or cause it to be present as a contaminant than addressing them through direct regulation of 1,4-Dioxane.*" EPA should provide a detailed discussion of the scientific basis for the exclusion of impurity or byproduct formation of 1,4-Dioxane.**

8. **EPA should provide the scientific basis for policy decisions, such as a detailed description of the scientific basis of how other regulatory authorities (Clean Water Act, Clean Air Act, etc.) are addressing any unreasonable risks associated with the impurity or byproduct formation of 1,4-Dioxane.**
9. **Concentrations should be provided in mass/unit volume and ppm consistently throughout the report.**
10. **Incorporate the tabular format for the risk determination as done in Section 6.**
11. **The Committee noted that EPA should provide definitions for all specific terms early in the main document, not just by giving a citation to other document. This could be done by incorporating a glossary of terms.**
12. **Incorporate a more complete glossary of terms.**

Question 2: Systematic Review (Section 2.5 of the Draft Risk Evaluation):

To meet the scientific standards required by TSCA, EPA applied systematic review approaches and methods to support the Evaluation of 1,4-Dioxane. Information on the approaches and/or methods is described in the Evaluation as well as the following documents:

- 1,4-Dioxane Problem Formulation
- Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental file for the TSCA Scope Document
- Application of Systematic Review in TSCA Risk Evaluations
- 1,4-Dioxane (CASRN: 123-91-1) Bibliography: Supplemental File for the TSCA Scope Document

Q2.1	**Please comment on the approaches and/or methods used to support and inform the gathering, screening, evaluation, and integration of data/information used in the Draft Risk Evaluation for 1,4-Dioxane.**

Response:

The Committee recognized the usefulness and identified deficiencies of the systematic review as it reviewed each Section of the Evaluation to answer the questions posed by EPA. At the same time, the Committee was able to assess if all key studies were identified and properly scored during the systematic review. The Committee identified mistakes and noted inconsistencies in the systematic review in almost every Section, and often disagreed with some of the document ratings.

Within the TSCA risk evaluation context, the weight of the scientific evidence is defined as:

> "*a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.*" (page 36)

EPA has modified existing systematic review practices to meet its unique regulatory and timeline needs under TSCA. Committee members did not find the systematic review to be a transparent and objective method to gather the relevant scientific information, score its quality, and integrate the information. Several Committee members brought up examples of references that were not in the systematic review bibliography and/or not considered in the Data Quality evaluation step, but which were used at different stages in the Evaluation. Several Committee members found that it was difficult to determine whether the relevant information was properly evaluated and considered in the Evaluation.

Committee members noted problems with both the systematic review design and consistent implementation of its protocols. Signs that the systematic review design has issues include the need for "backward reference searching" or "targeted supplemental searches," which shouldn't be required if the initial search finds all the relevant references. Similarly, the Committee noted a high fraction of studies where the initial quality score was later changed, indicating that the data quality evaluation protocol is not clearly defined and possibly inconsistently implemented by different reviewers. The automated gray literature search found mostly several off-topic documents and also missed other useful documents. A few Committee members concluded that possibly less-experienced staff members were performing the systematic review. One Committee member voiced an expectation that the systematic review should provide the reader a written justification for why any particular document was used or not used. The Committee was unable to make this determination from the tables provided in the Evaluation or supplemental information. The Committee agreed with EPA's plan to submit their process to the National Academy of Sciences for review.

Several Committee members recommended simplifying the scoring system or adopting an existing peer-reviewed method, such as the method used by the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR). One Committee member referenced the NTP-CERHR report on bisphenol A (BPA) (Chapin et al. 2008) as an example of a good systematic review protocol, because it allows the reader to easily see the strengths and weaknesses of each study reviewed. One Committee member acknowledged the public comments provided by Dr. Tracey Woodruff as providing a good summary of the issues including using a non-empirically based scoring system, excluding studies too stringently and not including the Occupational Safety and Health Administration (OSHA) study, and not providing definitions or criteria for identifying "influential information sources" and "key data," and for documents found to be "accepting for the most part." Committee members also requested better descriptions of the criteria used to identify "on-topic" versus "off-topic" documents, and more definition, examples, and clarity for the protocols for "backward screening" and "targeted supplemental searches."

One Committee member recommended the use of Population, Exposure, Comparisons, Outcome (PECO) statements to provide focus to the systematic review. These statements should include inclusion and exclusion criteria for assessing the literature on chemical properties that are separate from criteria used to assess toxicity and/or exposure literature. Higher weights should be given to estimates of chemical and physical properties derived from experimental data using peer-reviewed methodology (e.g., Cumming and Rucker 2017) than estimates reported in secondary sources using unsupported methods (e.g., Hansch et al. 1995) or from modeled estimates (e.g., Epi Suite™).

The Committee concluded that EPA should document how all the information was gathered and evaluated for possible use. The systematic review section is not clear on the fact that EPA seems to have started its systematic review using document lists identified in previous evaluations from EPA, Agency for Toxic Substances and Disease Registry (ATSDR), and others. EPA primarily

used the systematic review process in this Evaluation to identify newer references. The Evaluation flow charts (Figures 2-4 through 2-8) suggest a full systematic review was performed, but the text describes a more limited review. While this approach is efficient, the systematic review description does not address how the previous evaluations were identified and selected, or how their quality or the quality of their references was assessed. Criteria for which evaluations were used is not provided, and key references from the previous evaluations do not all seem to have been included in this data quality evaluation. The Committee recommended EPA state the criteria used for inclusion/exclusion of previous evaluations and their associated literature lists. In addition, the Committee recommended that all key data sources be subject to the same data quality review. Similarly, two Committee members noted that the protocol for identifying pertinent domestic and international laws, regulations and assessments as discussed in Section 2.3 is not provided in the: Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental Document to the TSCA Scope Document, CASRN: 123-91-1, *June 2017*.

The Committee noted the importance of going back to the primary literature for key information and not relying on secondary sources like large evaluations which may contain mistakes.

Several Committee members commented that the systematic review and associated data collection system appears to be overly stringent. When the metrics are overly stringent and exclude too many studies, then the risk assessment may be based on findings from very few studies. One example given was the significant exclusion of almost all the published literature related to Environmental Fate and Effects of 1,4-Dioxane. As a result, only one study is used to evaluate environmental fate, resulting in significant uncertainty in the estimated risk to the environment from 1,4-Dioxane exposures. Committee members noted that overly stringent exclusion criteria may introduce biases, especially when research studies are subject to this level of assessment but information from industry may be accepted without collaborating evidence.

One Committee member commented that there are different metrics used for different types of studies, which some members concluded is appropriate. Different aspects of the evaluation incorporate different data quality criteria, which may or may not be appropriate. For example, the environmental risk section only utilized information and data from sources that were assessed of high quality (page 79), whereas the human health risk section utilized information/data from sources assessed as having low, medium, or high quality (page 81). This changes on page 93, when only sources having medium and high quality are considered. Without a clear explanation, the decisions on which sources to utilize in any given situation appears ad hoc.

The Committee does not disagree with the definition in the strategy document that defines gray literature as sources not found in PubMed and that includes documents labeled as “technical reports.” Committee members agreed that gray literature is useful in risk assessment, but emphasized that it should be properly labeled. For example, in the systematic review bibliography government reports are identified as scientific literature rather than as gray literature.

Committee members noted specific examples in their area of expertise and the details are provided below.

Gray Literature search

One Committee member examined in more detail the automated gray literature search method and the search results in the bibliography. The gray literature search seemed like a lot of work when so many of the search results were not useful and, in some cases, useful results are missed. The majority of the useful results seemed to be electronic resources that EPA is likely to have already examined, such as EPA's Chemical Data Reporting (CDR) and ChemView databases, ATSDR profiles, NIH's household products database, National Toxicology Program Report on Carcinogens, NIOSH levels, International Agency for Research on Cancer (IARC) monographs, European Chemicals Agency (ECHA) documents (including their risk assessment), and the Nordic SPIN product database (i.e., Substances in Products in the Nordic Countries). "State sites" is not a very useful descriptor for gray literature from non-Federal domestic governmental sources. The federal sources have more descriptive names, such as Food and Drug Administration, ATSDR, Safer Choice, and CDC NIOSH. In addition, the sources found from the state sites are generally not useful. The Committee member looked in depth at one state to determine what results were found or not found. Reported in the systematic review spreadsheet for this Evaluation, is only one document from that state, a 2007 slide deck deemed off topic and no longer available. The automated gray literature search performed for this Evaluation did not find useful information in that state's product testing database, product testing reports, manufacturer reporting database, environmental monitoring database, or Health Consultations in cooperation with ATSDR. Further study indicated that there are 84 environmental monitoring studies that include 1,4-Dioxane in that state's archives that were not found in the grey literature search. The Committee member noted that it would be a lot of work to gather and look through each state's information archives, but this is an important evaluation that deserves attention.

Occupational sources

Two Committee members pointed out the lack of a Data Quality review for Bronaugh (1982), a key study on which the dermal exposure assessment relies. The reference is in the Bibliography under On Topic Human Health Hazard Literature Search Results but is not discussed in any of the Data Quality files. EPA should include all key on-topic studies in the Data Quality review for this to be a comprehensive systematic review.

The dermal exposure assessment within the Evaluation is highly dependent upon two documents describing experimental results, Bronaugh (1982) and Marzulli et al. (1981). Despite their citation in the risk evaluation, scoring could not be found in any Systematic Review supplemental document for either, and hence readers could not tell how EPA graded them. The Committee assumes EPA found them of acceptable data quality as the Evaluation relies on them, but review by one Committee member found both documents suffer from inadequate presentation of underlying experimental methods. Bronaugh (1982) is a non-peer-reviewed book

chapter that presents two types of data for 1,4-Dioxane: 1) flux and permeability coefficients for three vehicles (apparently from experiments carried out to steady state), and 2) fraction absorbed at 205 minutes (a non-standard interval) under either occlusive or non-occlusive conditions (in non-steady state experiments). Neither set of experiments is adequately described—mass loadings and concentrations in vehicles are provided. One of the vehicles is described only as a "popular lotion." Regarding the steady state experiments, the book chapter is a secondary reference to the primary source, which is a conference abstract that is even less informative (Bronaugh et al. 1980). This would more appropriately be cited as gray literature and not in the peer reviewed literature section. The second document, Marzulli et al. (1981) is from a peer - reviewed journal and presents fractions absorbed from experimental application of 1,4-Dioxane to the forearms of rhesus monkeys in methanol and a not otherwise characterized "skin lotion." Agent loads, but not vehicle loads are presented.

One Committee member commented that the systematic review did not include two papers (Kissel 2011, Frasch et al. 2014) that would be useful to aid understanding of the limitations of characterization of dermal absorption as a fixed fraction. This is an example of sources that were identified by a Committee member that were not identified in the systematic search and points to the limitations of the initial search.

One Committee member noted issues with the sources for the personal breathing zone data used to estimate occupational exposure. Committee members generally agreed with the approach described in the Evaluation that prefers monitored data over modeling data. However, the Evaluation notes (page 54): "The BASF data had limitations including lack of descriptions of worker tasks, exposure sources, and possible engineering controls." It makes little sense to use any monitoring data as the sole or even primary estimate of worker inhalation exposure when the critical contextual elements of the determinants of that measured exposure are not known. In addition, attempts to examine the first BASF reference in Table 3-3 of the report (BASF 2016) were disappointing and somewhat confusing. The BASF document in EPA's HERO database (No: 4491944) is dated 2013 (not 2016) and does not appear to have the 28 Personal Breathing Zone (PBZ) monitoring samples indicated in the report. Instead it appears to be a general document entitled: Employee Exposure Assessment. The Committee member could not find the 28 samples in any of the reference documents. The second document (BASF 2017) does contain the 4 PBZ monitoring samples as indicated in Table 3-3. Another reference (EUJRC 2002) contains exposure levels and descriptive statistics, but EPA discounted this source in the evaluation as less relevant and less current compared to the under-described BASF data. This example highlights issues discussed previously of not being able to find the stated information in the references, industry data being preferred even with significant limitations that would seem to make it unacceptable by the stated Data Quality criteria, an expert having a different opinion on data quality, and an effect on the risk evaluation.

One Committee member noted additional issues in the Occupational Data quality review. A HomeAdvisor® article on asphalt shingles that discusses whether someone should redo their own roof or hire someone is rated of "medium" value for data quality. This reference is not in the

Bibliography and there is no indication of how it ended up being in the Data Quality review. The data quality assessment said it was In Scope and High for Metric 3 Applicability because it included spray polyurethane foam, but the article made no mention of polyurethane foam or 1,4-Dioxane. Metric 6: Metadata Completeness is rated 'N/A' and the comment is that there is no discussion of methods, results, assumptions, etc. In contrast, several high-quality studies, such as the IARC monograph on 1,4-Dioxane, were rated "Unacceptable" overall because each was scored Unacceptable for Metric 3 Applicability. There is also an OSHA study rated Unacceptable because the reviewer could not download the data–with no indication of whether efforts were made to obtain the data via other routes or sources.

Human Health Hazard Studies - Animal and *In Vitro* Studies Data Quality Evaluation

One Committee member noted several concerns from the Data Quality Evaluation of Human Health Hazard Studies- Animal and *In Vitro* Studies:

- There are 30 evaluations in the table of contents, but the document is truncated at page 108, so only 21 scores are available (noted by two Committee members).
- Four of the 21 overall scores (17%) were changed by the reviewer, which indicates problems with the scoring protocol. Two were downgraded and two were upgraded.
- Some of the references were evaluated multiple times for different reasons and with different scores. While that may make sense for some metrics, there were also metrics where there were different determinations and it seems like they should have gotten the same determinations. No efforts were made by the Committee to determine which metric scores were incorrect. The disagreements point to issues with implementation of the systematic review protocols and training scores.
- Mattie et al. (2012) was reviewed four times and got three different scores. The four evaluations had some differences that made sense. For example, it was believable that statistics were presented for one assay and not another and thus Metric 23 could be "unacceptable" for one evaluation and not for another. However, there are other metrics where scores would be expected to be the same, especially based on the comments provided by reviewers.

  In all four evaluations, Metric 21 Confounding Variables in Test Design and Procedures had the same comment, but it was rated "medium" in study 1.2 and "low" in the other three studies.

  All four evaluations had a very similar comment for Metric 22 Health Outcomes Unrelated to Exposure, with study 1.2 adding a sentence that "This is not expected to impact neurological assessment." Nonetheless, study 1.2 rated it "medium," as did studies 2.3 and 2.4. Study 1.2 rated it "high."

- NCI 1978 “Bioassay of 1,4-Dioxane for possible carcinogenicity” was evaluated twice. The review comments used a lot of the same language but differed in their final determination for Metric 4 Negative and Vehicle Controls, which made one of the reviews Unacceptable overall.

  For Metric 12 Exposure Route and Method both have the same comment, but the final evaluation for 3.11 is High and for 3.10 is Medium.

Several Committee members also commented that it is not clear how this supplemental file on Data Quality relates to the Evaluation. One Committee member commented in the Evaluation document it is difficult to determine which studies were evaluated and what weights they were given. There is a listing of studies in Appendix H.1.5, however, the data quality column is blank for most of them and it is not clear how they were used in assessing the weight of evidence. Some, but not all the studies are evaluated in the Data Quality Supplemental file. Other Committee members pointed out mistakes where the data quality scores do not match in the supplemental file and in the Evaluation text or tables, or in Appendix H. For example, for Mattie et al, 2012, discussed above, in the Evaluation Table 4-1 and appendix both studies were referred to as being Medium, even though one was Medium, and one was High in the supplemental file on data quality evaluation.

Other examples

One Committee member commented that the systematic review excluded old studies that don't meet current guidelines (obviously not up-to-date or lacking complete descriptions), but that should be given at least some weight. Examples are described on page 26 of ATSDR 2006 Toxicological Profile for 1,4-Dioxane. These describe reports of “nasal discomfort”, “slight mucous membrane irritation,” “burning sensation” at airborne levels 300, 1,390, 1,600, 2,000 to as high as 5,500 ppm, for periods of a few minutes up to as long as 15 minutes. Dates of studies include 1934, 1930, 1946 [12 volunteers for 15 min at 300 ppm complained of nose and throat irritation]. The exclusion of these data may not affect the risk assessment, but the point of performing a systematic review without bias is not knowing which outcomes are important at the beginning of the process.

One Committee member noted that Torkelson et al. (1974) was excluded because only a single concentration was examined. This concentration is “in the middle” of the concentrations examined in the key study identified by EPA for use in the risk evaluation. The Torkelson study has 400+ animals and although it obviously does not meet current test guidelines or GLP, it adds to weight of evidence since no nasal lesions or tumors were observed. The study is also described on page 42 of ATSDR 2006. This information could be used in combination with the results of the key study to identify a chronic no adverse effect exposure in rats. This is an example of one unacceptable metric being used to exclude a reference that would otherwise be used in current risk assessment practice.

One Committee member commented on the study by Gi et al. (2018) that is scored as a high-quality study for genotoxicity in Table 4-4. The Committee member noted that reviewers missed some key details (Spi-mutations, 8OHdG, changes in gene expression, etc.) and discounted the results for a reason (length and possibility of clonality) that is not valid as the authors controlled for these factors. Also unclear is how this study was included in the first place, since it is not in the bibliography from the systematic review, implying it was not identified in the original search. Scored as a high-quality study, this source is not assessed for Data Quality nor can a score for it be found in Appendix H. It is likely an expert in the field read the study carefully and found high quality information, but this was not transmitted back to the systematic review findings. This further illustrates issues with inconsistent implementation of the systematic review protocols and transparency in findings.

Q 2.2	**Please also comment on the clarity of the information as presented related to systematic review and suggest improvements as warranted.**

Response:

Committee members noted several places where the clarity of the Evaluation could be improved and recommended including additional flow charts. There are places where summarizing the important points from referenced documents would improve clarity and reduce the expectation that readers will consume all of this several hundred-page document. For example, a few sentences summarizing the 93-page Strategy section and the 449-page bibliography would help. Someone who is really interested in the details could read the whole supplemental document, but for most readers broad summaries in the Evaluation would be preferred. For example, the risk evaluation document can be improved by including early in the document a statement indicating that the criteria defining conditions of use are broad at the scoping stage then refined at the problem formulation stage and the further refined for the risk evaluation. As a result, criteria defining consumer exposures are not refined, because consumer exposures in general were eliminated from consideration as a condition of use at the scoping stage. It is unclear why the *Strategy* and *Application* are not included in the References section of the document.

Recommendations for EPA to improve the Systematic review:

1. **Document how all the information was gathered and evaluated for possible use. This includes how previous chemical assessments, such as those done by EPA, were selected that formed the basis of the systematic review for this Evaluation.**
2. **Treat all studies that are used in the risk evaluation the same way in terms of being evaluated for data quality so readers can determine whether the relevant information was properly evaluated and considered in the Evaluation. EPA should not rely on sources of information that were not scored for data quality or were scored using a different system.**

3. **Develop a better search methodology for federal, European Union (EU) and other national, state, and industry websites that retrieves more useful information without retrieving such a high percentage of "off-topic" sources.**
4. **Be more descriptive and transparent in how sources were identified and evaluated.**
5. **Follow best practices in the field and simplify the data quality criteria.**
6. **Do not be overly stringent and exclude studies based on a single criterion.**
7. **Hold industry information to the same data quality standards as other information.**
8. **Provide additional explanation for items noted in our response as unclear or needing more explanation. This includes bringing pertinent information in from past documents such as the Problem Formulation.**
9. **Add flow charts to improve clarity.**
10. **Have the systematic review conducted by researchers with experience in the field.**
11. **Ensure the systematic review is implemented with minimal mistakes.**
12. **Properly label gray literature and not present it as peer-reviewed studies.**
13. **Check data in primary literature to ensure the data is correctly reported in secondary sources.**
14. **Continue with the EPA plan to submit its process for review to the National Academy of Sciences for review.**

Question 3: Environmental Fate, Exposure & Effects (Section 3.3 of the Draft Risk Evaluation):

As part of problem formulation, EPA qualitatively analyzed the sediment, land application and biosolids pathways based on 1,4-Dioxane's physical/chemical and fate properties. EPA also quantitatively assessed environmental exposures and hazards to aquatic receptors in surface water. The results of the analyses are described in the 2018 problem formulation for 1,4-Dioxane and presented again in Appendices D - F of the Evaluation.

Q 3.1	**Please comment on the data, approaches and/or methods used to characterize exposure to aquatic receptors in surface water. What other additional information, if any, should be considered?**

General Comments on Environmental Exposure Assessment:

The Committee was asked in questions 3 and 4 to address the characterization of specific aspects of the exposure assessment presented in Section 3 of the Evaluation. The Committee was not specifically asked to comment on the overall clarity, approach, methods and adequacy of the exposure assessment in general. As preface to the detailed discussions of questions 3 and 4, the Committee offered the following general comments on the exposure assessment. Since the 1,4-Dioxane Evaluation is only the second chemical assessment presented to the Committee for comment, the members looked to provide recommendations that refine the TSCA exposure assessments and as a result improve all future evaluations, resulting in better protection of the environment and human health.

Many of the inadequacies of the draft 1,4-Dioxane Evaluation have their genesis in what the Committee members—those specifically assigned to address question 4—concluded is an overly narrow problem formulation. There are several areas where the problem formulation strays from basic risk assessment principles. For example, the Evaluation omits well known exposure routes such as water consumption by all occupationally and non-occupationally exposed humans as well as such exposures to other biological receptors. In addition, the use of optimistic inhalation estimates rather than realistic, or near-worst-case conditions is typically not an appropriate assumption in risk assessment.

The Committee generally agreed that the exposure assessment presented in the Evaluation is inadequate in several ways. There is a dearth of measured data, and in the opinion of many Committee members, much more information is typically required/available to inform a robust exposure assessment. The Committee understands that it is much harder to prove "no exposure" for a use than to demonstrate potentially harmful exposure. This suggests the need for more documentation not less when concluding or even assuming "no exposure." Exposure scenarios that are tied to general consumers uses that are not considered in this TSCA Evaluation are still important given the known presence of 1,4-Dioxane in plastics and other commercially available products that are also known to contaminate surface waters, drinking waters, groundwaters, and

sediments. Excluding consumer uses of 1,4-Dioxane should not result in these non-site-specific environmental exposures being omitted from consideration in this Evaluation. For example, the Committee expressed concerns that the omission of these other routes of exposure results in an underestimate of risks to workers who inhale or ingest 1,4-Dioxane both inside and outside the workplace.

As mentioned in the Committee discussions of Question 1, there was concern with excluding general human and biota exposures from air and water from this TSCA evaluation and "assigning" them to other EPA regulatory processes (that is, not considering general population and environmental exposures as TSCA-related uses). The Committee finds little assurance that other regulatory processes will: 1) assess exposures to 1,4-Dioxane in a timely fashion, 2) perform as comprehensive an evaluation as is performed in this TSCA evaluation, and 3) integrate other regulatory process evaluation findings into these TSCA exposure findings to produce a complete picture of (cumulative) 1,4-Dioxane exposures to all human and biotic populations of concern. The Committee concurred with the public comments of Dr. Fenner-Crisp that the current process does not follow general EPA guidance for risk assessment. The Committee also expressed support for the National Tribal Toxics Council and the Environmental Defense Fund call for consideration of all exposure routes in this TSCA evaluation. The Committee noted that the American Grocers and the Cleaning Products Institute (both trade associations) agree that human exposure to residual 1,4-Dioxane as a byproduct should be assessed for commercially available products. The Committee recommended a comprehensive exposure assessment, including all routes to non-occupational exposures. In the absence of measured data, risks using near-worst case estimates of release and exposure scenarios should be assessed, along with incorporation of appropriate safety factors.

Response to Aquatic Assessment:

Clarity of the 1,4-Dioxane Evaluation Exposure section on Fate and Transport (Section 3.1) would be increased by including the Fate and Transport figure (slide 17) of EPA's presentation[2] at the public meeting. This visual aid reinforces the point that there are exposure routes that are NOT included in the current assessment. The context of the assessment would also be improved by including a graphic similar to the one presented by the National Tribal Toxics Council at the public meeting, that illustrates exposure routes for potentially sensitive or highly exposed populations.

The Committee is concerned that toxics release inventories (TRIs) data are used to inform releases to the environment rather than also incorporating available monitoring data. Although the Agency states (page 213) that "EPA used release estimates and measured effluent concentrations from EPA's Toxics Release Inventory (TRI) and Discharge Monitoring Report (DMR) Pollutant Loading Tool, respectively, to predict surface water concentrations near such discharging facilities," Table E-2 shows that in most recent years 95th centile estimates of discharges were 20,000-25,000 lb/yr, while means were 36 and 16. In no scenario are these

2 https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0028

estimated concentrations used. TRIs are self-reported and are not an objective measure of chemical release to the environment. To quote EPA's website: "The Toxics Release Inventory (TRI) is a resource for learning about toxic chemical releases and pollution prevention activities reported by industrial and federal facilities." TSCA does not call for use of voluntary data, rather the law "requires that EPA operate in a manner that is consistent with the best available science and make decisions based on the weight of the scientific evidence." The Committee noted that the statute does not say "best available data," but "best available science." Scientific procedures and peer-reviewed data gathering techniques are available to rapidly obtain measurements to inform exposure levels. Measurements of 1,4-Dioxane in biotic and abiotic environmental compartments should be obtained to fill gaps. Users and/or manufacturers may be required to have these studies performed. While the American Chemistry Council (ACC) presented at the public meeting results from a study that supports their position of limited genotoxicity, they did not report results that would fill information gaps needed to effectively assess environmental exposures. Examples of data gaps that can rapidly be filled include: 1) gene expression data from fish-embryo-toxicity tests, and 2) Proton Transfer Reaction-Mass Spectrometry assessment of airborne 1,4-Dioxane concentrations in workplaces or near manufacturing and wastewater treatment sites. Gene expression data would indicate exposure thresholds for adverse health outcomes, and knowledge of airborne 1,4-Dioxane concentrations would provide empirical data for inhalation exposure estimates. Both types of data would increase the certainty of hazard estimates.

The rationale for using modeled surface water data rather than measured data is unclear. The relative contribution of "estimated" and "predicted" modeling values seem to describe similar processes and are simply different tools to model concentrations that are unknown or assumed to be unknown. It is also unclear how ambient data were used to confirm model estimates. Given the databases available, there would be greater certainty to use Measured Environmental Concentrations (MECs) rather than Predicted Environmental Concentrations (PECs) for risk assessments.

While Monte Carlo analyses was used to incorporate variability and examine uncertainty in estimates obtained from models for inhalation exposure estimates. Monte Carlo methods were not similarly used in the examination of estimates of environmental exposures. No reasons were given for this decision. Regardless of whether Monte Carlo methods were used, uncertainty in the estimates presented for environmental exposures needs to be addressed in the Evaluation.

In the Evaluation (page 21, and also Table 2-8 in the Problem Formulation document (U.S. EPA 2018), EPA states it "did not identify any exceedances of benchmarks to aquatic vertebrates, aquatic invertebrates, and aquatic plants from exposures to 1,4-Dioxane in surface waters." Missing from this list is discussion of toxicity to benthic organisms. Adverse effects were assessed for only one aquatic invertebrate species (Evaluation page 80). The absence of benthic organism data represents a serious data gap, as does the absence of multiple chronic toxicity studies for any species or guild (Kaviraj et al. 2004, Bernot et al. 2005, Saha et al. 2006, Dobbins et al. 2009, Guo et al. 2012, Chen et al. 2018, Liu et al. 2018, Yang et al. 2018, Ibrahim and Sayed 2019, Kang et al. 2019). Sediment organisms have quite different sensitivities to many

toxicants than are surface invertebrates, and bivalves are often much more sensitive (Kaviraj et al. 2004, Liu et al. 2018, Dobbins et al. 2009). The assumption of similar toxicity to other species has questionable merit. Please note that the needed data can be obtained within the time frame of risk assessment finalization.

The data quality criteria seem to have been applied inconsistently to sources for some of the key physical/chemical property and environmental fate estimates.

The Committee noted one recent source that could be useful in confirming the estimate of K_{ow} for reasonably water- soluble compounds, such as 1,4-Dioxane. (Cumming and Rucker, 2017: ACS Omega 2017, 2, 6244−6249; DOI: 10.1021/acsomega.7b01102.) The estimate for logK_{ow} (page 24), is obtained from a source which has been scored as having high confidence, yet the underlying data for this K_{ow} estimate is a single unpublished study from the Hansch lab. In that paper, a model was fit to that data point and other data, much of which were from unpublished sources and from the Hansch lab. The Hazardous Substances Data Base (HSDB) lists this the Hansch source as peer reviewed and the EPI Suite™ LogK_{ow} estimate depends on the model of Hansch, and data from Leo, and others. The Committee noted that the peer review status of this source related to the book that is a compendium of data, not to the underlying data. If data quality for this one study is acceptable, then there is little justification for eliminating many of the other environmental fate studies from further consideration.

Air temperatures in many areas of the U.S. are 40°C for prolonged times and the magnitude of elevated temperatures as well as duration are likely to increase as a function of climate change. Temperatures of this magnitude would influence vapor pressure, water solubility, and this Henry's law constants (page 31), and these scenarios should be considered in exposures where inhalation is considered. Proper problem formulation and refinement of a risk assessment would include these scenarios.

The Henry's law constant is listed as coming from studies by Sander, Howard and Aitkins (see Evaluation page 25). Sander reports estimates of 220 and 140 mole/kg/bar (those are the reported units) without referencing the source of the original data or how these data were obtained. It is not possible to convert these data to atm-m^3/mole without knowing the temperature at which these data were obtained. Other data are modeled and are not empirically measured. The lack of experimentally measured data should be explicitly stated in the Evaluation. Estimates in original published units should be provided with conversions also reported in detail in the Evaluation. The Agency should acknowledge the fact that the data/data collection methods supporting these estimates are not readily available.

Exposure assessment through groundwater and other environmental pathways must be evaluated. Data on these pathways should be generated if unavailable. Groundwater is regulated by the Clean Water Act only if it is used for municipal purposes. Omission of groundwater in the exposure assessment means that risks to consumers of groundwater are unknown. Data are available to define the numbers of individuals consuming groundwater from private wells for

drinking water and/or irrigation of crops. These data can be used in conjunction with subsurface injection site location information to provide estimates of the numbers of potentially exposed individuals. In many areas, groundwater is directly recharged from surface waters (example: Edwards Aquifer in Texas) further increasing the numbers of potentially exposed. On page 46, the Agency should determine to what extent groundwater is contaminated by the million pounds of 1,4-Dioxane injected into subsurface zones over the past several years (Table E-1: Class 1 Underground injection column). This human exposure must be considered, given the current use and the fact that millions of U.S. citizens and residents consume and otherwise utilize groundwater from unregulated wells.

On page 44 the footnote to table 3.1 says "Measured unless otherwise noted." This should more realistically say "Estimated unless otherwise noted," since most of the values reported are from models rather than from measured values.

On page 45: Land-applied biosolids are often used in arid regions where soils desiccate rapidly. This poses an aerosol or particulate transport concern for workers and local residents. The Evaluation should include an evaluation of available data that identify where these types of applications are made, numbers of people exposed, and presence/numbers of sensitive biological receptors exposed by this pathway.

The frequency of detects in drinking water is less important than the number of persons who are exposed to those concentrations (Problem Formulation: page 43). A population exposure estimate should be provided in the assessment. To accomplish this, data would be needed for large, medium and small water management facilities as well as differing water types, soft, moderately hard, near brackish, effluent dominated, so forth. This should have been pointed out as a data need in the problem formulation process. The omission of exposure through drinking water leaves the 1,4-Dioxane Evaluation incomplete.

On page 46: Clarity is increased by listing the "conservative" assumptions in estimating values for surface water in a bulleted form. Unregulated Contaminant Monitoring Rule (UCMR-3) data can serve this purpose (Adamson et al. 2017). Similarly, surface water values (secondary and tertiary wastewater values) from the State of California can also be used for Measured Environmental Concentrations (MEC) (Anderson et al. 2018). Estimated concentrations can be placed in context by using UCMR data. Additionally, Simonich et al. (2013) determined that 38 of 40 wastewater treatment plant (WWTP) discharges contained detectable 1,4-Dioxane amounts, but at lower concentrations than modeled. This suggests that sorption or volatilization from WWTPs may not have been adequately assessed to protect workers and the broader population from 1,4-Dioxane inhalation or exposure to biosolids.

Using measured surface water concentrations is particularly important. The surface water data range of 0.5-100 µg/L appears to be erroneously low. Information published in 2016 by Sun, Loez, and Knappe, found 543 µg/L in one sample from the Cape Fe River, North Carolina and over 1,400 ug/L in WWTP effluent. The 543 µg/L concentration in surface water was

determined using an EPA method (Sun et al. 2016). These surface water measurements exceed the Agency exposure estimate for surface water by a factor of 4.4-5.4. The Committee recommended including these data in the estimates of chronic exposure and factoring these into the final risk. These values are useful in estimating the distribution function used in estimating higher centile concentrations.

Wastewater treatment almost always includes aeration which in essence sparges organics from water. Where is the assessment of this loss? A mass balance of 1,4-Dioxane through a variety or municipal and industrial treatment systems is needed. Otherwise 1,4-Dioxane not measure in sewage sludge or water, must be assumed to be released to the atmosphere. It is important that the Agency explicitly state whether the models used within Epi Suite™ are equilibrium or kinetic models. If equilibrium, that would be unsuitable to make this type of estimate so the data may be a low estimate.

Furthermore, omission of reproductive risks introduces uncertainty into the environmental assessment. Reproductive effects manifest at lower exposures than cause lethality. Exposure concentrations that produce lethality in aquatic species are often higher than concentrations that cause reproductive effects.

The Agency erroneously avoided using the aqueous concentration upper bound (11,500 µg/L: Table E-3) for the chronic aquatic environmental exposure assessment. The 11,500 µg/L value is not an acute value it was a 10-day average (Table E-3; footnote b) and it approaches the chronic toxicity threshold (14,500 µg/L effect). Unlike all other facilities for which releases were modeled, the DAK facility was not considered for the single day release. Considering only the 10-day release scenario decreased acute surface concentration estimates by factor of 10. Thus, neither a worst case nor high centile estimate is presented in this assessment. Using the upper bound is an appropriate choice given the modeled nature of this exposure estimate. Using 10 x 11,500 µg/L (to account for the unmodeled single day release rather than the modeled 10-day release) would produce an acute RQ of 0.46.

The exclusion of subsurface and land disposal from the Evaluation (Problem Formulation: page 44): leaves this TSCA Evaluation incomplete. The Agency must assess the concentrations of 1,4-Dioxane found in air and water (surface and ground) near these injection facilities. This determination cannot be made in the absence of such data.

On page 209: The rationale for no further evaluation of the disposal life stage seems to be tied to the comment in Table B2 that states “2015 TRI data indicates 3 sites reporting 13,422 lbs to landfills. However, 1,4-Dioxane has low sorption to soil.” If 1,4-Dioxane is not sorbed to soils it must be released as a vapor or transported to groundwater. Both events produce risks that should be evaluated for human and environmental health.

The Agency should consider human exposures from: lawn watering, public pools, and dust abatement at construction sites or on roads. The concentrations of 1,4-Dioxane in sediments

should be explicitly summarized or tabulated, not noted as present and dismissed (Problem Formulation: page 41)

The decision not to further analyze background levels of 1,4-Dioxane in any matrix (Problem Formulation: page 47) cannot be supported by any risk assessment principle. Any current use scenarios increase exposures over those currently being experienced.

Recommendations to Improve the 1,4-Dioxane Environmental Assessment:

1. **The Committee recommended inclusion of all reasonably reliable data for aqueous 1,4-Dioxane concentrations, 1,4-Dioxane concentrations in sediment, and aquatic toxicity results with aggregate weighting factors related to the quality of each study. This approach will reward studies of the highest quality, while not ignoring studies that may be outliers or that were performed in an era when the current record keeping rules were not established. For example, extant data describing 1,4-Dioxane in surface water could be used rather than modeled surface water concentrations.**
2. **Monte Carlo analyses should be included in environmental estimates, and this will require a robust data set.**
3. **Exposure assessment through groundwater and other pathways must be evaluated or generated if unavailable.**

General Exposure Recommendations:

4. **Exposure scenarios that include consumers should be included in the 1,4-Dioxane Hazard Determination. The presence of 1,4-Dioxane in plastic, other commercially available products, surface water, drinking water, groundwater, and in sediments is well documented and the risks to human health are as yet unassessed by the Agency. The American Grocers and the Cleaning Products Institute (both trade associations) agree.**
5. **General human population and biota exposure must be assessed by the Agency for inhalation, ingestion, and dermal routes of exposure within the defined time limit for a TSCA assessment. This appropriately broader population should include different sensitive or highly exposed sub-populations.**
6. **More conservative (protective) inhalation estimates must be considered rather than optimistic values that are included at this juncture.**

Question 4. Exposure and Releases (Section 3.4 of the Draft Risk Evaluation):

Key data that informed the occupational exposure assessment include: the OSHA Chemical Exposure Health Data (CEHD), ATSDR assessments, ECHA dossiers, and NIOSH Health Hazard Evaluation (HHE), program data.

Q 4.1	**Please comment on the characterization of occupational inhalation exposure for workers for each of the identified conditions of use. What other additional information, if any, should be considered?**

Response:

EPA's characterization of occupational inhalation exposure, which lead to its finding that 1,4-Dioxane as used in manufacturing (import), processing (repackaging) distribution and other industrial use (functional fluids in open and closed systems, spray polyurethane foam, dry film lubricant), does not present an unreasonable risk of injury to health of workers and occupational non-users (ONUs) is not adequately supported in this Draft Risk Evaluation of 1,4-Dioxane.

Given the available data at this time, EPA's conclusion that 1,4-Dioxane **represents an unreasonable risk to workers** on the specified conditions of use: manufacturing (domestic), processing, industrial use (intermediates, processing aids, laboratory chemicals, adhesives and sealants, professional film cement, printing and printing compositions), and disposal, is adequate, and unlikely to change with the recommendations provided by this peer review.

<u>Exposure Concentration Metrics and Occupational Exposure Limit(s)</u>

The basic industrial hygiene paradigm matches and measures airborne concentrations of a contaminant (as a surrogate for inhalation exposure) against exposure limits for that contaminant. As a result, this Evaluation would be expected to match exposure concentration metrics with anticipated occupational exposure limits.

The appropriate exposure metrics used to estimate exposure and risk are always predicated on the results of the hazard analysis. That is, the exposure assessment needs to be in line with the levels of exposure determined and believed to be health-protective; i.e., an assigned or ascribed exposure limit, or, in the terminology of the Evaluation, the concentrations of concern (COCs).

In Section 3 (page 50) EPA explains:

> "For occupational exposures, EPA used measured or modeled air concentrations to calculate exposure concentration metrics essential for risk assessment. These exposures are presented as 8-hour time weighted averages (TWAs) and used to calculate acute exposure concentrations (AECs), …"

The NIOSH Recommended Exposure Limit (REL) is currently set at 1 ppm (3.6 mg/m^3) that represents a concentration exposure limit for any 30-minute period.

The typical industrial hygiene risk characterization simply involves the comparison of the actual exposure with the exposure limit as a hazard index (HI): HI = exposure/exposure limit. For the HI to have any meaning, both exposure and exposure limit must have the same time frame. Given this NIOSH exposure limit and its time element, the Committee expected to see data consisting of 30-minute time-weighted average (TWA) exposures that would be compared to the NIOSH REL value. Unfortunately, most of the available exposure data is for an 8-hour TWA.

Possibly the reason that this REL and the time frame for the limit are not used in this report is because of the detailed and exhaustive quantitative cancer risk assessment contained within the current document. The inhalation unit cancer risk (IUR) in humans determined for combined portal and systemic effects of this chemical with and without consideration of the liver tumors was about 1/ $\mu g/m^3$ (1/0.001 mg/m^3). The risk of cancer at any dose can be readily estimated using the following simple equation:

$$\text{Risk} = (\text{Exp})\ (\text{IUR})$$

Risk = chance of cancer at the Exp (from 0 = no risk to 1 = certainty of cancer). For example, a risk of 0.001 would be a risk of 1 in 1000 for cancer.
Exp = 8-hour TWA concentration over a working lifetime (units: mg/m^3)
IUR = potency or cancer slope factor (units: $(mg/m^3)^{-1}$

The acceptable (or more precisely not unacceptable) level of exposure and risk for carcinogens in the workplace has a long history dating back over 35 years ago to the U.S. Supreme Court benzene decision. In that decision, Justice Stevens characterized a chance of one in a billion as an insignificant risk but odds of one in a thousand as potentially significant. He followed these quantitative examples with the statement that the "exact probability" of harm need not be determined (Latin 1982). As a result of that court decision, the standard level of putative risk that is considered to be not unacceptable as used by OSHA in **occupational settings** has historically been targeted at 1/1000 or 10^{-3} for the **Risk** value in the above equation.

This, of course, is in contrast to the historical EPA acceptable risk levels of 10^{-6} or 1 in a million for members of the general public. This difference between less protective occupational exposure limits versus acceptable exposures for the general population has been ubiquitous at least in the U.S. for cancer and for non-cancer health effects as well.

Given an **IUR** of 0.001/(mg/m^3) renders an **EXP** value at 10^{-3} risk of:

$$\textbf{EXP} = \text{Risk/IUR} = 10^{-3}/(0.001/(mg/m^3)) = \mathbf{1\ mg/m^3}$$

Thus, a reasonable and historically compatible occupational 8-hour TWA Exposure Limit for

1,4- Dioxane would be 1 mg/m^3 or 0.3 ppm. For comparison the NIOSH REL of 1 ppm occurring for 30 minutes during the workday (16 half hours in a workday) would be 1/16 = 0.06 ppm as an 8-hour TWA (with one exposure per day over a working lifetime).

This exposure limit of 1 mg/m^3 as an 8-hour TWA is relatively low compared with some monitored and modeled estimates of exposure potential on single days.

This occupational exposure limit of **0.3 ppm** over a working lifetime is comparable to other known or suspected carcinogens such as **benzene** which has an American Conference of Governmental Industrial Hygienist (ACGIH) 8-hour TWA occupational exposure limit of **0.5 ppm**.

The calculated (amortized) lifetime exposures (i.e., lifetime average daily concentrations (LADC)) are relatively low for repackaging primarily because of solid EPA documentation in the Evaluation showing how much 1,4-Dioxane is actually shipped to repackagers per year. The Committee noted, however, that standard industrial hygiene practice is concerned with the 8-hour exposure on just the day(s) the samples are taken or for the scenario which is modeled and that these exposures are compared to a single daily (8-hour TWA) exposure limits. Once an exposure limit is set, there is no provision for averaging the exposure for periods of greater than one day. Even so, using the EPA's LADC calculations with 8-hour workdays, 250 days/year, working for 31 years in a 78-year lifetime, the LADC exceeds 1 mg/m^3 when the 8-hour TWA airborne exposure to 1,4-Dioxane is 3 mg/m^3 or greater or about 1 ppm.

The point here is that if and when 8-hour TWA occupational exposure limits are set for 1,4-Dioxane based on cancer risk they will be relatively low at a 10^{-3} putative risk level and will be considered only on the day(s) of exposure and not amortized over an entire lifetime. Of course, if the EPA elects an acceptable risk of 10^{-4} this would render an 8-hour exposure limit of 0.1 ppm which is above some of the monitored results.

Thus, given such a low exposure limit and the relatively high volatility of this compound, understanding the true circumstances of the exposure potential of the employees of the manufacturers and their direct downstream customers is critical. As discussed below, not understanding the conditions of the monitored exposures reported by the manufacturers and direct downstream users dramatically increases the uncertainty as to whether workers are being over-exposed via inhalation.

Given that 1,4-Dioxane is an irritant, some consideration should be given to acute exposures that are less than 8-hours. In the realm of industrial hygiene, "acute" exposure typically refers to 15 minutes of exposure matched to a 15-minute short-term exposure limit (STEL) or ceiling (C) exposures of even shorter duration. In short, an 8-hour TWA is not an acute exposure. The industrial hygiene community also has methodologies for adjusting 8-hour TWA exposure limits downward to be compared to exposures for daily exposures greater than 8-hours.

The Hierarchy for Breathing Zone Exposure Potential should be Adjusted

EPA states the following in Section 3 (page 50) of the report:

> "EPA followed the hierarchy below in selecting data and approaches for assessing inhalation exposures. In the hierarchy, monitoring data is preferred over modeling approaches and occupational exposure limits are least preferred. Within each of the three categories, the sources are listed in a descending order of preference. For example, 1a [breathing zone air monitoring values] is preferred over 1b [area monitoring]. **Once a satisfactory source of information is identified in this list, sources below that point are not used,** although they can provide useful information for other purposes of this evaluation. For example, if 1a satisfies the data needs, **no other sources of data in this hierarchy are typically used for purposes of assessing inhalation exposures**. However, if the quality of data is deemed too low or uncertain, EPA will not use those data and will provide justification." (***emphasis added***)

Hierarchical top category 1 is monitoring with category 2 being modeling.
In Section 3.4, page 54 of the Draft Risk Evaluation EPA advises that:

> "Occupational exposures to 1,4-Dioxane during manufacturing were estimated by evaluating full-shift, personal breathing zone (PBZ) monitoring data obtained by BASF during internal industrial hygiene (IH) studies. BASF monitoring data was selected as it is more relevant and recent compared to the manufacturing data cited in other sources [such as (EUJRC 2002)] and lack of availability of monitoring data from other U.S. manufacturer."

Later in that same paragraph EPA says:

> "The BASF data had limitations including lack of descriptions of worker tasks, exposure sources, and possible engineering controls."

It makes little sense to use any monitoring data as the sole or even primary estimate of worker inhalation exposure when the critical contextual elements of the determinants or causes of that measured exposure are not known.

The BASF (2016) report contains some monitoring data from the manufacturing of 1,4-Dioxane over a few days from 2008-2017. In general, these data show average values of about 0.5 ppm or less but no details as to exactly what is being monitored.

The second document (BASF 2017) does contain the 4 PBZ monitoring samples as indicated in Table 3-3. There is also a brief description of the samples; for example, 38 ppm (137 mg/m^3) as a PBZ sample against a 15-minute STEL during an "Evaporator dump step during production". This was the highest of the four values reported.

The reference (EUJRC 2002) provides Table 4.1, which contains the range, arithmetic average and 90th percentile of 1,4-Dioxane "exposure levels," presumably from industrial scenarios ranging from 0 to 2880 mg/m^3. As noted above, these values are discounted within the assessment as less relevant and less current compared to the under-described BASF data. These data definitely demonstrate that there is potential for relatively high, short-term acute inhalation exposure to 1,4-Dioxane, especially if one accepts the above analysis of an 8-hour TWA exposure limit of 1 mg/m^3 (0.3 ppm) as appropriately protective for workers at 10^{-3} putative lifetime cancer risk.

All of this is not to say that use of monitoring data should be avoided. It does say that these monitoring data are not sufficient, and that the Agency simply needs more information concerning the context of these data.

None of these monitored data points are definitive for a satisfactory formal assessment of the exposure potential of this chemical during its manufacture and downstream use. The reason for this is there are no contextual elements of the determinants for these monitored values in the Evaluation. One Committee member noted that because of many factors, the available monitored data may not be reflective of periodic circumstances that could result in higher exposures. Except for the one value of 137 mg/m^3 shown above, the Committee did not see any other situation where the chemical is both near workers and out of a relatively closed system such as might occur during sampling, pack-out, proximity to fugitive emission points, or periods during upset conditions such as unintended spills, pressure releases or leaks.

Modeling allows the formulation of a meaningful contextual analysis using realistically formulated, detailed, transparent and potentially verifiable exposure scenarios. Given the monitoring data available to the EPA are not robust enough, first principle modeling should be used before relying on incomplete data.

The Evaluation makes a good case for the use of drumming and bottling scenarios for models. As mentioned below, over 30 years ago, the EPA pioneered these source rate models as strong primary first principle tools to formally estimate the rate of contaminant ejected into the workplace air volume during these standard operations.

Models should be used and placed next to the top of an adjusted hierarchy as exampled below:

1. Monitoring data with a complete set of quantitative determinants relative to worker activity and source characteristics, time course, ventilation and non-ventilatory loss mechanism (Jayjock and Hawkins 1995).
2. Estimates using realistically formulated models – with assumptions subject to adjustment by formalized and certified responses by all of the manufacturers and significant downstream users.
3. Typical monitoring data such as that provided in this report with incomplete context.

In addition to the drumming/bottling scenario, it is recommended that a spill scenario be formulated for modeling of the potential exposure to this chemical.

Another scenario that addresses fugitive emissions should be included. Many plant operatives will bag and monitor sources of emissions (*e.g.,* valves) in an effort to estimate their losses and to determine the need for intervention (*e.g.,* valve or connector replacement). Specific requests should be made to both manufacturers and direct downstream users to determine if these data of mg/min emission fugitive emission rates are available and if so to require these data be made available to the Agency. Information or assumptions can be obtained or made relative to how close workers and ONU might be to these sources for two-zone modeling as described below.

In Section 3.4.1.6 Function Fluids (Open Systems) one is given the impression that the cited reference (Burton and Driscoll 1997) contains data describing the exposure from 1,4-Dioxane contained within these fluids. As it turns out, there are actually no data regarding this compound and this reference only mentions that the analyte was detected in vapors above flow coat paints. This should be acknowledged within the Evaluation and the uncertainty addressed with an uncertainty factor.

For open system functional fluids there is additional personal breathing zone and area concentration data that were collected as part of occupational epidemiology studies of machining fluids in the U.S. motor vehicle industry. EPA does not mention these studies, so it is not clear whether they were not captured in the first stage of systematic review or were excluded at later stages. These data may not have specific 1,4-Dioxane information, and the samples could include other chemicals present in the workplace close to machine cutting operations. However, the studies provide data on exposures and area concentrations to mists, and at least some volatile organic compounds. These data could be useful for deriving exposure estimates assuming different concentrations of 1,4-Dioxane or for evaluating modeled exposure estimates. In addition, these studies contain information on workplace conditions relevant to exposures for workers other than machinists. A review can be found in Park et al. 2009.

<u>The Mass Balance Inhalation Model Used in this Assessment is Outdated</u>

It appears that the inhalation exposure potential determined in the Evaluation comes primarily from sparsely documented worker monitoring data, as discussed above, and modeling exposures using the EPA AP-42 Loading Model and the EPA Mass Balance Inhalation Model.

An excerpt from the documentation for this model (U.S. EPA 2013) is presented below:

> "The airborne concentration of the chemical is estimated to be a function of the source vapor generation rate and the volumetric ventilation rate within a given space and includes simplifying assumptions of steady state (constant generation rate and constant ventilation rate) and a **mixing factor [m] (for non-ideal mixing of air)**. The default ventilation rates and mixing factors provide a typical and worst case estimate of

exposure. The airborne concentration of the chemical cannot exceed the level of saturation for the chemical." ***(emphasis added)***

This model uses the following general relationship for steady state:

$$\mathbf{C = G/((Q)(m))}$$

C = concentration (mg/m^3)
G = contaminant generation rate (mg/min)
Q = whole room ventilation rate (m^3/min)
m = mixing factor (dimensionless between 0 and 1)

Thus, this model assumes that the contaminant steady state concentration can be estimated into any volume so long as the mixing factor **m** is appropriately assigned. For example, in a very large industrial room with a point source of **G**, the value of m would be very small because the average concentration would be quite low within the entire room, while the exposure near the source would be relatively high. Of course, the most important concentration for workers would be those who are close to the source and here the value of **m** would be smaller but never zero and never greater than 1. Thus, the choice of **m** is quite arbitrary and subjective. Indeed, its use has been the subject of technical criticism (Mage and Ott 1996).

The use of **m** in a room concentration modeling scheme was developed over 30 years ago, however, inhalation exposure modeling has significantly advanced in the interim and there are simply much better models available. In this instance, the two-zone model developed and promoted by the modeling team of the American Industrial Hygiene Association (AIHA) represents a significantly more objective approach that allows quantitative description of the near-field volume; that is, the space containing the source and the worker breathing zone (BZ). This model also uses the far-field volume or the remainder of the room and the inter-zonal flow between near and far fields in industrial rooms as used by the EPA from Baldwin and Maynard (1998). The far-field airborne concentration provides an estimate of the ONU individuals within the room who would typically not be close to the source. The two-zone and other models, including the EPA Evaporation Rate Model, are available as a free download Excel Workbook (IHMOD 2.0) from the American Industrial Hygiene Association (https://aiha.org/public-resources/consumer-resources/topics-of-interest/ih-apps-tools). Complete documentation of all the models is available in the book: "Mathematical Models for Estimating Occupational Exposure to Chemicals" (AIHA Press 2009).

Additional Vapor Source Terms Needed

As mentioned above, the source terms used in the risk evaluation document for the drum and bottle filling scenarios make sense and are based on the pioneering modeling efforts of the Agency initiated in the mid-1980s. The treatment of this source uses well-established first principles of conservation of mass and volume that are so basic that they have not and cannot be

improved upon. Historically, these can represent the potential for a primary source of vapor generation in the workplace. However, the EPA should also include a spill scenario as potential and probable occurrences in the occupational environment. Indeed, one Committee member noted spills and leaks typically happen with remarkable frequency in many operations. An example of spill scenario modeling using the two-two zone model is available (Jayjock et al. 2011).

Evaporation can be estimated in a number of ways with the most straightforward being the measurement of weight loss over time. One can also estimate evaporation using the EPA model (Fehrenbacher and Hummel 1996). Another method is to calculate the value of alpha (α) from the vapor pressure and surface area-to-volume ratio (SA/V) of the evaporating liquid (Kiel and Nicas 2003).

The point of this discussion is that several methods should be used to estimate the generation rate caused by evaporation of 1,4-Dioxane during spills from industrial production and use which can be assumed to be reasonable worst case for worker exposure during these predictable events. Fugitive emissions mentioned above are another source of vapors that should be assessed.

The Assumed Use of PPE (i.e., Respirators) is Not Appropriate

As mentioned above, most of the inhalation exposures to 1,4-Dioxane are assumed to occur in an 8-hour time frame. This was the time frame for most monitoring data from BASF that the report relies on for its primary determination of worker inhalation exposure potential. The Evaluation assumes the use of respirators without consideration of engineering or other higher-level controls. Because respirators are inherently uncomfortable and potentially unreliable for long term use, the use of respirators for more than relatively short terms is not considered appropriate in typical industrial hygiene practice. Thus, 8-hour use of PPE should not be used in the risk characterization of inhaled 1,4-Dioxane. Risk estimates should be presented without the use of PPE as reasonable worst case.

Worst-case assumptions can be revised with facts from on-site inspections or comprehensively certified conditions by stakeholders.

Recommendations:

1. **Include members on the assessment team with a strong industrial hygiene background relative to modeling and the setting and comparing of occupational exposure limits to estimated levels of potential exposure.**
2. **Add more information concerning the context (e.g., measurement and methodology details) of monitoring data used in the Evaluation.**
3. **Obtain, using TSCA authority, additional monitoring and specific scenario data on workers and ONUs linked to the specific drivers within the scenarios causing that**

exposure that would help to reduce uncertainties associated with this assessment.

4. **The hierarchy for breathing zone exposure potential should be reformulated to put modeling ahead of monitoring for poorly described scenarios.**
5. **The steady-state breathing-zone concentration model used by the Agency for interior rooms should be discarded as out-of-date. A team member (see #2 above) with knowledge of contemporary AIHA models should handle the modeling in this document.**
6. **Add a spill scenario to this assessment.**
7. **Add a fugitive emissions scenario to this assessment.**
8. **Add scenarios in which respirators are not used for an entire 8-hour work shift.**
9. **Consider scenarios in which acute exposures occur on time frames of less than 8 hours.**
10. **Present worst-case inhalation exposures for workers with estimates from scenarios assuming no use of PPE.**
11. **In addition to a qualifier for the quality of data used for estimating inhalation exposures, EPA should add a qualifier for the overall confidence in the final exposure estimates (in addition to the description of uncertainties).**

Q 4.2	**Please comment on the characterization of occupational inhalation exposure for occupational non-users for each of the identified conditions of use. What other additional information, if any, should be considered?**

Response:

Occupational non-user (ONU) exposures are dismissed on the basis that they are likely to be smaller than exposures to users. However, user exposures are found to be unacceptable without use of PPE (respirators). EPA should clarify how ONU exposures compare to both unprotected and protected user exposures.

Understanding ONU exposure is particularly important in some modes of use such as 3D printing, where only one area monitoring sample was used with no PBZ data. In this condition of use, ONUs may have increased exposure given the type of work, and the generally relaxed occupational hygiene measures in this type of activity, which increasingly is done in domiciles and schools.

Clearly the ONU population will have lower exposure than the primary workers. Also, there appears to be even less exposure data on this population than the user population. Characterizing the exposure of this population would benefit from the use of the 2-zone model with reasonably constructed scenarios such that the far-field concentrations would represent the primary inhalation exposure of these users.

As mentioned above, the modeling scenarios need to be deliberated and detailed relative to the ascribed determinants of exposure extant within them.

Recommendation:

1. **Clarify how ONU exposures compare to both unprotected and protected user exposures.**

Q 4.3	**Please comment on the characterization of occupational dermal exposure for workers. What other additional information, if any, should be considered?**

Response:

Glove use should not always be assumed to be protective. Two scenarios discussed by EPA (untrained use of impermeable gloves and use of permeable work gloves designed for abrasion protection in a chemical environment) could actually lead to higher exposures due to contamination of the interior of the glove in the first case and due to the glove acting as a reservoir in the second. The range of glove protection factors should therefore extend from <1 to some upper limit rather than from 1-20. A stochastic approach using these ranges in a Monte Carlo uncertainty analysis would be appropriate.

As in the case of respiratory protection, the assumed exposures to gloved and ungloved users should be clearly stated and contrasted with assumed ONU exposures.

EPA's analyses of dermal exposure to 1,4-Dioxane include recognition that dermal absorption and evaporation can be in competition for volatile compounds, with the latter process partially mitigating the former. EPA has attempted to increase the sophistication of its dermal exposure calculations by incorporating information from several well-regarded peer reviewed papers including Kasting and Miller (2006), Frasch (2012), and Frasch and Bunge (2015). Unfortunately, EPA has misinterpreted those papers and created an erroneous result. Contrary to EPA (Evaluation, page 290), the $m_{abs,infinity}/M_0$ quantity in Frasch (2012), which is just a refinement of Kasting and Miller (2006) to make the math more tractable, represents systemic absorption, not mere absorption into the stratum corneum. Subsequent adjustment of inhalation dose response factors for ostensibly low dermal "fraction absorbed" (based on questionable experimental literature) is inappropriate. The large discrepancy between the theoretical prediction of a relatively minor impact of evaporation (as calculated by EPA in Appendix G) and the apparently low systemic uptake reported by experimentalists (Bronaugh 1982, Marzulli et al. 1981) is troublesome. This issue requires resolution.

The assumption that dermal absorption can be well-represented as a fixed fraction is not grounded in good science. The fraction absorbed is variable and dependent on the conditions of

exposure. Literature that would be useful in interpreting the fraction absorbed data, but that is not cited in the report includes Kissel (2011) and Frasch et al. (2014).

Available fractional absorption data used in the report come from Bronaugh (1982) and Marzulli et al. (1981). The Bronaugh (1982) data are taken from a book chapter, which is: 1) not peer-reviewed, 2) provides inadequate description of experimental methods, and 3) is a secondary citation of a 1980 Society of Toxicology (SOT) conference abstract (with even less experimental detail). Table 35-4 data are from a 205-minute trial, which is a very nonstandard interval and subject to variable interpretation. The vehicle termed "lotion" is not described. Table 35-5 implies attainment of steady state conditions without specification of initial load or experimental duration.

The reported permeability coefficient for 1,4-Dioxane is similar to what would be predicted using the approach described by EPA in Risk Assessment Guidance for Superfund (RAGS, Part E; U.S. EPA, 2004). Multiplying a permeability coefficient of $4x10^{-4}$ cm/h by an aqueous solubility of 800,000 $\mu g/cm^3$, implies a maximum steady state flux on the order of 300 $\mu g/cm^2/h$. This outcome is consistent with a hypothesis that dermal uptake of 1,4-Dioxane is rapid. Evaporation trials (Fig. 35.3) were done: 1) on wax paper, which is a poor surrogate for skin, 2) at unspecified load, 3) using unspecified vehicle, and 4) probably in a hood where air velocity would be relatively rapid. Rapid air velocity would over-predict evaporation and under-predict dermal exposure potent while its pertinence to actual exposures is questionable. The Marzulli *et al.*1981 results are cited as supportive of Bronaugh 1982, but similar fractions absorbed are from the unoccluded Marzulli trials and the occluded Bronaugh trials. The Marzulli experiments are also inadequately described. The Committee concluded that, EPA could have done more to attempt to reconcile theoretical predictions of high dermal doses and experimental observations including conducting some simple in-vitro absorption studies.

Given the lack of data, the Agency should conduct relatively simple *in vitro* skin absorption tests (OECD, 2004) on this chemical.

Another area of concern comes from the lack of rigor used in the development of the European Centre for Ecotoxicology of Chemicals - Targeted Risk Assessment (ECETOC TRA) dermal exposure model. In the primary reference cited (Marquart 2017) we find the following text:

> "…The ECETOC TRA model itself uses protection factors between 5 and 20 if gloves are assumed to be used, depending on professional or industrial setting and on whether training and management supervision is in place. In the estimation of exposure levels in this study, default protection factors of 5 (80% reduction) for professional situations and 10 (90% reduction) for industrial situations were taken into account."

Also,

> "…The input values for the parameters in ECETOC TRA were assigned by an expert

elicitation and consensus building process, based on descriptions of relevant contextual information."

Essentially, these factors and other parameters in this model are not data based but assigned based on judgment. Also, this paper reports that during the validation, the model only explained 37% of the variance (i.e., $r^2 = 0.37$) in the 75th percentile of measured values.

Considerably more work is needed to develop the models in this sequential construct in the document especially ECETOC TRA.

Recommendations:

1. **Engage an expert in dermal exposure assessment from within the Agency or a consultant to provide quantitative estimates of the amount of 1,4-Dioxane absorbed systemically in reasonably anticipated scenarios.**
2. **Strengthen the discussion and analysis for uncertainty for dermal exposure by quantitatively defining the assumptions made in each scenario using a Monte Carlo simulation.**
3. **Clearly state the estimated exposures to gloved and ungloved Users.**
4. **Contrast ONU estimated exposures to estimated exposures of gloved and ungloved Users.**
5. **Resolve the large discrepancy between the theoretical predictions of high dermal doses and apparently low systemic uptake as reported by experimental observations.**
6. **Conduct *in vitro* testing (OECD 2004) of the dermal absorption of 1,4-Dioxane.**

Q 4.4	**Please comment on the approach for characterizing the different use scenarios. Are there any additional 1,4-Dioxane specific data and/or information that should be considered?**

Response:

Table B-1 in Appendix B presents a very comprehensive and understandable listing of the different uses (but not scenarios) for commercial occupational exposure scenarios which should present the highest human exposure potential. As mentioned above, a spill scenario should be included as a reasonably anticipated occurrence and exposure. Also, exposure from fugitive emissions for both workers and ONU could be considered given source leakage data that is often available for specific points in the manufacturing process liable to emission to the workplace. The fugitive emission of 1,4-Dioxane byproduct from the manufacturer or processing of surfactants should also be considered.

As mentioned above, but worthy of repeating, “uses” are not exposure scenarios and exposure scenarios need to have holistically described determinants of exposure including the estimated values for room size, general ventilation, local exhaust ventilation (if any), random air movement, complete source details relative to its nature (evaporation, drum injection, fugitive emission), dimensions, temperature, location within room and proximity to workers and ONUs.

Estimating these critical values will allow for uncertainty and sensitivity analysis in an effort to portray this potential reality and our level of uncertainty around each variable. Such work can point the way to further research or information gathering to lower the uncertainty born of a lack of knowledge. Such an approach would allow for the consideration of mixtures which present a new but important dimension to the exposure analysis.

Recommendation:

1. **Define scenarios as exposure settings that have a comprehensive set of the determining factors that cause the exposure. When these are matched to monitoring data, it is a very powerful tool for assessing exposure and risk. Without monitoring data, models should be used with these scenarios.**

Question 5: Human Health (Section 4 of the Draft Risk Evaluation):

The evaluation of human health hazards included:

- Reviewed reasonably available human health hazard data.
- In evaluating reasonably available data, determined whether particular human receptor groups may have greater susceptibility to the chemical's hazard(s) than the general population.
- Conducted hazard identification (the qualitative process of identifying non-cancer and cancer endpoints) and dose-response assessment (the quantitative relationship between hazard and exposure) for all identified human health hazard endpoints.
- Derived points of departure (PODs) where appropriate and conducted benchmark dose modeling, when data supported the approach.
- Adjusted the PODs to conform (e.g., adjusted for duration of exposure) to the specific exposure scenarios evaluated.
- Considered the route(s) of exposure (inhalation and dermal) and route-to-route extrapolation approaches.
- Evaluated the weight of the evidence of human health hazard data.

EPA has provided a summary of mode of action information for a mutagenic mode of action and non-mutagenic mode of action, in particular for rat liver tumors.

EPA has also provided alternative dose-response analyses for non-linear and linear extrapolation for cancer.

Q 5.1	**Please comment on the evaluation of human health hazards including evaluation of portal of entry and systemic toxicity for cancer. Are there any additional 1,4-Dioxane specific data and/or information that should be considered?**

Response:

The EPA concluded that evidence from very limited human studies did not support or refute an association between occupational or general population exposure and increased risk of cancer, and by itself did not establish a clear causal relationship. However, 1,4-Dioxane in drinking water and inhaled air is shown in numerous animal studies to induce tumors in the liver, kidney, nasal cavity, peritoneum and mammary gland. Based primarily on the evidence in experimental animals, despite the inadequate evidence in humans, the U.S. EPA (2013) has classified 1,4-Dioxane as "likely to be carcinogenic to humans."

It initially seemed appropriate to identify a respiratory portal of entry for cancer in view of the numerous types of nasal tumors (i.e. nasal cavity squamous cell carcinoma and Zymbal gland

adenomas) described in 1,4-Dioxane inhalation studies. One of the Committee members pointed out that the types of nasal tumors found in the 1,4-Dioxane-treated rodents are rare, and thus most likely to be compound-specific. However, the Committee member also noted that the widespread olfactory mucosal distribution of the lesions is typical of systemic compounds, not inhaled agent delivery, suggesting that it may not be appropriate to identify a portal of entry for cancer, given these effects may in fact be caused by secondary exposure via the blood stream.

The Committee members generally agreed that there was a high degree of confidence that cancer of the liver (e.g., hepatocellular adenomas and carcinomas) was the most sensitive endpoint for systemic cancer toxicity, and that there is a moderate degree of confidence that kidney (renal cell carcinomas), and peritoneal mesotheliomas also represent appropriate endpoints for systemic toxicity. No other 1,4-Dioxane-specific studies were identified.

Q 5.2	**Please comment on the evaluation of human health hazards including evaluation of portal of entry and systemic toxicity for non-cancer. Are there any additional 1,4-Dioxane specific data and/or information that should be considered?**

Response:

Epidemiology of 1,4-Dioxane is very limited and is confined to occupational inhalation. No oral studies in humans were found. There are no human studies of reproductive or developmental toxicity. The identification of portal of entry and systemic toxicity for non-cancer are based on animal studies.

Once again, the Committee was not convinced that nasal toxicity represented a route of entry rather than systemic toxicity via the blood. A Committee member noted that the nasal toxicity data are incompletely interpreted and not fully consistent with the current scientific understanding of the mechanisms underlying these outcomes.

Sub-chronic exposure studies in rats and mice described hepatic changes (e.g., lesions, liver swelling, single cell necrosis, increase in alanine aminotransferase (ALT) in the liver). Chronic exposure in rats ranging from 63 weeks to 2 years also showed liver effects (e.g., histopathology, necrosis, hepatocytomegaly, increased ALT). Multiple papers also found kidney pathology in rats following short-term and chronic exposure to 1,4-Dioxane. Lung lesions were increased after short-term exposure, and several studies in rats, mice and guinea pigs demonstrated respiratory effects (increase in lung weight, histopathology changes in lung, rhinitis, increased incidence of pneumonia) following chronic exposure. Thus, in general, the Committee agreed that the liver, kidney, and respiratory tract represented appropriate systemic non-cancer toxicity outcomes.

Other effects, such as changes in the brain, were found in animals exposed to 1,4-Dioxane. However, the Committee concluded that overall, there are insufficient data to assess the potential neurotoxicity of 1,4-Dioxane. Similarly, there is insufficient evidence to assess the toxicity of

1,4-Dioxane on other non-cancer outcomes such as immunotoxicity.

The Committee discussed a study in which pregnant rats were exposed to 1,4-Dioxane via oral gavage on days 6-15 of gestation. Sacrifice of the dams on gestational day 21 showed alterations in fetal weight and ossification of sternebrae at the highest 1,4-Dioxane exposure. However, in view of the scarcity of the data on reproductive/developmental toxicity, and the high concentrations required to induce toxicity in the one rat study, reproductive and developmental toxicity was not considered as an endpoint of systemic toxicity.

Q 5.3	**Please comment on any other aspects of the human health risk characterization that have not been mentioned.**

Response:

Aside from occupational exposures, the general population is exposed to 1,4-Dioxane via inhalation of air or vapors during cleaning activities, ingestion of contaminated food and drinking water, and dermal contact with consumer products. However, EPA did not consider 1,4-Dioxane exposures to consumers and bystanders from by-products or contaminants in this Evaluation. Rather, EPA anticipates that 1,4-Dioxane by-products and contaminants exposures will be considered in the scope of a risk evaluation of ethoxylated chemicals. In addition, "EPA has determined that chemicals present in various media pathways (i.e., air, water, land) fall under the jurisdiction of existing regulatory programs…" and that "other environmental statutes administered by EPA adequately assess and effectively manage these exposures." As one Committee member pointed out, given there is no drinking water maximum contaminant level (MCL) for 1,4-Dioxane and there are no national standards for ambient air (ATSDR 2006), this rationale, at the very least, needs a better explanation. There was general dissatisfaction in the Committee that the human health risk characterization did not extend to the general population since there was no indication in the Evaluation that other offices in the EPA had plans to conduct such a characterization. Such a characterization is important; the ATSDR (2006) has documented on-going exposures of the general public to 1,4-Dioxane in ambient air and drinking water.

The Evaluation does not consider pregnant workers as a possible susceptible population and hence no analysis of this scenario is given. The Evaluation states that "the acute effects on liver and CNS effects are not expected to preferentially affect women" (page 150). The Committee did not think this statement was self-evident, and thus needed more explanation. The Evaluation does not account for the potentially increased susceptibility of the fetus.

Q 5.4	**Please comment on the mode of action discussion and provide feedback on mode of action analysis**.

Response:

The Evaluation summarizes information for both a mutagenic mode of action (MOA) and non-mutagenic mode of action, and in particular for rat liver tumors.

The main points of contention that were discussed were: 1) whether the MOA can be distinguished based on the available DNA mutagenicity and DNA damage information, and 2) depending on the MOA identified, whether a linear or nonlinear (i.e., threshold) extrapolation is appropriate to estimate cancer risk.

Given studies in both mice and rats found liver toxicity to be the most sensitive endpoint, the Committee agreed that liver tumors should be the focus of the MOA determination.

In numerous *in vitro* systems 1,4-Dioxane was not found to be mutagenic, with or without exogenous metabolic activation. In the few cases where genotoxicity is observed, it is generally linked to cytotoxicity. Similarly, 1,4-Dioxane has shown mixed, largely negative results in *in vivo* mutation assessments, and has been non-genotoxic in approximately 50% of micronucleus assays. When positive results are reported, they occur at high to very high doses, which are above those at which tumors have been induced in the rodent cancer bioassays. Thus, several Committee members agreed with the Evaluation conclusion that genotoxicity (either DNA mutation or DNA damage) is not an early and influential key event in carcinogenesis. The Health Canada (2010) 1,4-Dioxane in Drinking Water report describes why the preponderance of evidence does not support genotoxicity-induced carcinogenicity, but rather supports regenerative proliferation-induced carcinogenicity. Several Committee members stressed the importance of the Dourson et al. (2017) paper that reanalyzed data from several chronic and short-term 1,4-Dioxane exposure studies in mice and rats. The data from the cancer bioassays, together with the negative mutagenicity of 1,4-Dioxane, its lack of up-regulated DNA repair in most studies, and the high incidence of liver tumors are not inconsistent with rodent liver tumors being caused by a regenerative hyperplasia MOA.

On the other hand, several Committee members remained unconvinced that there is sufficient evidence that 1,4-Dioxane induces cancer via regenerative hyperplasia. One Committee member noted that there are at least three mechanisms by which proliferation occurs in the liver, and in the case of 1,4-Dioxane that proliferation is most likely caused by a yet-to-be determined mechanism. Another Committee member pointed out that increases in mutagenicity or genotoxicity are not the only mechanism by which a toxicant can promote cancer. For example, toxicant-induced alterations in DNA methylation of oncogene expression, or suppression of key components of the immunological cancer-monitoring system can also promote cancer. Other Committee members noted that 1,4-Dioxane is a multi-site carcinogen and may have more than

one MOA, and that there were several uncertainties surrounding dermal exposure.

After much discussion, the Committee members concluded that there is not sufficient information to specify a definitive MOA for 1,4-Dioxane-induced carcinogenesis. Under these circumstances and according to EPA guidelines, the default definition of a linear extrapolation was deemed appropriate to estimate cancer risk.

It was noted that the Evaluation also provides analyses of alternative dose response models accommodating both non-linear and linear extrapolation for cancer.

Q 5.5	**Please provide comment on the presented approaches. Please provide comment on any additional model consideration that EPA could include for cancer characterization.**

Response:

This question was not discussed in detail, given the Committee's general consensus that there is insufficient information to specify a MOA for 1,4-Dioxane-induced carcinogenicity, and hence the default linear extrapolation for cancer is appropriate in this case. However, several Committee members provided written comments on issues related to use of a linear vs threshold extrapolation.

One Committee member questioned whether the decision to use a linear or a threshold approach in assessing cancer risks from low dose exposures is ultimately a risk management or a policy decision. For technical reasons it is not possible to detect effects occurring at low and ultralow doses.

Another Committee member stated that the EPA default linear treatment of the 1,4-Dioxane animal data is not scientifically credible and emphasized that the Government of Canada document on 1,4-Dioxane is sufficient to determine a MOA, and that this MOA clearly leads to the assumption of a threshold extrapolation. There is increasing recognition that genotoxic and mutagenic agents can exhibit thresholds in their responses and that the use of non-linear, threshold-like extrapolation approaches can at times be appropriate (Eastmond 2008, MacGregor et al. 2015, Klapacz et al. 2016). These arguments support the decision by the EPA to present both threshold and non-threshold approaches in their dose-response modeling.

One aspect of 1,4-Dioxane toxicity that would help determine the validity of a threshold model involves its potential dependence on metabolism. Tumor incidence and metabolic saturation occur in a similar dose range. One Committee member described the initiating event for a threshold MOA as metabolic saturation of 1,4-Dioxane. Above metabolic saturation, higher doses of the parent compound caused an ever-increasing toxicity in the rodent liver as evidenced by higher levels of liver enzymes and associated histopathology. This Committee member then concluded that alternative modes of action can be excluded. However, as pointed out by another

Committee member there is no real evidence that carcinogenicity requires metabolism of the chemical. No studies have shown that blocking metabolism of 1,4-Dioxane increases carcinogenicity (providing support for the threshold MOA) or suppresses carcinogenicity (providing support for a linear but undefined MOA).

General recommendations to improve TSCA Risk Evaluation:

1. **Clarify why a flawed Reference Concentration (RfC) methodology for portal of entry effects is used in this Evaluation.** The approach and calculations for the inhalation POD appear to follow standard EPA procedure and are calculated correctly according to that procedure. However, it needs to be recognized that the RfC procedure for portal of entry effects itself is fundamentally flawed. It is based on faulty assumptions and the RfC procedures provide dosimetry estimates that are widely variant from actual experimental measurements. The EPA recognized this problem; a subsequent review of the 1994 EPA RfC procedure clearly described the inadequacy of the RfC protocol [U.S.EPA (2009). Advances in inhalation dosimetry of gases and vapors with portal of entry effects in the upper respiratory tract (Vol. EPA/600/R-09/072). Washington, DC].
2. The EPA needs to explain and follow its guidelines for evaluating the MOA Framework

Recommendations to improve Section 4 of the Draft Risk Evaluation:

1. **Add a justification for excluding all nasal effects in the extrapolation to dermal routes from inhalation exposures.** Delivery of 1,4-Dioxane (or metabolite) in the blood stream may well have contributed to the observed nasal effects. This is documented by the widespread olfactory mucosal distribution of lesions (which is typical of systemic agents, not inhaled agent delivery). Also, nasal injury was seen after oral exposures. Although aspiration of drinking fluid might have occurred it can't be excluded as a cause. More justification is needed.
2. **Clarify the reasoning leading to the weight of evidence statement on page 96**. Immediately after discussing a study in which a significant increase in point mutations was seen, the TSCA document states: "Therefore, EPA concluded that the weight-of-the-scientific evidence supports that 1,4-Dioxane is not mutagenic but may elicit clastogenicity *in vivo* at high doses." The study does provide some evidence that 1-4-Dioxane is mutagenic. However, because the evidence for the induction of gene mutations in vivo comes from a single dose in one experiment, the Committee member cautions about drawing a positive conclusion about a mutagenic mode of action from the Gi et al. (2018) study alone. The member recommended that at this time it would be more scientific to state that there is insufficient evidence to conclude that 1,4-Dioxane is mutagenic or induces cancer through a mutagenic mode of action.
3. **Clarify and expand on environmental exposure and MOA**
4. **Improve the discussion of toxicokinetics (Section 4.2.2) which the Committee found confusing and vaguely worded.**

5. **Explicitly define qualifying terms used throughout the text (e.g., "acceptable," "high," "extensive," "appreciable accumulation," and "rapid").**
6. **Clarify how the relative weight given the neurotoxicity studies of Mattie and Goldberg was determined.** An additional study by Kanada (1994), which was apparently not considered in the Evaluation, may need to be included in the neurotoxicity systematic review and subsequent discussion.
7. **Clarify the text on page 153 regarding the entry for NIOSH (2017).** As written this entry could be interpreted to suggest NIOSH developed its criteria document and the Recommended Exposure Limit (REL) for 1,4-Dioxane using a linear 10^{-4} theoretical excess cancer risk level—the REL was derived in 1977, which is 5 years before publication of the Howe and Crump (1982) GLOBAL82 method report to OSHA.
8. **Given there seem to be some populations/situations involving chronic (repeated) exposures, metabolism and elimination must be treated quantitatively to determine temporal (spikes and troughs) patterns in blood levels as part of the toxicokinetic evaluation.**
9. **There were several issues with the nasal toxicology that need to be addressed.** For example, the term "nasal" is too vague. More specific language should be used to distinguish respiratory and olfactory effects. The description of the nasal tumors should include information on their distribution; this could help define MOA. The document would be strengthened by inclusion of a nasal toxicologist on the writing team, and inclusion of a cogent discussion of the nasal lesions relative to the current state of the art.
10. **In addition, the benchmark modeling of the respiratory metaplasia would benefit from additional explanation and clarity. This includes explaining why a high confidence benchmark dose (BMD) can be derived from only two dose groups plus controls.**
11. **The section discussing the importance of 1,4-Dioxane metabolism in its MOA needs to be edited.** It should be made clear that high systemic concentrations of 1,4-Dioxane does not necessarily indicate metabolic saturation but could result from decreasing hepatic blood flow. And, if there is extensive first pass clearance in the liver, then overall hepatic metabolic clearance may be perfusion limited.
12. **Justify the use of Mattie et al. (2012) given its lack of critical detail (no histological slides) and unclear quality control.**
13. **Provide more justification for the selection of 50 ppm as a LOAEC rather than as a frank effect given the finding in the Kasai et al. (2009) paper.**
14. **Given that this document is relying upon the RfC methodology, it is important that the document explicitly state whether 1,4-Dioxane is viewed as a category 1, 2 or 3 gas.**
15. **Include the rationale for not including a toxicokinetic uncertainty factor given the toxicokinetic uncertainties associated with route to route extrapolation.**

Question 6: Risk Characterization (Section 5 of the Draft Risk Evaluation):

For manufacturing (domestic), processing, industrial use - (intermediates, processing aids, laboratory chemicals, adhesives and sealants, professional film cement, printing and printing compositions), and disposal, EPA preliminarily concluded that the conditions of use present an unreasonable risk of injury to health, as set forth in the risk determination section of the draft risk evaluation. Human health effects include non-cancer and cancer effects. EPA did not find unreasonable risks to the environment for any of the conditions of use for 1,4-Dioxane examined in this risk evaluation. EPA also did not find unreasonable risks to the health of occupational non-users for any of the conditions of use for 1,4-Dioxane in this risk evaluation. EPA made these determinations considering risk to potentially exposed and susceptible subpopulations identified as relevant, under the conditions of use without considering costs or other non-risk factors.

Q 6.1	**Please comment on the objectivity of the underlying data used to support the risk characterization and the sensitivity of the agency's conclusions to analytic assumptions made.**

Response:

The Committee agreed that there is a lack of quantitative uncertainty analyses in the Evaluation. Some Committee members noted that there is qualitative discussion on the impact of specific assumptions on the final determination of risk. The Committee noted that Evaluation authors were striving for objectivity and transparency. Efforts are made to identify the key uncertainties in the underlying data used, to identify potential biases in these data, and identify data gaps. One Committee member noted a specific example of this in Section 5.3: “Because of these limitations, EPA acknowledges that the reported inhalation exposure concentrations for the industrial scenario uses may not be representative for the exposures in all industries within that group, the pharmaceutical industry in particular.”

Committee members discussed issues with the underlying data and identified additional data gaps. Some information was harder to find because it exists in the Problem Formulation document but not in the Evaluation. This include such information as the safety factor rationale and the endpoints for chronic assessment. Data gaps include limited monitoring data and ONU calculations.

Several Committee members noted that due to the lack of rigorous uncertainty and sensitivity analysis, it is difficult to know whether filling certain data gaps would make a material difference to the Agency’s conclusions. In addition, it is difficult to know if the data and assumptions used are robust enough to support the Evaluation conclusions. One Committee member noted that Evaluation authors clearly explained that the current risk assessment took previous assessments into account, including the EPA IRIS assessment, and assessments from the ATSDR, Health Canada, and the European Union. However, while a discussion of data quality is included in the

Evaluation, the specific criteria for assessing quality determination, and the appropriateness of evaluating hazards from different routes of exposure, are not explicitly stated. Accordingly, the overall presentation of the underlying data and the criteria used for inclusion in the hazard assessment seems to have appropriate objectivity but requires more details.

Specific examples cited by Committee members:

1. Uncertainties include the provision of unmeasured exposure concentrations in the Bringman and Kuhn (1977) study. It is also uncertain how "intoxication" is defined for that study. While the fathead minnow study provided data regarding hatch and development which were used in the chronic threshold, no fish reproduction study could be found. The lack of reproduction assessment suggests significant uncertainty and may require implementation of an additional safety factor.

2. There are what appear to be inconsistencies or flawed assumptions in the discussion of the estimates of number of workers exposed (page 146).

    - "Furthermore, market penetration data was unavailable, therefore, EPA was unable to estimate the number of establishments within each NAICS code that used 1,4-Dioxane instead of other chemicals. This would result in a systematic overestimation of the count of exposed workers." The assumption of overestimation in the count of exposed workers is not self-evident. It could be more establishments actually use the chemical and thus more workers are actually exposed.
    - "Second, EPA's judgments about which industries" (represented by North American Industrial Classification System (NAICS) codes) and occupations (represented by Standard Occupational Classification (SOC) codes) "are associated with the uses assessed in this report are based on EPA's understanding of how 1,4-Dioxane is used in each industry. Designations of some industries/occupations with few exposures might erroneously be included, or some industries/occupations with exposures might erroneously be excluded. This would result in inaccuracy but would be unlikely to systematically either overestimate or underestimate the count of exposed workers." There does not appear to be enough evidence to make the case that number of workers would not be systematically influenced.
    - "Exposure data for ONUs were not available for most scenarios. EPA assumes that these exposures are expected to be lower than worker exposures, since ONUs do not typically directly handle the 1,4-Dioxane nor are in the immediate proximity of 1,4-Dioxane. Only inhalation exposures to vapors are expected, which will likely be less than worker exposures." However, given that inhalation is the primary route of exposure, such an assumption requires knowing something about the layout of the facilities and how close ONUs may actually be to where 1,4-Dioxane is being used by workers. Given that this is a vapor, it is likely not to be contained to direct use areas.

- The Evaluation shows bias in its discussion of potential bias: "Some data sources may be inherently biased. For example, NIOSH HHEs for the open system functional fluids and film cement uses were conducted to address concerns regarding adverse human health effects reported following exposures during use. Both HHEs were requested by relevant workers' unions (United Paperworkers International Union and Film Technicians Union, respectively)." Industry monitoring data are possibly biased towards lower values, via, e.g., repeated measurements or representativeness, as also cited in the limitations.
- There are serious limitations regarding the exposure data, as cited in the section on limitations: "The 95th and 50th percentile exposure concentrations were calculated using reasonably available data. The 95th percentile exposure concentration is intended to represent a high-end exposure level, while the 50th percentile exposure concentration represents typical exposure level. The underlying distribution of the data, and the representativeness of the available data, are not known." Recognizing the limitations, this nonetheless raises serious questions about the risk characterizations for the inhalation exposures overall.

3. One Committee member noted several examples of weaknesses in the text that do not reflect a lack of objectivity.

- In Section 5.2, the various sub-sections are not written in consistent style. For example, the short-term section (5.2.2) lists the critical study, the derived HEC and the benchmark MOE. The chronic inhalation section does not.
- On page 138 it states: "…as shown in Table 5-6, all exposure scenarios … ." This is not true—for most exposure scenarios there were no calculations. (The same is true in the first sentence on page 141)
- Section 5.2.7 is very confusing. Is 22% volatilization used for these calculations? This is not done for any of the other dermal extrapolations. If this is correct, then a thorough explanation of why differing approaches are used for differing exposure (acute vs chronic) scenarios.

Q 6.2	**Please comment on the characterization of uncertainties and assumptions including whether EPA has presented a clear explanation of underlying assumptions, accurate contextualization of uncertainties and, as appropriate, the probabilities associated with both optimistic and pessimistic projections, including best-case and worst-case scenarios. Please provide information on additional uncertainties and assumptions that EPA has not adequately presented**

Response:

There is overlap with 6.1 and this question (6.2). The Committee members wanted more uncertainty and sensitivity analysis to ascertain whether the underlying data are sufficient for the risk characterization. Also, some Committee members included characterization of uncertainties, explanation, and context as part of their comments on objectivity of the underlying data used to support the risk characterization.

EPA relies on standard risk assessment approaches that have uncertainties and assumptions. Committee members acknowledged EPA's practical need for assumptions in the Evaluation due to the lack of data or inadequate data. As noted in the Committee's response to Question 6.1, EPA seemed to have made an effort to identify key uncertainties and offer qualitative assessments of the impacts of that uncertainty on final conclusions. The Committee recognized that uncertainties throughout a risk assessment impact final risk estimates. The Committee recommended that EPA clarify exactly where uncertainties are quantified and provide justification where they are not. The Evaluation presents risk calculations for multiple scenarios that produce exposures estimates that range from optimistic to conservative. The Evaluation strives to highlight the uncertainties and limitations of the data that support these scenarios. In some scenarios where exposure is described as a "reasonable worst case," the Evaluation does not provide sufficient details on how exposure estimates are determined to guess the percentile represented by the exposure (e.g., is it an upper 10%, 5% or 1% scenario). One Committee member provided references on quantifying uncertainties to inform decision making (NAS 2014, Simon et al. 2016)

Several Committee members were not comfortable with the reliance on a single government report that was not published in a peer-reviewed journal, Mattie et al. (2012). It was also noted that Mattie et al. (2012) is a limited repeat of the study reported in Kasai et al. (2008) and that each time Mattie et al. (2012) is cited Kasai et al. (2008) should be included.

Individual Committee members requested more explanation on several specific topics:

- What information does EPA consider to be "reasonably available?" That phrase is used throughout the document without adequate explanation.

- Some of the assumptions and the resultant uncertainty factors require more detailed explanation. Examples include dermal absorption fractions and interspecies uncertainty factors (UF_A). Considering statements about the lack of data in some of the human studies, despite some degree of correspondence between effects observed in humans and experimental animals, the UF_A of 3 seems unjustified; a full value of 10 seems more appropriate.
- On page 149, there is brief discussion of metabolism. There is a seeming presumption that metabolism is not required, but it is unclear what the plausible mechanism would be for the parent compound as opposed to a reactive intermediate.
- On what did EPA base the cutoff age of 16 for adult that is used in several places? The Department of Human Health Services (DHHS) standard cutoff is age 18.
- In 5.3.3, the first full paragraph on page 149 states that the main uncertainty for the human health hazard is the unknown mode of action (MOA). What is the basis for this assertion? Is this greater than the potential for species difference or other factors? The statement that there is no information on the MOA for tissues other than the liver is not strictly correct. The comprehensive evaluation of the totality of the nasal toxicity/cancer data could indeed provide insights into modes of action at this site. Such an evaluation was not done.
- In 5.3.3, on page 149 in the second paragraph it states metabolic saturation is a proposed event in the MOA. As highlighted above in this review, the evidence for metabolic saturation is weak at best. Indeed if 1,4-Dioxane is a high extraction compound (in the liver) then perfusion limitation or capacity limitation are potential events, not metabolic saturation. Moreover, while hepatic metabolic saturation may reduce active metabolite formed in the liver it would also serve to diminish hepatic clearance and increase delivery of 1,4-Dioxane to other tissues.

Q 6.3	**Please comment on whether the information presented supports the findings outlined in the risk characterization section. If not, please suggest alternative approaches or information that could be used to develop a risk finding in the context of the requirements of the EPA's Final Rule, Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act (82 FR 33726).**

Response:

Individual Committee members expressed a wide array of responses to this charge question, ranging from the conclusions being reasonable and supported by the data, to the conclusions are unsupported by the data or based on over-interpreted data. The Committee mentioned concern due to a specific substantial error in the dermal risk estimates that makes the risk characterization not valid for that exposure pathway. Several Committee members noted the data are not sufficient to draw a conclusion of no unreasonable risk. Many Committee members requested additional explanations in specific areas.

Many Committee members were concerned with the reliance on PPE or engineering controls to reduce risk, as that is contrary to the hierarchy of controls. As EPA noted earlier in the Evaluation, the hierarchy of controls begins with prevention as the most effective and ends with PPE. Several members noted that it was unreasonable to assume workers would wear PPE for entire 8-hour shifts due to underlying medical conditions, facial hair, discomfort, and other issues. A different Committee member noted that it is reasonable to expect workers to wear PPE if it is part of their job and to assume that exposures are controlled in an industrial setting. One Committee members asked for additional data underlying PPE use assumptions. Another Committee member suggested that if use of PPE to reduce risk is an EPA policy decision, then that should be explained up front to alleviate requests for data on PPE use. Several Committee members noted that it is reasonable for EPA to provide information on how to safely work with the chemical. Several members suggested that EPA include a statement about "if appropriate personal protective equipment is used" along with any statement of "no unreasonable risk" to avoid being misleading.

Several Committee members noted a concern on the exclusion of the general population and susceptible populations from the Problem Formulation under the assumption that other regulations (e.g., Clean Water Act, Clean Air Act, Safe Drinking Water Act) cover the pathways and noted this is counter to the state-of-the-art practice for risk assessment. Several committee members also observed that failure to assess 1,4-Dioxane exposure in the general population may leave substantial portions of the population at risk. This is particularly concerning for drinking water. If insufficient data generated in the Unregulated Contaminant Monitoring Rule (UCMR) database or the published literature to inform an assessment for the entire U.S. population, releases from point sources should be measured by the Agency or those releasing 1,4-Dioxane along with immediate downstream concentrations over time at several sites to confirm the

estimates based on TRI data.

Committee members also suggested including general population exposure to consumer products. One member reminded the Committee that TSCA gives the Administrator the authority to define the Conditions of Use. Several Committee members suggested EPA should include the combined exposures from these pathways in assessing the risk.

The Agency utilized environmental data related to environmental systems that are at least a decade old. The assessment should have determined where uncertainty could be minimized and proceeded to obtain data to reduce that uncertainty. For instance, in estimating toxicity, a point estimate provides no information about the range of effect levels that could reasonably be expected in the environment. A similar situation exists for estimates related to transformation processes. Exposure data are available but have not been reanalyzed. Data to inform critical effects can be readily attained within months with current tools. Thus, more exposure and effect data are needed for an assessment of this magnitude.

Several Committee members brought up their concern that pregnant women were not included. One member specifically brought up the last sentence on page150 and noted that there are no data presented on potential reproductive/developmental effects of 1,4-Dioxane. This member disagreed with the conclusion that in the absence of data that female workers (who may be pregnant) or their fetuses are not at increased risk and asked for more clarity from EPA. Committee members asked where the evidence is to support the Agency's assertion on the CNS effects, particularly given that this chemical is likely to move easily into brain (page 150): "Workers were identified as relevant potentially exposed or susceptible subpopulations, but EPA did not include women of reproductive age or pregnant women who may work with 1,4-Dioxane or children ages 16 to 21 years because the acute effects on liver enzymes and CNS effects are not expected to preferentially affect women or developing children." One Committee member suggested that EPA declare their statement on limited CNS effects was based on limited data.

Specific data gaps and limitations noted by individual Committee members:

- limited data sets from the EU risk assessment
- limited chronic toxicity studies available for assessing the long-term effects to aquatic species
- only one developmental study available
- high degree of uncertainty in the MOA evaluations in general
- monitoring data lacked descriptions of worker tasks, exposure sources, and possible engineering controls, assumed as personal breathing zone (PBZ) measurements, sampling rate missing for some 2016 data
- the Agency recognizing some data sources may be biased

- uncertainty on the underlying exposure distribution
- skin sensitization and respiratory sensitization were not considered
- take home exposure from workers to family members was not considered

Specific notes on the Evaluation's presentation or where clarification is needed from individual Committee members:

- One member noted that in Table 6-1 there are instances where the MOE is less than 30 with PPE, but no unreasonable risk is noted and suggested this is an error. This points to the difficulty interpreting these tables as other Committee members noted the determination of unreasonable risk came from a different table.
- One Committee member presented an idea for a different table to clarify presentation of risk estimates for a different audience. The Committee member had started filling in a sample of what it could look like (see below). Several members agreed that this would be helpful in addition to the existing tables. The Committee noted that the existing tables are helpful and should be retained. In particular Table 6-1 follows TSCA and is full of information for a specific audience.

Table 1 Example of summary table suggested as one way of clarifying conclusions on risk by linking back to components of conceptual model presented in Figures 2-2 and 2-3 (provided by K. Portier.)

Activities and Uses	1,4-Dioxane									
Receptors	Exposure Route	Exposure Pathway	Risk Mitigation Practices	Driver Benchmark	Risk Estimate			Presents Unreasonable Risk (Yes/No/Not Evaluated)		
			(W/WO/-)[1]	Max exposure	Acute (MOE<300)	Chronic Non-Cancer (MOE<30)	Chronic Cancer (R>1.0E-4)	Average Healthy	Highly Exposed	Susceptible Popn
Workers (Tables 3-27, 5-9,5-10, 5-11)	Dermal	Solid Contact	W	88 mg/day	960	76	**360.0E-4**	YES	YES	-
	Dermal	Solid Contact	WO	1759 mg/day	**48**	**3.8**	**7.3E-4**	**YES**	NO	-
	Dermal	Liquid Contact	W	192 mg/day	239902	35	**400.0E-4**	YES	NO	-
	Dermal	Liquid Contact	WO	1924 mg/day	47980	**3.5**	**8.0E-4**	**YES**	NO	-
Workers	Oral	Solid Contact	-							
	Oral	Liquid Contact	-							
Workers	Inhalation	Indoor Air	W							
	Inhalation	Indoor Air	WO							
	Inhalation	Outdoor Air	W							
	Inhalation	Outdoor Air	WO							
Occupational Non-Users	Dermal	Waste Handling	WO							
	Dermal	Waste Handling	WO							
	Dermal	All Other Activities	-							
Occupational Non-Users	Inhalation	Waste Handling-Outdoor Air	WO							
	Inhalation	All Other Activities-Indoor Air	WO							
	Inhalation	All Other Activities-Outdoor Air	WO							
Consumers	Dermal	Solid Contact	-							
	Dermal	Liquid Contact	-							
Consumers	Oral	Solid Contact	-							
	Oral	Liquid Contact	-							
	Oral	Solid Contact Mouthing	-							
Consumers	Inhalation	Indoor Air-Buildings	-							
	Inhalation	Indoor Air - Automobiles	-							
	Inhalation	Outdoor Air	-							

- On page 173, for disposal, workers are inappropriately included in both assessment statements. There is either an unreasonable risk of injury or not, it can't be both:

  "Presents an unreasonable risk of injury to health (workers)"

  "Does not present an unreasonable risk of injury to health (workers and occupational non-users) or to aquatic vertebrates, aquatic invertebrates, and aquatic plants from exposures to 1,4-Dioxane in surface waters.

- Under Risk Considerations, EPA acknowledges that some models and/or assumptions could lead to overestimation of risk (conservative assumptions) and then the text proceeds to give examples of where these uncertainties might exist. However, the text proceeds to read "For this pathway, EPA expects that the risks are not underestimated." Shouldn't this read: "As a result, EPA expects that the risks are not underestimated for this pathway." given this seems a likely conclusion if models and assumptions increase the likelihood of overestimation?

- In Section 5.2.4 Risk Characterizations the second paragraph on page150 is confusing. Is the critical effect (respiratory metaplasia) evaluated by a BMDL (lower confidence limit for BMD)? If so, what is the point of raising concerns about using LOAECs?
- The third paragraph on page150 is confusing. Evaporation from skin is assumed to not occur for some of the dermal extrapolations, but it was assumed to occur for others. Much more clarity is needed. The last sentence of this paragraph makes no sense. "Metabolism occurs in both oral and dermal routes and inhalation is not as relevant to dermal as absorption is more rapid by inhalation." Also, many of the dermal extrapolations are determined from inhalation data, which apparently this sentence is saying is inappropriate.
- In Section 6, related to the risk characterization assumptions, the text of the table (first on page 158 and then repeated) indicates that whole body inhalation studies overestimate the risk for portal of entry effects because of uncertainty with respect to the actual doses received. The justification for why an overexposure would be expected from consideration of only whole-body inhalation exposures is not clear. The risk evaluation should discuss more the pathways (indirect via blood concentration or direct via direct deposition via dust inhalation and/or preening) expected for nasal tissue exposures and whole-body inhalation study data would lead to overestimation of risk.

- How can the following conclusion be determined given the absence of any separation of effects by gender in these studies?

  > "In developing the risk evaluation, the EPA analyzed the reasonably available information to ascertain whether some human receptor groups may have greater exposure than the general population to the hazard posed by a chemical. The results of the available human health data for all routes of exposure evaluated (i.e., dermal and inhalation) indicate that there is no evidence of increased susceptibility for any single group relative to the general population. Exposures of 1,4-Dioxane would be expected to be higher amongst workers and ONUs using 1,4-Dioxane as compared to the general population." (page 151)

In fact, prior statements in the document contradict this, stating: "Information on induction of liver enzymes, genetic polymorphisms and gender differences was inadequate to quantitatively assess toxicokinetic or toxicodynamic differences in 1,4-Dioxane hazard between animals and humans and the potential variability in human susceptibility."

- Page 151, last paragraph, does this describe an approach that EPA will take in the future to differentiate the risk for subpopulations with varying exposure or severity of the health effects? An alternative way to describe this is to discuss the limitation of the current approach.
- Page 152, line 16, states: "As a result of the limited nature of all routes of exposure to individuals resulting from the conditions of use of 1, 4-Dioxane, a consideration of

aggregate exposures of 1, 4-Dioxane was deemed not to be applicable for this risk evaluation": This does not seem a strong justification for not considering aggregated exposure. If all routes of exposure are of limited nature, then would not a single route be of even more limited nature? From a practical standard point, there are technical challenges to combining cancer and non-cancer risk when different approaches are taken to quantify non-cancer risk (MOE) and cancer risk (slope factor). While it is in principle possible to combine different health outcomes or risk metrics into a joint estimate of risk associated with aggregated exposure from multiple route, this is an area that requires more research. EPA can be more transparent with these limitations.

- Define Benchmark MOE formally, preferably using an equation, giving adequate references and interpretation.
- Give reference for the cancer benchmark level of 10^{-4} (e.g., Table 5-3). Referencing the key findings in the result tables would improve the presentation.
- Explain why 10^{-4} is appropriate for ONUs given that 10^{-6} is usually used for the general population.
- In many incidences EPA shows the use of protective devices with a certain level of Assigned Protection Factor (APF) would bring the risk level (MOE or cancer slope factor) to a reasonable level (in reference to benchmark). If the intention is to demonstrate the effectiveness of use of a protective device, EPA should report the results associated with the smallest Protection Factor (PF) that achieves the desired level of risk reduction when such a device is available. The Evaluation's presentation, in the current version, is inconsistent in that in some cases the "risk level" (MOE or cancer slope) is below and in other cases remained above the benchmark level.
- Explain or give an example how values of column 1 (PF=1) in tables 5-9, 5-10, and 5-11 are calculated. In table 5-10 the risk estimates for import/packaging are given by ratios (e.g., 30/16 for PF=1). Why are they different from the other bin 1 values?
- Move 2nd paragraph page 143 to Section 3.4.1.14 where dermal exposure assessment is discussed.

Recommendations:

Q 6.1

1. **Clarify portions of text as indicated above, including adding additional details and pertinent information from Problem Formulation.**
2. **The Agency should use its authority to obtain additional data to fill data gaps and/or perform a quantitative sensitivity analysis. This could further direct the Agency to areas where additional important data are to be obtained, clarified, and/or to apply a quantitative uncertainty analysis.**

Q 6.2

3. **Provide more explanation where requested.**
4. **Each time Mattie et al. 2012 is cited that EPA add "after Kasai et al. (2008)."**
5. **Make it more transparent where uncertainties are quantified and provide justification where they are not.**

Q 6.3

6. **Provide more clarity where requested. Specifically, add the suggested table to clarify where EPA has and has not determined there to be risk and unreasonable risk**
7. **Correct the substantial error in the dermal risk estimates that makes the risk characterization invalid.**
8. **EPA should more fully address susceptible populations including pregnant women or women who may become pregnant. Modeling and sensitivity analysis may help address these data gaps.**
9. **Include estimates of risk to general population and susceptible populations, especially in other pathways of exposure such as drinking water.**
10. **EPA should evaluate combined exposures through several pathways, including pathways that were not evaluated such as drinking water.**
11. **Modify statements of no unreasonable risk with appropriate qualifiers such as "if appropriate personal protective equipment is used" or if "engineering controls are used."**
12. **Further explain PPE use and its relation to risk assessment and risk evaluation.**

REFERENCES – 1,4-DIOXANE

Adamson, DT, Piña, EA, Cartwright, AE, Rauch, SR, Hunter Anderson, R, Mohr, T, Connor, JA. 2017. 1,4-Dioxane drinking water occurrence data from the third unregulated contaminant monitoring rule. Sci Total Environ 596-597:236-245.

AIHA Press. 2009. Mathematical Models for Estimating Occupational Exposure to Chemicals. Stock #: AEAM09-379, ISBN #: 978-1-935082-10-1. Edited by Charles B. Keil, Catherine E. Simmons, and T. Renee Anthony AIHA.

Anderson P., Drewes JE, Denslow N, Jakubowski W, Olivieri, A, Schlenk, D, Snyder S. 2018. Monitoring Strategies for Constituents of Emerging Concern (CECs) in Recycled Water Recommendations of a Science Advisory Panel. Southern California Coastal Water Research Project; SCCWRP Technical Report 1032 http://ftp.sccwrp.org/pub/download/DOCUMENTS/TechnicalReports/1032_CECMonitoringInRecycledWater.pdf

ATSDR. 2006. Toxicological profile for 1,4 dioxane. Agency for Toxic Substances and Disease Registry. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=955&tid=199

Baldwin, PE, Maynard, AD. 1998. A Survey of Wind Speed in Indoor Workplaces. Ann Occup Hyg 42: 303-313.

BASF. 2016. Analytical Reports and Data Summaries from Worker Monitoring at the U.S. Facility for 1,4-Dioxane Production.

BASF. 2017. Information in response to the "Preliminary information on manufacturing, processing, distribution, use, and disposal: 1,4-dioxane" document. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0012

Bernot RJ, Brueseke MA, Evans-White MA, Lamberti GA. 2005. Acute and chronic toxicity of imidazolium-based ionic liquids on Daphnia magna. Environmental Toxicology and Chemistry 24(1): 87-92.

Bringman G, Kuhn R. 1977. Limiting values of the harmful action of water endangering substances on bacteria (*Pseudomonas putida*) and green algae (*Scenedesmus quadricauda*) in the cell multiplication inhibition test. Z f Wasser- und Abwasser-Forschung 10: 87-98.

Bronaugh, RL. 1982. Percutaneous absorption of cosmetic ingredients. In P Frost; SN Horwitz (Eds.), Principles of cosmetics for the dermatologist (pp. 277-284). St. Louis, MO: C.V. Mosby.

Bronaugh RL, Congdon FR, Stadtmauer RJ, Scheuplein RJ. 1980. Percutaneous Absorption of 1,4-Dioxane through excised human skin. Presented at Nineteenth Annual Meeting of the Society of Toxicology; March 9-13, 1980; Washington, DC

Burton NC, Driscoll RJ. 1997. Health hazard evaluation report no. HETA-95-0293-2655, Dana Corporation, Spicer Axle Division, Fort Wayne, Indiana. (HETA-95-0293-2655). Cincinnati, OH: National Institue for Occupational Safety and Health.

Chapin RE, Adams J, Boekelheide K, Gray LE, Hayward SW, Lees PS, McIntyre BS, Portier KM, Schnorr TM, Selevan S., Vandenbergh JG, Woskie SR. 2008. NTP-CERHR expert panel report on the reproductive and developmental toxicity of bisphenol A. Birth Defects Res B Dev Reprod Toxicol 83(3): 157-195.

Chen LY, Li X, Hong H, Shi D. 2018. Multigenerational effects of 4-methylbenzylidene camphor (4-MBC) on the survival, development and reproduction of the marine copepod Tigriopus japonicus." Aquatic Toxicology 194: 94-102.

Cumming H, Rucker C. 2017. Octanol-water partition coefficient measurement by a simple H-1 NMR method. ACS Omega 2: 6244- 6249.
https://pubs.acs.org/doi/pdf/10.1021/acsomega.7b01102

Dobbins, LL, Usenko S, Brain R.A., Brooks BW. 2009. Probabilistic ecological hazard assessment of parabens using *Daphnia magna* and *Pimephales promelas*. Environmental Toxicology and Chemistry 28(12): 2744-2753.

Dourson ML, Higginbotham J, Crum J, Burleigh-Flayer H, Nance P, Forsberg ND, Lafranconi M, Reichard J. 2017. Update: Mode of action (MOA) for liver tumors induced by oral exposure to 1,4-dioxane. Regul Toxicol Pharmacol. 2017 Aug 88:45-55.

Eastmond DA. 2008. Evaluating genotoxicity data to identify a mode of action and its application in estimating cancer risk at low doses: A case study involving carbon tetrachloride. Environ Mol Mutagen. 2008 Mar;49(2):132-41.

ECJRC. 2002. European Union risk assessment report: 1,4-Dioxane. (EUR 19833 EN). Luxembourg: Office for Official Publications of the European Communities.
https://echa.europa.eu/documents/10162/a4e83a6a-c421-4243-a8df-3e84893082aa

Fehrenbacher, MC, Hummel, AA. 1996. Evaluation of the Mass Balance Model Used by the Environmental Protection Agency for Estimating Inhalation Exposure to New Chemical Substances. American Industrial Hygiene Association Journal. June. 57: 526-536.

Frasch, FH. 2012. Dermal Absorption of Finite doses of Volatile Compounds. J Pharm Sci 101: 2616-2619. http://dx.doi.org/10.1080/15287394

Frasch, HF, Bunge AL. 2015. The transient dermal exposure II: post-exposure absorption and evaporation of volatile compounds. J Pharm Sci 104: 1499-1507.
http://dx.doi.org/10.1002/jps.24334

Frasch HF, Dotson G, Bunge A, Chen C-P, Cherrie J, Kasting G, Kissel J, Sahmel J, Semple S, Wilkinson S. 2014. Analysis of Finite Dose Dermal Absorption Data: Implications for Dermal

Exposure Assessment. J Expos Sci Environ Epid 24(1):65-73.

Gi M, Fujioka M, Kakehashi A, Okuno T, Masumura K, Nohmi T, Matsumoto M, Omori M, Wanibuchi H, Fukushima S. 2018. In vivo positive mutagenicity of 1,4-dioxane and quantitative analysis of its mutagenicity and carcinogenicity in rats. Arch Toxicol 92: 3207-3221. http://dx.doi.org/10.1007/s00204-018-2282-0

Guo F, Wang L, Wang WX. 2012. Acute and chronic toxicity of polychlorinated biphenyl 126 to *Tigriopus japonicus*: Effects on survival, growth, reproduction, and intrinsic rate of population growth. Environmental Toxicology and Chemistry 31(3): 639-645.

Hansch, C, Leo A, Hoekman D. 1995. Exploring QSAR: Hydrophobic, electronic, and steric constants. In C Hansch, A Leo, DH Hoekman (Eds.), Exploring QSAR: Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society.

Health Canada. 2010. Screening assessment for the challenge: 1,4-Dioxane. Environment Canada, Health Canada. http://www.ec.gc.ca/ese-ees/789BC96E-F970-44A7-B306-3E32419255A6/batch7_123-91-1_en.pdf

Howe RB, Crump KS. 1982. GLOBAL 82: A Computer Program to Extrapolate Quantal Animal Toxicity Data to Low Doses. Contract 4IUSC252C3. Prepared for the Office of Carcinogen Standards, Occupational Safety and Health Administration, U.S. Department of Labor Washington, DC

Ibrahim AM, Sayed, DA. 2019. Toxicological impact of oxyfluorfen 24% herbicide on the reproductive system, antioxidant enzymes, and endocrine disruption of *Biomphalaria alexandrina* (Ehrenberg, 1831) snails. Environmental Science and Pollution Research 26(8): 7960-7968.

Jayjock MA. 1988. Assessment of Inhalation Exposure Potential from Vapors in the Workplace, Am. Ind. Hyg. Assoc. J. 49(8): 380-385.

Jayjock MA, Hawkins NC. 1995. Exposure Database Improvements for Indoor Air Model Validation, Appl. Occup Environ Hyg 10 (4), April 379-382.

Jayjock, MA, Logan, B, Mader, J, Owens, J, Eldridge, M, Costello, M, Morken, P, Lieder P. 2011. Modeled Comparisons of Health Risks Posed by Fluorinated Solvents in a Workplace Spill Scenario, Ann Occup Hyg 55(2): 202-213 first published online September 13, 2010 doi:10.1093/annhyg/meq062

Klapacz J, Pottenger LH, Engelward BP, Heinen CD, Johnson GE, Clewell RA, Carmichael PL, Adeleye Y, Andersen ME. 2016. Contributions of DNA repair and damage response pathways to the non-linear genotoxic responses of alkylating agents. Mutat Res Rev Mutat Res. 2016 Jan-Mar;767:77-91.

Kanada M, Miyagawa M, Sato M, Hasegawa H, Honma T. 1994. Neurochemical profile of

effects of 28 neurotoxic chemicals on the central nervous system in rats (1). Effects of oral administration on brain contents of biogenic amines and metabolites. Ind Health. 32(3):145-64.

Kang HM, Kim MS, Hwang UK, Jeong CB, Lee JS. 2019. Effects of methylparaben, ethylparaben, and propylparaben on life parameters and sex ratio in the marine copepod Tigriopus japonicus. Chemosphere 226: 388-394.

Kasai T, Kano H, Umeda Y, Sasaki T, Ikawa N, Nishizawa T, Nagano K, Arito H, Nagashima H, Fukushima S. 2009. Two-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male rats. Inhal Toxicol 21: 889-897. http://dx.doi.org/10.1080/08958370802629610

Kasting BG, Miller MA. 2006. Kinetics of finite dose absorption through skin 2: Volatile compounds. J Pharm Sci 95: 268-280. http://dx.doi.org/10.1002/jps.20497

Kaviraj A, Bhunia F, Saha NC. 2004. Toxicity of methanol to fish, crustacean, oligochaete worm, and aquatic ecosystem. International Journal of Toxicology 23(1): 55-63.

Keil CB, Nicas, M. 2003. Predicting Room Vapor Concentrations Due to Spills of Organic Solvents, AIHA Journal, 64:4, 445-454,

Kissel JC. 2011. The mismeasure of dermal absorption. J Expos Sci Environ Epid. 21(3): 302-9.

Latin, HA. 1982. The Significance of Toxic Health Risks, An Essay on Legal Decisionmaking under Uncertainty. Ecology Law Quarter, Volume 10, Issue 3, Article 1, September

Liu, N, Jin X, Zhou J, Wang Y, Yang Q, Wu F, Giesy JP, Johnson AC. 2018. Predicted no-effect concentration (PNEC) and assessment of risk for the fungicide, triadimefon based on reproductive fitness of aquatic organisms. Chemosphere 207: 682-689.

MacGregor JT, Frötschl R, White PA, Crump KS, Eastmond DA, Fukushima S, Guérard M, Hayashi M, Soeteman-Hernández LG, Johnson GE, Kasamatsu T, Levy DD, Morita T, Müller L, Schoeny R, Schuler MJ, Thybaud V. 2015. IWGT report on quantitative approaches to genotoxicity risk assessment II. Use of point-of-departure (PoD) metrics in defining acceptable exposure limits and assessing human risk. Mutat Res Genet Toxicol Environ Mutagen. 2015 May 1783:66-78.

Mage DT, Ott WT. 1996. Accounting for Nonuniform Mixing and Human Exposure in Indoor Environments, Characterizing Sources of Indoor Air Pollution and Related Sink Effects, B. Tichenor (ed), ASTM STP 1287, p. 263-278.

Marquart H, Franken R, Goede H, Fransman W, Schinkel J. 2017. Validation of the dermal exposure model in ECETOC TRA. 61: 854-871.

Mattie DR, Bucher TW, Carter AL, Stoffregen DE, Reboulet JE. 2012. Acute Inhalation Toxicity Study of 1, 4-Dioxane in Rats (Rattus norvegicus). GRA and I: 29.

Marzulli FN, Anjo DM, Maibach HI. 1981. *In vivo* skin penetration studies of 2,4-toluenediamine, 2,4-diaminoanisole, 2-nitro-p-phenylenediamine, p-Dioxane and N-nitrosodiethanolamine in cosmetics. Food Cosmet Toxicol 19: 743-747. http://dx.doi.org/10.1016/0015-6264(81)90530-7

National Academy of Sciences Committee to Review the IRIS Process. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. The National Academies Press, Washington. DC. 170 pages.

NIOSH. 1994. Dioxane: Method 1602, issue 2. In NIOSH manual of analytical methods (NMAM) (Fourth Edition ed.). Washington, DC: National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/docs/2003-154/pdfs/1602.pdf

OECD. 2004. Test 428: Skin Absorption: *In-vitro* Method, November 23, ISBN 9789264071087 (PDF), https://doi.org/10.1787/9789264071087-en

Park D, Stewart PA, Joseph B, Coble JB. 2009. Determinants of Exposure to Metalworking Fluid Aerosols: A Literature Review and Analysis of Reported Measurements. Ann Occup Hyg ., 53(3): 271–288.

Saha, NC, Bhunia F, Kaviraj A. 2006. Comparative toxicity of three organic acids to freshwater organisms and their impact on aquatic ecosystems. Human and Ecological Risk Assessment 12(1): 192-202.

Simon TW, Zhu Y, Dourson ML, Beck, NB. 2016. Bayesian Methods for Uncertainty Factor Application for Derivation of Reference Values. Regulatory Toxicology and Pharmacology 80: 9-24

Simonich SM, Sun P, Casteel K, Dyer S, Wernery D, Garber K, Carr G, Federle T. 2013. Probabilistic analysis of risks to U.S. drinking water intakes from 1,4-dioxane in domestic wastewater treatment plant effluents. Integr Environ Assess Manag. Oct;9(4):554-9.

Sun M., Lopez-Velandia C, Knappe DR. 2016. Determination of 1,4-Dioxane in the Cape Fear River Watershed by Heated Purge-and-Trap Preconcentration and Gas Chromatography-Mass Spectrometry. Environ Sci Technol 50(5): 2246-2254.

Torkelson R, Leong BKJ, Kociba RJ. 1974. 1,4-Dioxane. II. Results of a 2-year inhalation study in rats. Toxicol. Appl. Pharmacol. 30: 287-298.

U.S. EPA. 2004. Risk Assessment Guidance for Superfund (RAGS), Volume I: Human health evaluation manual, (part E: Supplemental guidance for dermal risk assessment): Final. (EPA/540/R/99/005). Washington, DC. http://www.epa.gov/oswer/riskassessment/ragse/index.htm

U.S. EPA. 2009. Toxicological review of 1,4-dioxane (CAS No. 123-91-1) in support of summary information on the Integrated Risk Information System (IRIS) [External Review Draft]

[EPA Report] (pp. 1-276). (EPA/635/R-09/005). Washington, DC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=199330

U.S. EPA. 2013. ChemSTEER User Guide - Chemical Screening Tool for Exposures and Environmental Releases. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2015-05/documents/user_guide.pdf

U.S. EPA. 2017. Scope of the risk evaluation for 1,4-dioxane. CASRN: 123-91-1 [EPA Report]. (EPA-740-R1-7003). https://www.epa.gov/sites/production/files/2017-06/documents/dioxane_scope_06-22-2017.pdf

U.S. EPA. 2018. Problem formulation of the risk evaluation for 1,4-dioxane. (EPA-740-R1-7012). Washington, DC: Office of Chemical Safety and Pollution Prevention, United States Environmental Protection Agency. https://www.epa.gov/sites/production/files/2018-06/documents/14-dioxane_problem_formulation_5-31-18.pdf

Yang X, Sun Z, Wang W, Zhou Q, Shi G, Wei F, Jiang G. 2018. Developmental toxicity of synthetic phenolic antioxidants to the early life stage of zebrafish. Science of the Total Environment 643: 559-568.

SESSION 2: Peer Review for EPA Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster (HBCD)

EXECUTIVE SUMMARY OF SACC REVIEW – CYCLIC ALIPHATIC BROMIDE CLUSTER (HBCD)

The EPA requested input and advice from the Science Advisory Committee on Chemicals (SACC or Committee) on several issues posed as questions for topics including: Draft Risk Evaluation (Evaluation) content and organization, systematic review, human health and the environment.

Committee members generally agreed that the overall **content, organization, and presentation** of the HBCD Evaluation document is the best of the three risk evaluation dossiers examined to date. Many useful improvements, such as hyperlinks between sections of the documents, made the document clearer and more readable. The Committee made several recommendations to EPA for the HBCD document specifically, that could also be adapted for future risk evaluations. Further, the Committee found the at-meeting slide presentation summarizing EPA's overall strategy helpful for assessing risk evaluation and characterization and suggested that for future reviews that EPA make available a summarizing PowerPoint presentation *prior to the meeting*.

Systematic Review (SR) of the relevant literature for a well or moderately studied compound produces a voluminous record that is necessarily difficult to evaluate. Members generally agreed that they could not assimilate the full content of the HBCD SR in the time allotted and had to approach this review by selective query in their area of expertise. This activity was further hampered by lack of an index. Members encouraged EPA to provide explicit, succinct rationales for both inclusion and exclusion of prior studies in a manner conducive to searching by a subject matter expert. Members viewed the EPA methodology as still subject to amendment and/or replacement by an alternative approach and encourage EPA to seek additional review of their SR procedure.

The **Fate and Transport** (Section 2.1) introduces estimated values of critical environmental properties (e.g., water solubility, bioaccumulation potential, and environmental persistence). These are subsequently used in the prediction of HBCD exposure of humans and wildlife later in the document. As such, uncertainties in these values will propagate into these higher-level predictions. This is problematic in terms of associated confidence in their estimates. Committee members noted that reliable studies determining these critical parameters were limited. In some cases, values relied on a single point estimate, with no estimate of variability.

HBCD has been used primarily in polystyrene insulation products. Therefore, its environmental fate will be a function of its residence in, and bioavailability from, this polymeric media. This observation is not considered in the EPA Evaluation. The document also does not discuss transport (e.g., long-range atmospheric transport and impact on the Arctic environment) of HBCD in detail.

HBCD bioaccumulation factor (BAF) estimates are based on two published Chinese studies. EPA relies on high trophic level fish species under the assumption that these would generate the most protective estimates. However, BAF values are actually higher in some cases for lower trophic species in the same studies, as well as in studies brought forth by Committee members.

Thus, Committee members questioned the applicability and uncertainty related to these BAF estimates.

Biodegradability of HBCD under the conditions of use (COU) concept, as well as fate in wastewater treatment, also would be affected by its presence within polymer products, such as polystyrene, high impact polystyrene (HIPS), textiles and solder/flux. Half-lives for any of these matrices are not available, but likely are in the range of years to decades. This far exceeds the "free" HBCD half-life determined in the HBCD biodegradation studies cited in the Evaluation. Hence, HBCD likely—as do other persistent, bioaccumulative, and toxic (PBT) halogenated chemicals—remains in the environment for periods much longer than one might project based on laboratory studies of "free HBCD" evaluated in lab scenarios.

While methods and approaches to estimate **environmental release** were generally appropriate, the Committee expressed concerns that estimations of environmental concentrations associated with demolition and disposal are not adequately addressed. Leachate from landfill is not considered, nor is the potential exposure through movement of polystyrene.

Approaches, methods and rationale for **occupational inhalation exposure** estimation are presented and described clearly. The Committee questioned whether particles of the size of commercially-available HBCD would be expected to reach the lower airway, and a consensus of the Committee believes that PPE may not be consistently and properly worn, as EPA assumed.

The models used for **environmental, general population, and consumer exposure** are complex in construction and incorporate multiple assumptions. Beyond the recommendations for the HBCD Evaluation, the Committee expressed a need for additional peer review expertise to assess the adequacy and appropriateness of use for each complex model EPA uses for the evaluation of chemicals under TSCA. The Committee recommended a panel of modeling experts be convened to assess the conservativeness of model estimates. Several Committee members agreed that the concept of using progressively more informative/conservative screening tools makes sense in terms of efficiency, especially in this case where the chemical is likely to partition out of the aqueous phase (the first-tier model assumes total chemical is in the aqueous phase, and therefore, in this case, overestimates the concentration). The Committee was unable to determine if the sensitivity analysis for infant exposures by consideration of varying percentiles is valid, and further, the Evaluation excludes soil ingestion rates by children exhibiting soil pica – a relevant susceptibility. The Committee concluded that to be protective and account for susceptible populations, the Evaluation should consider the use of consumption rates on the high end when estimating exposures. The Committee recommended that definitions or descriptions of the "High," "Moderate," and "Low" modifiers of uncertainty and variability must be provided in the Evaluation's tables to be truly useful.

There is sufficient information in relation to **environmental hazards** to expect that exposures to higher trophic level wildlife species will be of greatest concern. The Committee recommended trophic level transfer and/or biomagnification should be discussed and evaluated. Lacking data to evaluate transfer and biomagnification, modifications to Uncertainty Factors (UFs) or Adjustment Factors (AFs) may be needed to address this concern.

Models and methods used to estimate exposures and hazards to wildlife need to be clear and well supported. Exposures to birds and mammals are apparently based on actual yet limited environmental monitoring data. However, precise criteria and the use of models are not specifically delineated. This is needed to understand whether oral dose is compared with oral dose estimates using assumptions modeled from environmental media concentrations ***or*** whether environmental media concentrations are compared to modeled exposure assumptions to derive a media-screening level similarly to the process used by EPA in the development of EcoSoil Screening Levels. The Committee suggested that the EPA provide a transparent process (i.e., an algorithm) for estimating oral dose/exposures from media concentrations and fully describe the process used to develop toxicity reference values for mammals and birds.

Additionally, the process for choosing toxicity benchmarks for wildlife are not provided. It appears that the critical study approach used is based on the no-observed adverse-effect level (NOAEL); however, the justification for selecting the study is not provided. The Committee recommended that rather than taking the most sensitive study, the Evaluation employ an evidence integration procedure. Data from studies of highest quality and relevance are used to establish a benchmark dose, if possible, from which a toxicity reference value (TRV) is derived (as is typically done with human health data). It would be beneficial to provide a diagram to assist reviewers in understanding the spread of the toxicity endpoints. This would also facilitate corroboration of reported outcomes, but only if there are adequate data within a vertebrate class to do so.

Wildlife exposures are calculated and evaluated with toxicity information only for birds and mammals. HBCD has reported thyroid effects in mammals. However, amphibians may be a sensitive model for thyroid effects due to delayed metamorphosis. Additionally, some amphibians can occupy higher trophic levels. The Committee suggested that the EPA consider effects on amphibians and reptiles although there are likely few toxicity data available for reptiles. If adequate toxicity data are not available, then this shortfall would be identified as an uncertainty. Alternatively, the Agency could consider requesting and obtaining those data.

The **human health hazard** assessment indicates data from human epidemiological studies is limited and the Agency considered whichever data are available to be inadequate for conducting a risk assessment. Therefore, the Agency relied on rodent studies. Rodent studies are considered in relation to whether they were acute or chronic. After reviewing the literature, the EPA narrowed the studies it used for the risk assessment to two. One is a two-generation feeding study (Ema et al. 2008) and the other is from a 90-day oral toxicity study (WIL Research 2001) of HBCD. The Committee had a number of questions and clarifications on how and why some of the Ema et al. (2008) data were used. The main concerns were related to the NOAEL chosen by the Agency. The Committee members noted that multiple endpoints show effects at 1500 and 15,000 ppm of HBCD and suggest that the Agency lacked adequate justification for not using 1500 as the NOAEL. The members recommended that EPA reconsider this decision and use 1500 ppm as the NOAEL. For number of pregnancies in the Ema et al. (2008) study, the Agency combined the F0 and F1 data, dropped the high dose group, and found that when it did so, a significant HBCD-related effect is found whereas the authors of the study found that when the

F0 and F1 data are analyzed separately, no significant effect is found. Several concerns were raised about the Agency's merging of these datasets:

1) It was not clear to reviewers that these datasets represent the same effect of HBCD and merging disparate data might not be appropriate.

2) The method of merging the data was a concern and a different way of analyzing these data that may be more statistically valid was proposed.

This different approach may change the point of departure (POD) and the Agency is urged to consider this alternate approach. Some issues were raised about the WIL study (WIL Research 2001). Although conducted in accordance with good laboratory practice (GLP), some concern was raised about whether the study had undergone peer review. The major finding from the WIL study is an increased liver weight that is not statistically significant. EPA still uses the study in the Evaluation. Another specific concern about the WIL study was that for a number of the endpoints, the sample sizes are small; as low as 5 rats/sex/group in some cases. In addition, studies were identified by Committee members that the Agency should be aware of, and these citations are provided in the Committee's discussion. Although the Agency relied on reproductive and developmental toxicity studies, it was noted that liver toxicity was relevant and possibly immunotoxicity as well. There were a number of specific comments pointing out areas in the Evaluation that would benefit from further clarification. Nevertheless, the overall view of the Committee was endorsement of the EPA's Human Health Hazard risk assessment section for charge question 8, with the caveats noted above.

Overall, for the **environmental risk characterization**, appropriate methods were used to assess risk quotients (RQs) for water and sediment exposure. However, the Committee had concerns that the threshold used for soil was inappropriate. In addition, the Committee suggested that given this compound is lipophilic and has poor water solubility, body burden assessments in aquatic organisms are likely a more relevant measure of exposure, and that comparison to critical body burden thresholds may be more appropriate for RQ measurements. The Committee also had concerns regarding the lack of inclusion of birds as a receptor for hazard quotient analyses. Some Committee members also had concerns that predicted environmental concentrations (PEC) in water, sediment and soil were highly uncertain and should have included an overall probabilistic assessment rather than the 50th percentile measure used for the PEC.

The human health risk characterization focuses on HBCD exposures. The Committee commended the EPA for the thorough presentation of scenarios, populations of interest and toxicological endpoints used for acute and chronic exposures, and noted that assumptions, application of uncertainty factors, and choices of key hazard effects followed standard EPA policies and are generally well-justified and appropriate. Concerns were noted about the use of thyroid effects as the most sensitive hazard endpoint due to underlying mechanistic differences in thyroid physiology between rodents and humans. Although exposure groups and age groups are presented with considerable detail and clear rationale, the Committee noted the need to: 1) use a consistent and more appropriate age to differentiate between children and adults, 2) add

consideration of special populations who, due to unusually high amounts of fish consumption, are likely to be exposed to higher amounts of HBCD than most other sub-populations, 3) add consideration of several preexisting health conditions that result in higher fat content in the liver and thus, lower-biologically-effective HBCD exposures, 4) consider the impact of socioeconomic status on mobility as this can impact duration of chronic HBCD exposure, and 5) consider modes of action (MOAs) established for polychlorinated biphenyls (PCBs) as providing potential insights for HBCD. Further the Committee noted EPA's limited consideration of exposure pathways other than workplace exposure scenarios, which is currently limited to one commercial operation with perhaps no more than 10 to 25 employees engaged in HBCD solder flux production. Given the international ban on HBCD export and decisions of U.S. firms to voluntarily cease HBCD production, there are few HBCD primary receptors (primary occupational/occupational non-users) as defined by TSCA. The Committee considered the lack of quantification of uncertainties as a lingering concern for EPA's process of risk assessment/evaluation, leading to EPA needing to develop a practical and sensible process where uncertainties can be quantified systematically and consistently. Risk evaluation of HBCD presents such an opportunity to do so.

DETAILED COMMITTEE DISCUSSION AND RECOMMENDATIONS – CYCLIC ALIPHATIC BROMIDE CLUSTER (HBCD)

As amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act on June 22, 2016, the Toxic Substances Control Act (TSCA), requires the U.S. Environmental Protection Agency (EPA) to conduct risk evaluations on existing chemicals. The cyclic aliphatic bromide cluster (HBCD) is one of the first ten chemical substances and the third of ten to undergo a peer review by the Science Advisory Committee on Chemicals (SACC or Committee). In response to this requirement, EPA has prepared and published a Draft Risk Evaluation (the Evaluation) for HBCD. The Risk Evaluation process is the second step, following Prioritization and before Risk Management, in EPA's existing chemical process under TSCA. The purpose of risk evaluation is to determine whether a chemical substance presents an unreasonable risk to health or the environment, under the conditions of use, including an unreasonable risk to a relevant potentially exposed or susceptible subpopulation. As part of this process, EPA must evaluate both hazard and exposure, exclude consideration of costs or other non-risk factors, use scientific information and approaches in a manner that is consistent with the requirements in TSCA for the best available science, and ensure decisions are based on the weight-of-scientific-evidence.

The SACC was requested to provide advice and recommendations on the following questions.

Question 1. Content and Organization (Draft Risk Evaluation and Supplemental Files)

EPA's Final Rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726) stipulates the process by which EPA is to complete risk evaluations under the Frank R. Lautenberg Chemical Safety for the 21st Century Act. To that end, EPA has completed a draft risk evaluation for HBCD.

As part of this draft risk evaluation for HBCD, EPA assessed potential environmental, occupational, consumer, and general population exposures. The evaluation considered reasonably available information, including import, processing, distribution in commerce, use, and disposal information. It is important that the information presented in the draft risk evaluation and accompanying documents are clear and concise and describe the process in a scientifically credible manner.

Q 1.1	**Please comment on the overall content, organization, and presentation of the draft risk evaluation of HBCD.**
Q 1.2	**Please provide suggestions for improving the clarity of the information presented in the documents.**

Response (*Recommendations in italics*):

Committee members generally agreed that the HBCD document was the best of the three chemical Evaluations they had examined to date. The precise choice of wordings, such as "data are consistent with" or "data suggest" indicates that a thoughtful and objective review of the existing literature was performed. The use of references to other relevant sections of the report, supporting information, and appendices, and hyperlinks between those references are helpful to the reader. Hyperlinks in the Table of Contents were also useful. In addition to hyperlinks, it was suggested that the Agency provide location information (e.g., page number, chapter) where applicable when citing reference documents. One member remarked that the conceptual model figures generally provide good diagrammatic representation of the fate of HBCDs. It was also noted that the exposure assessment section is thorough and the uncertainty analyses in the source sections are well done, although *a Committee member expressed some concern that there are discrepancies regarding exposure assessments of polystyrene (PS) insulation exposure, particularly on page 39 where text indicates reuse and/or disposal will not be evaluated.*

Several Committee members suggested that *adding a brief discussion on why the substance was initially selected for review* would help to make the document more complete. Additionally, the Introduction could include:

- *A summary of scoping and problem formulation findings*
- *The initial conceptual model as well as the final model on which the Evaluation is based*
- *Background information on HBCD's manufacturing and production to provide context for the assessment*

Several Committee members remarked that the summarizing presentation given by EPA staff at the in-person July 2019, meeting was clear and easy to understand. The Committee discussed whether reorganizing the final risk assessment in a manner similar to this presentation, where exposure, hazard and risk characterization were presented as a block, first for environmental risk and then for human health risks, might produce a more concise and easier to read document. There was some concern that *the Evaluation, as currently drafted, seems to contain a lot of repeated text, and this repetition may be due to the way the document is structured*. Using a structure like that used in the presentation might lead to reduction in repetition and hence to a shorter and more concise risk assessment document.

It was also noted that *the graphics and tables used in the summary presentation may also be helpful in the document itself to improve clarity*. In general, the Committee encourages the use of graphics, tables or bulleted lists. For instance, on pages 26 and 27 under Risk Determination, the

sentence starting with "… EPA considered relevant risk-related factors, including, but not limited to: …" could be made into bullets, and the graphic from slide 19 of the summary presentation could be added to Section 2.2.

Some Committee members noted that Table 5-1 summarizing the risk determination is helpful. The Committee referred to an alternative tabular format mentioned in the 1,4-Dioxane review that could be used as an alternate to or to support risk communication.

A Committee member noted that the integration of the HBCD database with the existing literature is quite strong. For example, the integration of the thyroid response data not only included the HBCD studies, but also cites and discusses the broad mechanistic literature of thyroid hormone-mediated toxicities. In this way, the integration of the toxicity data and the mechanistic data appear to be thoughtful and cogent.

Mentioned in the uncertainty analyses is the fact that the fate and biological effects of HBCD compounds are stereoselective, and the fact that there is limited data on these diastereomers.[3] *This should probably be mentioned in the Introduction. In addition, a limited discussion of the role of micro- and nano-plastic inputs from HBCD-containing polystyrene as vectors to aquatic systems could be included.*

Places where the Evaluation can be improved:

- *The description attached to the statement "does not present an unreasonable risk" should be expanded to clearly describe the uncertainty in this conclusion and the extent to which it is driven by a lack of firm data on exposures. This is especially problematical with exposures during manufacture of HBCD given the compound is no longer being manufactured in the U.S. and imports are reported as declining.*

- *The use of personal protective equipment and its impact on risk considerations needs more clarity. This is discussed in more detail in the Committee response to later questions.*

- *The definition of "reasonably available" as a modifier of sources of information/data is inadequate. (e.g., one definition stated "reasonably" available literature is that which can be "reasonably" obtained). Similarly, the Evaluation needs to define the terms "conditions of use" and "exposure scenarios" and how they are used.*

- *The Evaluation would benefit from an Index. EPA could consider pulling out Data Integration as its own section.*

- *Increase use of graphics, tables, and bulleted lists where possible, to improve clarity.*

3 Diastereomers are stereoisomers that are not mirror images of one another and are non-superimposable on one another. Stereoisomers with two or more stereocenters can be diastereomers. (from: http://www.chemeddl.org/resources/stereochem/definitions17.htm)

- *Include a brief discussion on why the chemical was originally included in the Work Plan.*
- *Include a summary of scoping and problem formulation in the Introduction.*
- *Include the initial conceptual model as well as the final.*
- *Include background information on chemical's manufacturing and production in the Introduction to provide context for the assessment.*
- *Consider mentioning in the Introduction the fact that the fate and biological effects of these compounds are stereoselective, and there is limited data for the diastereomers.*
- *Consider including a limited discussion of the role of micro- and nano-plastic inputs from HBCD-containing polystyrene as vectors to aquatic systems.*
- *Revise discussions on use of PPE to clarify the impact on the risk evaluation.*

Editorial recommendations to improve clarity

- *Page 24, 1st sentence – "EPA ~~believes~~ has concluded that manufacturing by large manufacturers ~~is no longer ongoing~~ has ceased, at least in the U.S., based on communications with industry, and it is assumed that for small manufacturers, it would be cost prohibitive to produce HBCD in small quantities."*
- *Page 29, 4th paragraph, last sentence – "Section 5 presents EPA's proposed determination of whether the chemical presents an~~d~~ unreasonable risk under the conditions of use, as required under TSCA 15 U.S.C. 2605(b)(4)."*
- *Page 30, 2nd paragraph – "As explained by the EPA ~~explained~~ in the Risk Evaluation Rule (82 Fed. Reg. 33726 (July 20, 2017)), it is important for peer reviewers to consider ~~how~~ the logical presentation of the underlying risk evaluation analyses ~~fit~~ and the extent to which results support ~~together to produce~~ an integrated risk characterization on which the conclusion of an unreasonable or not-unreasonable risk determination is made."*
- *Page 31 – Missing hyperlink to (EPA-HQ-OPPT-2016-0735-0049) in Section 1.2.1*
- *Page 50, Section 1,5, 2nd paragraph –Citation needed in last line- "considering the deadlines for completing the evaluation (Citation to Final Rule)."*
- ***In 3.1.1 (page 278) the document references the data quality evaluation results in the statement:** "The data quality evaluation results are outlined in Tables 1 and 2 in Appendix G of this document…" The data quality result tables referenced here can be found in the supplemental document Risk Evaluation for Cyclic Aliphatic Bromide Cluster (HBCD), Systematic Review Supplemental File: Data Extraction Tables of Environmental Hazard Studies. (U.S. EPA 2019), which is indirectly referenced in Appendix G.1.*

- *Inconsistent use of past, present, and future tense. (See for example Section 4.1.1.1 where "are based," "is based," and "will be based" are used in the same paragraph. "are/is based" should be consistently used.)*

Question 2. Systematic Review (Section 1.5 and Supplemental Files)

To meet the scientific standards required by TSCA, EPA applied systematic review approaches and methods to support the Evaluation of HBCD. Information on the approaches and/or methods is described in the Evaluation as well as the following documents:

- Application of Systematic Review in TSCA Risk Evaluations
- Strategy for Conducting Literature Searches for HBCD: Supplemental file for the TSCA Scope Document
- HBCD (CASRN: 25637-99-4, 3194-55-6, 3194-57-8) Bibliography: Supplemental File for the TSCA Scope Document
- Problem Formulation for Cyclic Aliphatic Bromides Cluster (HBCD)
- *Risk Evaluation for Cyclic Aliphatic Bromides Cluster (HBCD), Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies*
- *Risk Evaluation for Cyclic Aliphatic Bromides Cluster (HBCD), Systematic Review Supplemental File: Data Extraction Tables for Human Health Hazard Studies*
- *Risk Evaluation for Cyclic Aliphatic Bromides Cluster (HBCD), Systematic Review Supplemental File: Data Extraction Tables for Environmental Fate and Transport Studies*
- *Risk Evaluation for Cyclic Aliphatic Bromides Cluster (HBCD), Systematic Review Supplemental File: Data Extraction Tables for Environmental Hazard*
- *Risk Evaluation for Cyclic Aliphatic Bromides Cluster (HBCD), Systematic Review Supplemental File: Data Extraction Tables for General Population and Environmental Exposure Studies*
- *Risk Evaluation for Cyclic Aliphatic Bromides Cluster (HBCD), Systematic Review Supplemental File: Data Quality Evaluation for Occupational Exposure and Release Data*
- *Risk Evaluation for Cyclic Aliphatic Bromides Cluster (HBCD), Systematic Review Supplemental File: Data Quality Evaluation of Ecological Hazard Studies*
- *Risk Evaluation for Cyclic Aliphatic Bromides Cluster (HBCD), Systematic Review Supplemental File: Data Quality Evaluation of Environmental Fate and Transport Studies*
- *Risk Evaluation for Cyclic Aliphatic Bromides Cluster (HBCD), Systematic Review Supplemental File: Data Quality Evaluation of General Population and Environmental Exposure Studies*
- *Risk Evaluation for Cyclic Aliphatic Bromides Cluster (HBCD), Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies*

Q 2.1	**Please comment on the approaches and/or methods used to support and inform the gathering, screening, evaluation, and integration of data/information used in the Draft Risk Evaluation for Cyclic Aliphatic Bromides Cluster (HBCD).**

Response (*Recommendations in italics*):

This is the third chemical Draft Risk Evaluation (Evaluation) that the SACC reviewed. The Committee previously identified generic issues with the TSCA Systematic Review (SR), and most of these issues were also discussed for the HBCD Evaluation SR. Issues discussed for HBCD that were also discussed previously include: alternative review methods, scoring

methods, treatment of excluded papers, handling of prior reviews, and treatment of physical-chemical property estimation as a distinct category in the literature review.

The Committee was provided an extensive text describing the SR for HBCD. Given the length of the various supplemental documents, it was difficult to find reviews of key sources, including ratings of specific interest to specific subject matter experts. Some type of key word indexing of all sources (not just newly added sources) would allow quicker and easier access and greatly improve the ability of peer reviewers to evaluate the quality of EPA's SR. Those review outcomes can reasonably be reported in either supplemental documents (as done for all current evaluations) or online, as long as clear links and indexing are provided.

Committee members discussed SR processes that have appeared in the peer-reviewed literature. One member suggested that *the SR process would benefit by application of either a condensed data quality scoring system (e.g., Klimisch et al. 1997) for each study—including those identified in the initial literature survey that were excluded from further consideration—or by following the National Toxicology Program's (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) method (e.g., Chapin et al. 2008)*. An advantage to Klimisch scoring is condensed presentation with the rationale for study-score assignment placed in a document appendix or an online annex. The same member cautioned, however, that simplified scoring might raise issues of acceptance by stakeholders. The advantage to the CERHR method, which incorporates commentary on each study followed by assessment on strengths/weaknesses and utility (e.g., "study adequate and of high utility," "study is inadequate for the evaluation process based on lack of adequate control"), is that the rationale for inclusion/exclusion is readily apparent. A disadvantage to the CERHR method is that it may result in unwieldly and long reports depending on the extent of the database for an individual substance. Nevertheless, the members saw room for improvement in EPA's description and presentation of the SR, and one member suggested that EPA submit its methodology to a peer reviewed journal for further vetting. This approach might be more rapid than attempting to obtain a review by the National Academy of Sciences (NAS) as previously recommended. One member noted Public Comments (submitted to the HBCD docket) included criticism of the SR. *At a minimum, clarity of the SR in the Evaluation would be improved by providing a brief statement explaining the reasons for inclusion or exclusion of each source in subsequent analyses.*

Members generally agreed that *prior evaluations that are foundational should be explicitly identified, and justification of their inclusion should be provided either individually or as a group.* Specifically, prior studies that form the basis of a "systematic review" (i.e., that introduces a collection of sources that are included in subsequent analyses, but which essentially bypass steps in the TSCA SR), should themselves display the critical characteristics of an SR. It may be reasonable to accept the utility of older sources based on previous evaluations, but this should be explicitly shown in the flow diagram describing the Evaluation's SR. *Use of prior reviews should also not preclude examination of newer literature*. It is important to distinguish between a source that has been critically reviewed by this TSCA SR protocol and from sources included as part of a "legacy" determination. At least one member suggested that, given the two-tiered nature of the SR process, it might be better to refer to current efforts as a "limited SR," or

if justified, an "updated SR." Another member suggested that sources identified in prior reviews by bodies judged "authoritative" (e.g., IARC, IPCS, ATSDR) might be assigned higher status and subjected to less scrutiny than previously unreviewed sources.

The Committee recommended that all sources reporting estimates of physical-chemical properties be subjected to the same TSCA SR criteria as are other sources. The chemical property data (Section 1.1) appear in the Evaluation prior to discussion of Systematic Review (Section 1.5). This gives the impression that the selection and review of sources reporting chemical property estimated values occurs outside of the TSCA SR process. The Committee expressed concern that estimates obtained or derived from the chemical property literature are often adopted from a single source without determining whether the value is supported by other studies. In the case of HBCD, heavy reliance on estimated values from Epi Suite™ is evident.

Q 2.2	**Please also comment on the clarity of the information as presented related to systematic review and suggest improvements as warranted.**

Response (*Recommendations in italics*):

The Committee did not conduct a thorough review of the Systematic Review. The Committee members raised the following issues related to the SR during its discussion of the Evaluation, thus the following should not be considered a comprehensive list of SR issues.

EPA's overall strategy is described in the Application of Systematic Review in TSCA Risk Evaluations which is referenced in the Evaluation. However, *there should be enough explanation of the SR process in the Evaluation to allow the reader to proceed without first reading the SR methodology document in its entirety*.

Excluded studies, as well as cited/included studies, should be enumerated.

The expansive nature of the Evaluation, and the inclusion of links to references, although laudable, made it sometimes difficult to pull out the conclusions, especially for sections that are outside a member's expertise (see for example Section. 2.1.2.6). *A summary of the findings placed at the beginning or end of each section would be helpful.*

Information in Section 3.2.4 describing the studies used to assess the Non-Cancer Hazards of HBCD does not specify HBCD concentrations, making it difficult to estimate the relevance to human exposures.

On page 300, the two epidemiological studies (Roze et al. 2009, Kiciński et al. 2012) that did not find consistent nervous system effects following developmental exposure to HBCD are not referenced, unlike the rodent studies that did find neurological effects. *More information regarding the human studies is very important in order to appreciate the relevance of the rodent studies.*

The results of the same animal studies are discussed more than once, which led to some confusion. For example, the thyroid effects of HBCD on rodents are discussed on page 299 in Section 3.2.1 Non-Cancer Hazard section, and again on page 302 in Section 3.2.4 Weight of Evidence (WOE). The same is true for other parameters. It is not clear whether this duplication is a requirement of the risk evaluation framework or a result of the document outline that discusses WOE after identification of available data.

Recommendations to improve the general TSCA SR:

- *Establish an indexing system to facilitate searching for both cited/included and excluded studies.*

- *Consider submitting the SR protocol to a journal to obtain further peer review feedback and/or support for use of EPA's TSCA specific SR process.*

- *When prior reviews conducted by the EPA or other regulatory and non-regulatory agencies are integrated into a current review, EPA should explain why those prior reviews are viewed as methodologically equivalent to the approaches specified in the Application of Systematic Review in TSCA Risk Evaluations.*

- *When prior chemical assessments conducted by the EPA or other regulatory and non-regulatory agencies are used to identify key information, those assessments should be updated to ensure new information sources are not excluded.*

- *The Populations, Exposures, Comparators, and Outcomes (PECO)) statements, including inclusion and exclusion criteria, for chemical properties should be distinguished from other problem formulation statements (e.g., human health toxicity, exposure environmental toxicity, etc.).*

Recommendations to improve the HBCD SR:

- As stated in Section 3.2 Human Health Hazards "EPA considered studies of low, medium, or high confidence for hazard identification (ID) and dose-response analysis. Information from studies that were rated unacceptable were only discussed on a case-by-case basis for hazard ID and weight-of-evidence assessment but were not considered for dose-response analysis. EPA considered the specific reasons for the unacceptable scoring in determining whether unacceptable studies could remain useful for hazard ID or weight-of-evidence." *EPA should explain how this language is consistent with screening techniques for data exclusion described in Section 1.5 of the Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster (HBCD).*

- *In chemical property value selection, higher weight should be assigned to experimental data (see Cumming and Rucker 2017) from primary references than to secondary sources (e.g., Hansch et al., 1995) or modeled estimates (e.g., Epi Suite™).*

Question 3: Environmental Fate and Transport (Section 2.1 of the Draft Risk Evaluation)

Preface to Committee Response:

Section 2.1 focuses on estimates of required physical properties, and on modeling approaches used for estimating HBCD burdens in sediment, biotic tissues, as well as its aerobic and anaerobic biodegradation in water, soil and sediment.

The following paragraph, extracted from the EPA TSCA website, outlines how the phrase Conditions of Use is used under TSCA:

> *"Conditions of use" under TSCA means "the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used or disposed of." For purposes of prioritization, the Administrator may determine that certain uses fall outside the definition of "conditions of use." During the risk evaluation scoping process, EPA may decide to narrow the scope of the risk evaluation further, potentially excluding conditions of use that present low risk.*

In the HBCD problem formulation document, EPA states and justifies which conditions of use it will consider in the evaluation of HBCD. EPA also states that activities outside "intended, known, or reasonably foreseen to be manufactured processed, distributed, in commerce, used or dispose of," in other words, any legacy uses, will not be considered. Because HBCD has been identified as a Persistent, Bioaccumulative, and Toxic (PBT) chemical, it has the capacity to remain in the environment for years after release, and legacy uses may impact background exposures, particularly for consumers, and future releases due to use and disposal. The Evaluation appears inconsistent in its handling of disposal and existing burdens of HBCD in the environment and indoors.

The HBCD problem formulation document also identifies certain exposure pathways that are under the purview of other regulatory programs, e.g., the Safe Drinking Water Act or the Clean Air Act, and states that EPA has decided to not consider these exposure pathways under TSCA. This division of purview is of concern in that, as with 1,4-Dioxane, these other exposure pathways may also affect the pathways under consideration here. As a result, the extent of overall risk from HBCD exposures assessed across all pathways will be difficult if not impossible to gauge. Several public commenters also noted this issue.[4]

For both reasons, this Evaluation is likely to underestimate exposure to both the general population and consumers. It is critically important that this risk evaluation incorporate extensive and reliable monitoring data and that the assumptions underpinning exposure modeling are carefully considered and reviewed.

---

4 Comments submitted by the Environmental Protection Network, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0019; the Environmental Defense Fund, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0024.

The Committee found Slides 7 – 11 of the EPA[5] (at-meeting) technical presentation from Dr. Wong particularly helpful in understanding the links between EPA's included uses, conditions of use, and how that leads to specific releases that expose the various considered receptors. The Committee recommended including these figures in the Evaluation document.

The HBCD problem formulation document lists many historical uses that EPA considers to be discontinued (summarized in Table 2-2 of the problem formulation) based on limited monitoring data and self-reporting by industry, and through responses (or lack of responses) to a Significant New Use Rule issued in 2015. HBCD has been essentially banned and 171 of the 183 signatories to the Stockholm Convention on Persistent Organic Pollutants have ratified their adherence to restricted use (the U.S. is not a participant, and China and India have not fully ratified) and, therefore, global production and use has decreased dramatically in recent years.

Based on Chemical Data Reporting (CDR) reporting and personal communications with industry, domestic manufacture is reported to have ceased in 2017 and one Committee member expressed that domestic production and importation of HBCD *per se* is minimal and limited to specific industries such as those needing to meet stringent flammability requirements. However, in comments provided by the Washington State Department of Health,[6] the reliability of industry self-reporting was called into question. *EPA has novel mechanisms available to request information from industry under the revised TSCA and should request import and use information from known and suspected users of HBCD within the time of the risk evaluation*.

The Evaluation lists import volumes for 2016 through October of 2018 obtained by reviewing a database containing import data (Datamyne.com) and shows 0 pounds for 2018. However, this database also lists 46,096 pounds as being imported in 2017 by one consignee, yet EPA states that Dow Chemical reported importing approximately 48 metric tons (105,822 pounds), that same year which calls into question the completeness and/or accuracy of the DataMyne database. *The Committee suggested that EPA re-query the DataMyne database to ensure imports have ceased or to account for the "missing" Dow imports.* Depending on the result, EPA may reconsider its confidence that dependence on this information as complete is a conservative overestimate.

The Committee wondered how confident EPA is that the Toxics Release Inventory (TRI) data is complete and accurate. The Evaluation points to the TRI report from 2017 as the sole source of release data – reporting 724 pounds total from four facilities. This value is used for predicting release for several scenarios. Assuming Dow was the sole user in 2017 and it processed all 48 metric tons it imported that year, the value of 724 pounds does not seem reasonable for the reported processing of approximately 108,000 pounds of material at a minimum. The Committee also noted that in addition to the two Dow Chemical sites, there were two additional reporting facilities processing an unknown amount of HBCD.

---

5 Slides presented: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0028.
6 Oral comments submitted by the State of Washington Department of Heath Office of Environmental Public Health Sciences: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0041

In the Evaluation, EPA assumes an ongoing import volume of 100,000 pounds given that is the reporting threshold for small manufacturers and EPA assumes that no small manufacturers are importing HBCD, thus EPA considers this a protective overestimate. However, confidence in the overestimate depends on the confidence of the previously described reporting values. If the import or TRI data are incomplete, then it is also possible that 100,000 is not an overestimate, particularly for near future uses. In addition, it is possible that there are other existing stockpiles of HBCD. For example, Dow Chemical imported 48 Metric Tons (MT) (105,822 pounds) in 2017 and reported having a stockpile of 41 MT (90,389 lbs.) in 2018. *Is it assumed that all of this material has now been processed?*

There is also the possibility that HBCD-containing expanded polystyrene (EPS) foam is being imported into the U.S., either as part of a product or as packaging material for some products. Some of this may be due to manufacturers of EPS foam parts not wanting to maintain inventories of EPS beads; another possibility is that HBCD-containing EPS is being recycled into new parts. This is a potentially significant use, as the Alliance of Foam Packaging Recyclers reports 2016 recycling of EPS as 63 million pounds in the U.S., with a 2018 estimate of 118 million pounds. In addition, in public comments, the State of Washington provided evidence of recent findings of HBCD in consumer (children's) products. Therefore, there seems to, in fact, be some uncertainty around how much HBCD is in stockpiles, in use, or in disposal, and calls into question the EPA assumption that given almost all use of HBCD has ceased, exposures to humans and the environment from legacy uses will slowly be reduced. As a result, and as requested above, *current, ongoing and future monitoring is critical for supporting and validating EPA assumptions and modeling predictions used in this Evaluation*. EPA may also reconsider its confidence that dependence on this information as complete is a conservative overestimate.

As described above and in the Washington State Department of Health's comments, there may be some uncertainty that the assumption of import/use of 100,000 pounds per year is accurate; therefore, to address this uncertainty, it would be good to *include in the sensitivity analysis a value greater than the assumed 100,000 future use, e.g., 400,000, based on the last higher import volume for 2016.*

The Committee recommended including references in tables where appropriate and in addition, it would be helpful to include conclusions/summaries reached at the end of each section.

HBCD is a PBT chemical and most manufacturing of HBCD and production of products that contain HBCD appear to have ceased in the U.S. at this time with one small use exception. It appears likely that some HBCD-containing electronics may still be imported into the U.S. *Given this situation, the primary "condition of use" concern should be exposures from in-use products and the fate and disposal of these products after useful service life.*

The form and mode of entry of HBCD into the workplace, indoor and outdoor environment will have a profound effect on HBCD fate and transport. HBCD was until recently added into expanded polystyrene (EPS) and extruded polystyrene (XPS) insulation board as a flame retardant at ~0.5% by weight. This is equivalent to 5 million µg/kg (ppb). Thus a 1g fragment of

polystyrene foam may contain 5,000 µg of HBCD. *As a result, considerable HBCD will be transported with these plastic products, and associated debris or polymer fragments into these environments.*

The presentation by F. Corey (National Tribal Toxics Council) during the July SACC meeting showed the presence of "blue and pink (insulation) board in standing water at an unlined landfill." The presentation also described tribal concerns regarding insulation board debris and e-waste at construction and demolition (C&D) landfills and waste transfer sites. Aeolian transport of HBCD may occur in the context of plastic debris as well as via global distillation (Gouin et al. 2004), whereby semi-volatile persistent contaminants are concentrated in polar zones and resident biota over time.

Small plastic fragments (microplastics) <0.5 mm, including polystyrene and associated additives such as HBCD, have been found in drinking waters and in environments all over the world. These findings have raised concern among environmentalists given the risks to human health are not well known. This pathway of exposure is not covered in the HBCD Evaluation and the term "micro-plastics" appears only once (see page 331). "Dust" is discussed multiple times in other sections of the Evaluation, largely in industrial/occupational contexts and, to a lesser extent, in indoor residential exposures. To have a toxic effect, much of the HBCD must move from the polystyrene or other media and reach biological receptors. Thus, consideration of its presence and behavior in such "intermediate" media is critical.

HBCD was also used at higher levels in textiles than polystyrene (both uses apparently have ceased). From the Kajiwara et al. (2009) study on HBCD in textiles:

> "With the exception of one textile sample, HBCDs were detected in all the samples analyzed, with concentrations ranging from 22,000 to 43,000 mg $kg(^{-1})$ (i.e., 2.2-4.3%). "

Past European Union (EU) studies indicated that the total amount of HBCD used in textile-related processes were greater than 20% of that used in polystyrene but such processes released three times greater amounts of HBCD to waste waters. Estimated HBCD releases in 2007 were 350 kg/year for insulation boards versus 1,197.5 kg/year for textile coatings (Table 7 of Posner, Roos and Olsson 2010).

Page 39 indicates: "Based on the information provided in the Problem Formulation, EPA has determined that these discontinued uses are not included as a condition of use." This decision is problematic as some HBCD-treated textiles, as well as treated high impact polystyrene (HIPS) products remain in use in U.S. homes, vehicles and businesses, or have been disposed of properly or improperly, and thus serve as a source for human and wildlife exposure. This HBCD contributes to the existing and future sediment and biota HBCD concentrations.

Recent studies (e.g., Jang et al. 2016) have also detected the presence of HBCD in polystyrene products expected to be flame retardant-free. These include fishing floats and material packaging. HBCD levels up to 5160 µg/kg lipid weight were detected in mussels inhabiting the surface of polystyrene floats.

Other HBCD environmental exposure sources of significance include polystyrene insulation board lost during natural disasters such as the 2011 Japanese tsunami. Large amounts of polystyrene board later washed up (and much remains) on Northwest United States and Canadian shorelines (Rosen 2013). If not removed it will weather and fragment into microplastics.

During the EPA Voluntary Children's Chemical Evaluation Program (VCCEP) examining human exposures to PBDE flame retardants (using similar Kow's considering use as polymer additives), results were initially presented to the VCCEP Panel using model estimates and based on the assumption that industrial workers are the most exposed. Later it was found that the greatest exposure was to children from residential indoor dust from household products treated for flame retardancy. This new understanding was revealed through analysis of newly acquired human tissue and indoor dust levels. From this the Committee noted that lack of data regarding bioavailability, form and levels of HBCD (or any other toxicant) in the environment and in humans, can lead to the wrong conclusion. Care must be exercised when coming to conclusions regarding the extent of HBCD (or other toxicant) exposures when there are little data to support assumptions.

---

a. Use of HBCD Bioconcentration Factors (BCF) and Bioaccumulation Factors (BAF)

Field measured HBCD BAF values in upper trophic level fish from heavily industrialized areas of China (He et al. 2013, Wu et al. 2010) and laboratory BCF values from edible portions of rainbow trout from (Drottar and Krueger 2000) were used to estimate potential human and wildlife exposure through fish ingestion. BAFs were preferentially used because they represent exposure to the chemical through aqueous and dietary pathways. The BCF study was selected to supplement the estimations because it was a guideline study conducted on an upper trophic level edible species.

Q 3.1	***Please comment on the use of field measured BAF values for upper trophic level fish from (He* et al. *2013) and (Wu* et al. *2010) for use in assessing human or wildlife exposure via fish ingestion.***

Response (*Recommendations in italics*):

It is generally logical to expect that upper trophic level fish (as well as other upper trophic level wildlife, such as otters and birds of prey) will exhibit higher burdens of persistent, hydrophobic contaminants than lower trophic level organisms; a phenomenon known as biomagnification. However, in the citations used in the Evaluation, some lower trophic level organisms exhibited higher burdens. This is discussed further in Question 3.3 below. *Caution should be exercised in focusing solely on higher trophic fish species such as the snakehead*.

Field-measured Bioaccumulation Factors (BAF) are cumulative factors derived from

measurements of tissue and ambient water concentrations. BAFs thus incorporate multiple routes of exposure, such as sediment or food ingestion, as well as aqueous exposure. There are, however, many issues with BAF estimates.

Wild fish collected for a BAF determination are mobile organisms. Thus, they may not reflect HBCD concentrations at the actual site of capture or of water sampling for HBCD concentration determination. In such studies, the duration of the HBCD exposure is unknown and the organisms sampled may not have reached steady state with respect to HBCD accumulation. Additionally, individual HBCD contributions from food, plastic debris, water or other exposure paths are uncertain; as is the extent of biotransformation. As HBCD sources are typically not known, or multiple possibilities exist in an area, identification of condition of use may be difficult to establish.

HBCD is very hydrophobic and hence dissolved water concentrations will be low. Measured values of hydrophobic organic chemicals in the field will likely encompass contributions that may be associated with colloidal or very-fine particles or show facilitated solubility due to the presence of dissolved organic matter. These associations may affect their bioavailability and toxicity (Mezin and Hale 2004a, 2004b).

An HBCD water solubility of 66 µg/L is identified in the Evaluation. This appears to be derived by summing the solubilities of the three individual diastereomers. *A concern expressed by the Committee was the limited measurements available for this critical parameter.* Subsequent fate/accumulation modeling utilizes this solubility value and incorporates no estimate of variability. Low HBCD water concentrations (low ng/L) are quite difficult to measure accurately. In fact, Table 1 in The Binational Strategy for Hexabromocyclododecane (HBCD) Risk Management (2017) provides an "average" water solubility for the three diastereomers of 0.0034 mg/L (or 3.4 µg/L), 20-fold lower than the value proposed in the Evaluation. In addition, a value from a low of 1.76 to a high of 65.6 µg/L were also observed in Posner et al. (2010). Hence, the estimated concentration in water, which is entered as the BAF denominator, presents a source of uncertainty. The three diastereomers (alpha, beta, and gamma) are present in varying abundances in the HBCD technical mixture, as well as in environmental media and show differences in water solubility and hence may have differing environmental fates. Being hydrophobic, most HBCD released to aquatic environments will associate with organic matter (including microplastics) and not be freely dissolved in water.

The dominant condition of use of HBCD is in polystyrene products. Therein, HBCD is not chemically reacted with the polymer, but its migration/release is reduced by the viscosity of the polymer. This influences HBCD bioavailability. Fragmentation of polymer into microplastics will increase polymer surface areas and enhance HBCD migration over time (e.g., Rani et al. 2017). The bulk of HBCD will remain in polystyrene insulation until demolition of structures. Thereafter, some polystyrene debris will be lost to the environment or transferred to landfills, which themselves may release HBCD in unknown amounts. Losses of HBCD-treated polystyrene may also occur at construction sites. In addition, polystyrene board has been readily available to ordinary citizens from hardware stores. Its use, misuse and disposal by these

individuals has also resulted in release and exposure to HBCD.

Sorption to ambient particulate organic matter, presence in (micro-) plastic debris and association with dissolved organic matter will reduce apparent HBCD bioavailability. Commonly applied analytical methods (e.g., organic solvent extraction at elevated temperature) do not differentiate the highly bioavailable "dissolved" HBCD fraction from these less bioavailable pools. Hence, the calculated BAFs may be in error.

The BAFs from He et al. (2013) and Wu et al. (2010) have merit for use in estimating (but with unknown certainty) human or wildlife exposure via fish ingestion. However, they involve only two sites and are from samples obtained from a foreign country (southern China), with attendant environmental (e.g., temperature, organic carbon characteristics) and anthropogenic differences (e.g., conditions of use, waste disposal, regulatory restrictions) from the U.S.

The source and form (e.g., polymer/HBCD association) of the HBCD in the Chinese environments in question may not be representative of that commonly occurring in the U.S., where most HBCD has been employed in polystyrene insulation board (the major focus of the Committee's discussion). In contrast, China produces considerable amounts of textiles and electronics, which may contain, or might have in the recent past contained, HBCD. In fact, samples from the Wu et al. (2010) study were taken from a "natural pond in an e-waste recycling site." EPA might find the Zhu et al. (2017) study useful.

In terms of e-waste sites, a large percentage of the HBCD therein might be associated with High Impact Polystyrene (HIPS) (a dense plastic) or electronics solder/flux. Note that the Evaluation states (page 37) that a single U.S. company (Indium) employs HBCD in making solder flux. The material is exported "to their overseas facilities for the final mixing step and for sales to electronics manufacturers in China and the United States." The presence of HBCD within solder, textile/latex back-coating and HIPS matrices would result in different bioavailabilities and hence BAFs from what might be seen with polystyrene-associated HBCD.

He et al. (2013) also notes that tissue HBCD levels in the fish they sampled in China were ~10% those reported in a U.S.-based study by Chen et al. (2011) and in some European studies. The concentration differences might also impact estimates of accumulation and therefore the BAF estimates. *The Committee considered the use of BAFs from these two China-based studies as not optimal, but unavoidable given that data for both ambient water and tissue in U.S. fish are lacking.*

Greater comparison ("ground truthing") of predicted concentrations with existing data on different media (tissue, sediments, etc.) would be insightful. Some of this is done with field residue data and some are discussed in later sections of the Evaluation and some in Appendix C. However, pertinent data are not always referenced in the body of the Evaluation.

Q 3.2	**Please provide any specific suggestions or recommendations for alternate approaches that could be considered for accounting for bioaccumulation of HBCD into food webs/diet of humans or wildlife.**

Response:

Modeling of HBCD bioaccumulation into food webs as described by EPA has value. However, this is an "indirect" approach, producing an estimate based on multiple assumptions and dependent on the scenarios considered. This approach presumes adequate knowledge of the form of the contaminant (i.e., degree of polymer association). As noted above, extremely low water concentrations are also difficult to measure analytically. HBCD is highly bioaccumulative, with Kow's comparable to other established, problematic chemicals such as PentaBDEs.

Availability of field monitoring data as both wet and lipid-based allows estimation of possible human and wildlife exposures. Some (human) cultures consume different tissues, species and quantities of seafood. Human consumption may include finfish, shellfish (such as mollusks or crustaceans), birds or mammals (e.g., seals, whales or bears). The different life histories of these organisms may result in varying HBCD exposure and accumulation. Unfortunately, only a modest amount of data exist (although some have been published; e.g., Chen et al. 2011) on HBCD concentrations in U.S. aquatic biota. Discussion of such data, in comparison to predicted model outputs would be useful. At a minimum, Section 2.3 should reference later sections (e.g., Section 3.1) of the Evaluation where such data are more completely described. Additional North American data may be extracted from the "Binational Strategy for HBCD Risk Management"[7] and the "AMAP 2016: Chemicals of Emerging Arctic Concern"[8] reports (Artic Monitoring and Assessment Programme 2017).

The EPA conducts periodic large-scale fish tissue and sediment monitoring studies. These include fishes from U.S. lakes, rivers and coastlines. Regrettably, HBCD does not appear to have been included as an analyte in these efforts. However, archived tissues or sediments may still be available and, if so, could be analyzed to provide a more complete picture of HBCD residues in these media. Analytical methods and analysis capabilities to accurately measure HBCD are improved and more widely available than 10 years ago. However, HBCD analysis is more specialized than for other persistent organic pollutants, such as PentaBromoDiphenylEthers (PBDEs) and polychlorinated biphenyls (PCBs). HBCD analysis is generally done with liquid chromatography/mass spectrometry (LC/MS) to determine the diastereomeric ratios. LC/MS techniques also generally employ specific ionization conditions to achieve adequate sensitivity. Hence, identification/quantitation of HBCD by reviewing existing instrument data files may not be possible. Gas chromatography mass spectrometry (GC/MS) utilizes high injection or column elution temperatures and hence diastereomer ratios typically are altered.

Bioconcentration factor (BCF) estimates from laboratory-based studies also have merit. Such laboratory studies allow for control of the mode, duration and composition (e.g., diastereomers)

7 https://binational.net/wp-content/uploads/2018/03/HBCD_Strategy-December-19-2017-FINAL.pdf
8 https://www.amap.no/documents/doc/AMAP-Assessment-2016-Chemicals-of-Emerging-Arctic-Concern/1624

of chemicals to which fish (or other organisms) are exposed. However, BCF calculation requires reliable and consistent water exposures and these may be difficult to achieve due to the hydrophobicity of HBCD. The Drottar and Krueger (2000) study cited in the Evaluation shows considerable variability in HBCD water concentrations over the course of the study, and measured water concentrations were about 53% of nominal/targeted values. It should be noted that this and several of the other studies cited (some externally peer-reviewed and published, others not) were conducted on the behalf of the flame-retardant industry.

The fact that HBCD exists as three diastereomers outcomes and interpretations. Commercial/technical HBCD formulations are dominated by gamma HBCD, but ratios may be altered by thermal processing during polymer product fabrication. Additionally, the diastereomers exhibit different physical properties including the potential for biotransformation in higher biota and biodegradation by microbial consortia. This results in different accumulation and toxicological potentials.

Q 3.3	**Please also comment on the use of the BAF data from Chinese predatory fish species to address human exposure via fish ingestion.**

Response:

Wu et al. (2010) analyzed only six samples of snakehead fish from an e-waste impacted pond in southern China. Total HBCD concentrations (mean 187 ng/g lipid wt.) in Chinese snakehead were about 10-fold less than in riverine fish collected in the U.S. by Chen et al. (2011). Chinese mud carp concentrations (n=12; mean 868 ng/g lipid weight) reported in the Wu et al. (2010) study are actually higher than in the predatory snakehead. The mud carp's diet is dominated by consumption of soft sediments (Bowen et al. 2006). This may have led to their greater exposure to sediment associated HBCD. Prawn levels (395 ng/g lw, n=7) were also higher and more reproducible (lower coefficient of variation (CV)) than snakehead concentrations. Additionally, the relationship between concentrations and trophic level for total HBCD was not found to be statistically significant (p=0.12) by Wu et al. (2010). These data demonstrate that selection of BAF for the snakehead is neither protective of human health nor ecological receptors.

Documenting the importance of "non-industrial" HBCD sources to the environment, Chen et al. (2015) observed HBCD in sewage sludge and local biota near the U.S. McMurdo Antarctic research facility, where no HBCD or HBCD product manufacturing occurs (i.e. HBCD apparently arose from products used inside the research base):

> 'Near McMurdo, maximum ∑HBCD levels in surficial marine sediments and aquatic biota (invertebrates and fish) were 2350 ng/g (total organic carbon basis) and 554 ng/g lipid weight, respectively.'

The Antarctic biota accumulated HBCD concentrations that were several times greater than the snakehead concentration reported by Wu et al. Interestingly, the highest HBCD concentrations

detected by Chen et al. (2015) were in invertebrates (sponges), not high trophic level fishes. Sponges are filter feeders and may have captured and retained polymer products with a high percent HBCD levels therein. The commonly used organic solvent extraction procedures employed here would not have differentiated microplastics entrained in the sponge and from that present inside the organism's tissues proper. The concentration reported by Chen et al. (2015) in "pristine" Antarctic biota exceeded the concentrations reported in the e-waste-pond inhabiting snakehead fish reported by Wu et al. (2010). Hence, "high trophic level" fish is unlikely to exhibit the greatest HBCD burdens.

In the He et al. (2013) study, highest total HBCD concentrations were reported in "*Plecostomus* (suckermouth catfish)." While this species exhibited a greater calculated trophic level than tilapia or mud carp, it is commonly known as an "algae eater" in the aquarium trade. It may be better classified as a detritivore. He et al. (2013) described the HBCD sediment concentrations at their Chinese sites sampled as "remarkably low" compared to European levels. HBCD may be present in sediments but would contribute to low water concentrations if still contained within microplastics. Consumption of HBCD-containing microplastics could result in unexpectedly high BAFs (depending on bioavailability), if the latter are deduced from measured water concentrations.

Note that He et al. (2013) and Wu et al. (2010) both examined fish fillets versus whole fish. However, calculation of lipid-based concentrations likely compensates for lower amounts of HBCD in fillets compared to whole fish (inclusive of internal organs).

---

b. Selection of HBCD Environmental Half-Lives for use in Draft Risk Evaluation

A wide range of degradation half-lives have been reported for HBCD in aerobic and anaerobic soil and aerobic and anaerobic sediment and were reviewed for the draft Risk Evaluation Table 2-1, Section 2.1.3, Appendix C1, Appendix C3. The selected half-lives (Table 2-2) were used as inputs to environmental and human exposure models. Three studies addressing five biodegradation endpoints were used to derive half-lives and were selected based on the relevance of the biodegradation studies to the environmental compartment HBCD is expected to be released or partition to, i.e., water, aerobic soils and sediments.

Q 3.4	**Please provide any specific suggestions or recommendations for alternate approaches to derive media specific degradation half-lives for use in exposure assessments from data sets where values for the same environmental fate endpoint (e.g., biodegradation half-life in aerobic soil) vary widely.**

Response:

As noted above, in the environment, much HBCD should still reside within polystyrene (or other polymeric) products into which HBCD was incorporated by the manufacturer and resulting product fragments (e.g., microplastics). In such a scenario, HBCD degradation rates would be expected to be much slower (being sequestered within the polymer matrix) than if freely dissolved or adsorbed to the surface of natural particles (e.g., sediments). The fate and half-lives of such polymeric fragments themselves are yet undetermined, but polystyrene persistence in the environment will depend on prevailing conditions but is believed to be measured in decades or longer. Likewise, extended contact of HBCD with sediments or soil may result in an increasing non-bioavailable (thus persistent) fraction. Degradation studies in the laboratory may show variations over time as acclimated microbial populations wax and wane. Pre- or chronic exposure to HBCD or to structurally similar compounds may also affect degradation rate. This complicates the calculation of a realistic half-life in the environment.

The Evaluation notes that several partially debrominated HBCD degradation products resulted from anaerobic sediment degradation. Fate and effects of these degradants merit investigation. Without corroborating data, such degradants cannot be assumed to be less toxic than HBCD. Further, if these transformation products are more bioavailable (and they are likely to be) then they may be more toxic than the parent HBCD. In terms of HBCD in wastewater sludges and degradation in soils, the data in Venkatesan and Halden (2014) should be considered.

The wide variations in abiotic and biotic characteristics of soils make derivation of HBCD half-lives a daunting problem. The best approach is to measure kinetic coefficients in several soil types (or other appropriate media). Modeling approaches require calibration with data from a range of soil types. More robust evaluation would also include testing at three or more environmentally relevant temperatures. To address this need, it would make sense to select soil types that are present in areas where manufacturing or end-product disposal is most likely. In the absence of such data, selection of the longest half-life estimate (or 90th percentile of media specific half-lives) is one approach that would be cautionary and more protective. There are also procedures to use an estimated mean and standard deviation combined with a reasonable distributional assumption to compute an upper 90th or 95th percentile confidence bound for half-life. It is possible to use information from surrogate polybrominated organics to inform modeling efforts if in addition the soluble/available fraction of the surrogates and HBCD could be determined. This would involve estimates using Kd or Koc. For example, PentaBDE (a polybrominated diphenyl ether commercial product) contains congeners with similar degrees of bromination and Kow's to HBCD, but the PentaBDEs are based on an aromatic (phenyl) structure.

Models that utilize parameter values (specifically degradation half-lives) estimated from other models have significantly high uncertainties and often produce unreasonable results. It may be argued that taking the more conservative and defendable approach of using worst- (or near-worst) case measured half-lives provides greater certainty that false negatives are not driving the TSCA risk assessment process. The Committee noted that other halogenated chemicals such as

PCBs and chlorinated insecticides that had been banned for decades are still circulating and detectable in the environment. However, there is a notable difference, in that the C-Cl bond is stronger than the C-Br bond. In summary, the Committee concluded that the HBCD half-lives chosen by EPA (see page 68: 2 to 6 months for aerobic soils and 11 days to 4 months for aerobic sediments derived from the Industry-sponsored Davis et al. studies (2005, 2006, 2009) are insufficiently conservative.

Recommendations:

- Evaluate how uncertainty in HBCD water solubility and other variables that form the basis of models impact the uncertainty in exposure estimates.

- Consider the long in-service lives and long environmental half-lives of HBCD products as a major HBCD legacy environmental deposit reservoir and incorporate this source of HBCD persistence in the assessment of exposure pathways.

- Incorporate exposures from imported products as a source of new HBCD introductions to the U.S.

- Rather than extrapolating bioaccumulation based on laboratory BCFs or field-derived BAFs alone from two Chinese studies, EPA should acquire more needed data by adding HBCD to the analyte list of major, existing monitoring programs; e.g., its National Study of Chemical Residues in Lake Fish Tissue, National Rivers and Streams Assessment Fish Tissue Study, National Coastal Condition Assessment/Great Lakes Human Health Fish Tissue Study[9]. The Great Lakes Open Lakes Trend Monitoring Program[10] may also be a source of data and opportunity. The possibility exists that archived tissue samples may be available from the above programs that could then be analyzed to determine contemporary biota burdens of HBCD.

HBCD analysis capabilities have improved and become more available over time. The EPA could also collaborate with the National Oceanic and Atmospheric Administration (NOAA) on its Status and Trends Program. Some elements of that program have already added HBCD to their analyte list.

- BCFs estimated using Canadian data, where available, would be more appropriate to this Evaluation than those derived using the Chinese data.

- Follow-up on intermediate degradation products in terms of properties and toxicity is indicated.

9 https://www.epa.gov/fish-tech/studies-fish-tissue-contamination
10 https://www.epa.gov/great-lakes-monitoring/great-lakes-open-lakes-trend-monitoring-program

Recommendations on Evaluation text:

- Add to Section 2.1: "Considerable amounts of polystyrene board may be lost or improperly discarded directly into the environment. The General Public typically considers polystyrene board to be harmless and handles and disposes of it without thought for its potential to contaminate the environment. For example, such board (included recycled material) has been used in arts & crafts, and even for insulation in beehives (see for example www.youtube.com/watch?v=egix-XrxDKk)."

- Add to Section 2.1.2, Table 2.1: Introduce a new property "Photolysis and hydrolysis" with value "HBCD is an acknowledged high production volume, PBT chemical. Estimation of HBCD photolysis and hydrolysis seems to be an unnecessary and possibly problematic shortcut as these tests are fairly straightforward."

- Add to Section 2.1.2, Table 2.1, last line, include the BCF value for whole fish—to in the value text, given it is likely what wildlife consume the whole fish. Indicate in the text if these BCFs are calculated on a wet weight or lipid basis.

- Note in Sections 2.1.2.2 and 2.1.2.3 that the presence of HBCD with the polymer matrix (e.g., polystyrene) will drastically alter fate.

- Add to Section 2.1.2.4: "WWTP removal processes will be a function of treatment steps applied. Some U.S. WWTPs (e.g., San Diego, as well as several facilities discharging in Maine and Alaska) receive waivers to practice less stringent treatment and thus may have lower HBCD removal rates than described in the Ichihara et al. (2014) citation. "

- Add to Section 2.1.2.4: "The density of polystyrene itself ranges from 0.96 to 1.04 (g/cm^3). This is close to neutral buoyancy. Therefore, its removal during wastewater treatment may be straight-forward. Biofilm formation on the surface of fragments and flocculation may facilitate sinking and removal in the solids. Voids in polystyrene foam will cause it to float and allow removal by skimming, but fragments may become waterlogged over time."

- In Section 2.1.2.6: In reference to the EPA cited Lindberg et al. (2004) study showing only 150 to 250 ng/g lipid in Swedish falcons, Guerra et al. (2012) observed a maximum level ~100 times higher in Canadian falcon eggs.

- In Section 2.1.3, paragraph 3: Provide specific supporting reference(s) for the statement "Half-lives estimated from studies ranged from days to greater than 6 months."

- In Section 2.1.3, paragraph 3: Provide references for the statement "…environmental monitoring showing the presence of HBCD in dated sediment cores it can be concluded that HBCD is persistent in the environment."

- In Section 2.1.3, paragraph 7: Provide references for the statement "…the reported dissolved HBCD concentrations in Chinese water bodies were in the range of 0.04 to 0.06 ng/L. These are about an order of magnitude lower than the range of dissolved HBCD surface water concentrations reported in surface water monitoring studies."

- In Section 2.1.3, paragraph 7: Provide references for the statement "Using available data, an upper trophic level lipid normalized field measured BAF (northern snakehead) was selected for use as a surrogate species for the fish ingestion exposure assessment."

- In Section 2.1.3, paragraph 7: Provide references for the statement "the limited number of species and field conditions add to uncertainty associated with the use of these BAFs in estimating human exposure to HBCD via fish ingestion."

- Add to Section 2.1.3, last paragraph, add discussion on the issue that alternatively, the simplest, approach may be to use field measurements in fish via EPA Lake, River & Streams Programs. However, at present HBCD was not included in the analyte list of these programs. Residual tissue aliquots may have been stored.

- In Section 2.1.3, page 70 EPA identified two BCF studies and two BAF studies on HBCD. BAF studies are preferred over BCF studies because they represent exposure of the organism to HBCD via all routes, including diet which is important for a hydrophobic chemical such as HBCD.

Question 4: Environmental Release (Section 2.2 of the Draft Risk Evaluation)

EPA used a combination of estimation methods and approaches to estimate releases for the various conditions of use (COU). Key environmental release data and data sources that informed the assessment of environmental releases include: release data from the European Communities' HBCD risk assessment reports, U.S.EPA Toxics Release Inventory (TRI) data, and Organization of Economic Co-Operation and Development Emission Scenario Documents (OECD ESDs) and U.S.EPA Generic Scenarios (GSs).

Q 4.1	**Please comment on the methods and approaches used for environmental release estimation.**

Q 4.2	**Please provide any specific suggestions or recommendations for alternative data sources, or estimation methods that could be considered by the Agency for conducting environment release assessment.**

Response:

The Committee indicated that reference to the ban on HBCD use as listed in the Stockholm Convention on Persistent Organic Pollutants (POPs) provides a false sense of security that production and use of HBCD will decline in the future. The Committee noted that the largest two economies in the world, the U.S. and China, are not bound by the Stockholm Convention on POPs. It appears that China has only agreed to the provisions for Hong Kong and Macao. It also appears that India has not agreed to these provisions. This is important and necessary contextual information to state if the current text regarding a HBCD global ban is included.

Several uses (conditions of use) brought up by public commenters and in discussion by the Committee do not appear to be included as use categories. Specifically discussed are conditions of use involving demolition and disposal which are modules in the conceptual model. The removal of HBCD from domestic product manufacturing suggests that inputs from disposal may constitute a significant input to the environment.

According to the phase-out information provided in the Evaluation, it is unclear how "condition of use" and current risks are related. Clearly, when HBCD is used or present during use of materials containing HBCD, there is apparent risk to ecological receptors. Consequently, it is unclear whether this constitutes a cleanup issue rather than a "use" issue.

Releases from many known sources of HBCD seem to be missing in the Evaluation. This omission is expected to lower exposure estimates and thus underestimate risk. If there is continued use of HBCD or presence in building materials, there is significant uncertainty in the movement and breakdown of disposed materials from soils and in particular from landfills into air and waterways (particularly oceans). Using a multimedia fugacity model, Tomko and McDonald (2013) showed that leachate from landfill and recycling facilities in Canada clearly moved into environmental media. They found that much of HBCD is lost to the atmosphere, but

measurable concentrations can be found in soil and sediment from locations with a history of recycling electronics. They conclude that the HBCD released from this source has the long-term potential to affect agricultural crops and surrounding ecosystems.

Without data, emissions scenario documents (ESDs) or generic scenarios (GSs) for plastics (see Section 2.2.1) cannot be used as surrogates. Use of ESDs or GSs in lieu of data represents another source of uncertainty that should be discussed, particularly for the demolition and disposal of polystyrene derived foam. Studies discussing the presence of HBCD in an expanded polystyrene (EPS) include Mi et al. (2017), and release of HBCD as discussed in an EPS in Manviri et al. (2017).

The Committee expressed concerns that there is no evidence to back up the statement on page 24 that "It is possible, however, that smaller processors may still be using the chemical, although evidence of this has not been found and EPA has not received information that this is occurring." The opposition to the Evaluation by industry groups suggests that not all manufacturing is transitioning to other chemistries, as assumed in the Evaluation. The Committee recommended that EPA actively seek use information from all potential pre-Stockholm convention users or assume that at least a sizeable fraction of pre-Stockholm convention users is importing 25 to 100,000 pounds per year. Perhaps a Significant New Use Regulation (SNUR) covering all uses would help fill this information gap. Data on imports of insulation foam should be obtained and incorporated in use estimates.

The magnitude and scope of releases assumed in the Evaluation are too constrained. After heavily relying on the EU 2008 report for some data, much of the remaining data and estimates are omitted or ignored. For example, ignored are measured releases reported in the data of 22 mg/g (dry weight) and 67 mg/g (dry weight) for solids in landfill leachate. The Committee considers that a scientifically defensible evaluation requires considerations of these releases and all other types of releases from materials actively in commerce or actively being disposed that contain HBCDs.

On page 80, the EPA states that they have medium to high confidence in the release estimates provided in Table 2-7; however, differences between disposal of transport bags and dust releases are exactly one order of magnitude. The Agency needs to support this assumption that would justify its medium to high level of confidence. This could be accomplished with a footnote to the table.

Recommendations:

- Consider disposal of polystyrene and other plastic components impregnated with HBCD in the analysis of environmental exposure routes and as Solid Waste Disposal activity/uses in the conceptual model for environmental releases.

- Consider leachate from landfills a source of input to the environment and as Liquid Waste uses in the conceptual model for environmental releases.

- Implement procedures to require manufacturers and users to provide the data on activities, uses, emissions, and disposal needed to perform a robust risk assessment.

Question 5: Occupational Exposure (Section 2.4.1 of the Draft Risk Evaluation)

Workers and occupational non-users may be exposed to HBCD when workers perform activities associated with the identified conditions of use. These activities include the following:

- *Handling of HBCD during repackaging or during transfer to storage or process vessels*
- *Machining and shaping of HBCD-containing XPS/EPS foam at industrial sites*
- *Cutting or breaking HBCD-containing XPS/EPS foam at construction and demolition sites*
- *Handling of small transport containers of solder/flux paste containing HBCD*

Approaches for estimating occupational exposure include use of monitoring data and modeling, including methods used in EPA's TSCA New Chemicals Program. Key data and data sources that informed the occupational exposure assessment include monitoring data reported in the European Communities HBCD Risk Assessment Report, data from the Bureau of Labor Statistics (BLS), Organization of Economic Co-Operation and Development Emission Scenario Documents (OECD ESDs) and U.S.EPA Generic Scenarios (GSs).

Q 5.1	**Please comment on the estimation methods and approaches used for occupational exposure assessment**

Q 5.2	**Please provide any specific suggestions or recommendations for alternative data, or estimation methods that could be considered by the Agency for conducting occupational exposure assessment.**

Response:

In general, the Committee agreed that approaches, methods, and rationale for occupational inhalation exposure estimation are described clearly and presented well in summary tables; Table 2-60 is particularly useful.

The Committee also agreed that, given the stated particle size of HBCD dust (excluding the finest grade, which is not used in the U.S.), the assumption that particles will deposit in the upper and ciliated airways and then be ingested is reasonable; very few of these particles would be expected to reach the lower respiratory tract. However, the Committee considers the assumption stated on page 178 that "…all inhaled particles that are not respirable are deposited in the upper respiratory tract" and "all inhaled particles are either absorbed in the lung or in the intestine after ingestion" and on page 352, "It is assumed that any inhaled particulate would either be absorbed through the lungs or swallowed and subsequently absorbed in the GI tract" not to be supported by the data (discussion not found in Section 4.2.1 as indicated on page 178, but in Section

2.4.2.5). *There is no supporting information as to why particles of this composition and size can be absorbed into the lung either passively or actively.* Additionally, EPA should consider that HBCD-containing foam particles are porous and hence have a larger effective surface of potential contact with lung lining fluid than the solid HBCD beads of similar size. Although leaching of HBCD into lung fluid is likely minimal due to HBCD's physicochemical properties, the large surface area of potential contact could result in more than minimal total leaching of HBCD from the foam particles into the lung lining fluid and partial absorption into the systemic circulation. These concerns are also relevant for Question 11.

The Committee agrees that occupational non-users (ONUs) would likely have lower exposures than workers. However, this may not be the case for some types of work where workers may be performing different tasks in close proximity to primary operations, with only some of them directly in contact with HBCD-containing materials. An example would be installation or removal of building materials in enclosed construction spaces where different categories of workers may be performing a variety of tasks, but all are exposed to the dust generated by some workers cutting insulating foam panels. At a minimum, EPA should recognize that ONU's exposures could be similar to those experienced by the workers and provide examples of work sites and jobs where this may be the case.

The Committee did not reach consensus on EPA's assumptions on the dermal absorption of HBCD from beads or foam particles deposited on the skin. Some Committee members agreed with EPA's approach. One reviewer felt that the assumption that HBCD in beads or in foam particles would not be available for contact with skin (and thus absorption, because it is captured within the matrix) should be supported by data, such as HBCD migration from beads or foam into simulated perspiration. In the case of beads, some HBCD could be present on the surface if the beads are not encapsulated. Another reviewer felt that because bromine atoms are very dense, and brominated compounds tend to have high specific gravities, quantitative structure activity relationship (QSAR) techniques that use molecular weight as a surrogate for molecular size tend to overestimate the size of brominated compounds. HBCD, with a molecular weight of 646, would be about the same size molecule as a hydrocarbon with a molecular weight of under 300. HBCD therefore may be small enough to permeate skin.

One Committee member provided extensive discussion on the approach to estimating dermal absorption. Use of fixed fractional absorption to predict dermal uptake is inferior to modeling using a flux-based approach. Fractional absorption depends on loading, so the fixed-fraction-absorbed approach can easily lead to overestimation of absorbed dose at high potential dose, and underestimation at low potential dose; EPA (page 215 of the Evaluation) assumes a potential dose of 11 mg of HBCD in solder paste. At the assumed 1% HBCD content, this corresponds to 1.1 g of solder paste. At 6.5% absorption through 1000 cm^2 (both hands) over 24 hours, the apparent average flux would be ~ 30 $ng/cm^2/h$. This value is probably at the high end of the plausible range.

Dermal absorption estimates in the HBCD Risk Evaluation are dependent primarily on Abdallah et al. (2015), with Yi et al. (2016) described as supporting data. Abdallah et al. is not a strong paper due to poor mathematical analysis of the experimental data, but the raw data may still be

useful. Yi et al. does not present original data and represents a secondary report of data from Roper et al. (2007)—more of an extended abstract than a paper. The Yi et al. text asserts a relationship between particle size and fractional absorption and appears to cite Roper et al. to that effect. However, a search within Roper et al. for "particle" or for "size" reveals no use of either term. The Yi et al. paper is therefore of questionable quality and should be reconsidered in favor of Roper et al.

The human skin results from Abdallah et al. should be preferred over the cell culture results based on historical experience with the latter approach (although in this case the cell culture results are not very different).

Average fluxes through human skin (post-deposition in acetone) reported by Abdallah et al. (c. 1 ng/cm^2/h) seem plausible at first glance. Using the methodology described in EPA's Risk Assessment Guidelines for Superfund (RAGS) Part E, a similar result (i.e., ~ 10 ng/cm^2/h) can be predicted using a permeability coefficient estimated from log Kow and (adjusted) molecular weight and the solubility of HBCD in water. Additional resistance in the viable epidermis would be expected to reduce that number. The uncited Roper et al. reference finds low fractional absorption (at high load) that translates to average (24 hours) permeation of about 2.5 ng/cm^2/hour, which also aligns with the prior two estimates.

Roper et al. note the formation of a skin depot that they interpret as evidence of poor permeability of the stratum corneum. What it may instead demonstrate is that the viable epidermis should control permeation to the blood stream for a lipophile like HBCD, and that a reservoir builds up above the viable epidermis. This reservoir would be available to support maximum flux through the viable epidermis beyond the workday and making the exposure duration 24 h. The depot reported by Roper et al. is so large that it implies flux into the stratum corneum that is disproportionate to flux into the receptor fluid. This observation merits further consideration (i.e., might reflect an experimental anomaly).

The Committee agrees that mitigation approaches are well summarized. However, many members of the Committee believed EPA should place more emphasis on the limited likelihood that respiratory protection will be adopted without specific occupational exposure guidelines for HBCD (one reviewer stated that the general dust exposure limits are appropriate). Dust exposures in the construction trades (especially residential construction) continue to represent an occupational health concern because of the many small-to-medium size operators and the use of temporary (and, not infrequently, undocumented) workers. Workers in these small-to-medium enterprises may not be likely to adopt personal protective equipment (PPE) controls, so EPA's characterization of reasonable risk relying on use of PPE is not sufficiently supported by the practical realities of many workplaces. In addition, EPA's estimates of exposure to dust generated during building demolition do not rely on monitoring data but instead on the OSHA's Particulates Not Otherwise Regulated (PNOR) standard. While EPA's assessment may be conservative in assuming 100% of the dust up to OSHA's PNOR Permissible Exposure Limit (PEL) is HBCD, there is concern that demolition sites may routinely exceed nuisance dust standards and, therefore, EPA underestimates exposures to dust. The Committee recommended that EPA contact NIOSH's National Center for Construction Safety and Health Research and

Translation as a potential source of information for work practices and exposures in the construction sector that may help increase the reliability of exposure estimates.

The Committee agrees that using surrogate European data for packaging is acceptably justified and EPA recognizes most of the limitations of doing so. However, the Committee notes that the European occupational standard for the equivalent of the Particulates not Otherwise Regulated (PNOR) 8h-TWA is 10mg/m^3, lower than the U.S. OSHA PEL of 15mg/m^3 (although similar to the California (CAL)-OSHA PEL of 10mg/m^3). Consequently, occupational exposures in Europe may be controlled to meet a lower standard than in the U.S., resulting in potential underestimation of U.S. workers' exposures when basing these estimates on European occupational exposure data. The Committee recommended that EPA describe this potential source of bias in its exposure estimates and incorporate this into the analysis of uncertainties and confidence around these estimates.

The Committee agrees that EPA's approach of providing a qualitative level of confidence for the overall estimates of exposures for each Condition of Use (COU) is appropriate and should be adopted for other TSCA Risk Evaluations (REs). However, it is not clear why sometimes the same qualitative level of confidence is applied to estimates that do not appear to have the same level of reliability. For example, the same level of confidence is applied to estimates derived from actual monitoring data and from surrogate data without any clarification.

The Committee questions whether any attempt was made by EPA to obtain the original and complete data from the European studies. EPA's treatment of the summary data is satisfactory, but it is not clear whether the individual point data can be judged as not reasonably available without evidence that there was an attempt to obtain it from the authors and/or sponsors of the study. Similarly, it is not clear why EPA could not attempt to contact the authors or organization funding the European studies to get information about the treatment of lower limits of detection (LOD) values.

Recommendations:

- Provide data or other justification in support of the assumption that any inhaled particulate would either be absorbed through the lungs or swallowed and subsequently absorbed in the GI tract.
- Recognize that ONU's exposures in certain work environments could be similar to those experienced by the workers and discuss how this potentially changes ONU exposure estimates.
- Compute dermal uptake using the flux-based approach and compare results to estimates obtained via the fixed fractional absorption approach.
- Present scenarios and base final risk decisions on the assumption of limited likelihood that respiratory protection will be adopted without specific occupational exposure guidelines for HBCD.
- Describe the potential for underestimation of U.S. workers' exposures when basing occupational exposures on the European PNOR TWA of 10mg/m^3, which is lower than the

U.S. OSHA PEL of 15mg/m^3. Incorporate this discussion into the analysis of uncertainties and confidence around these estimates.

- Justify why sometimes the same qualitative level of confidence is applied to exposure estimates that are derived from monitoring data as to estimates derived from surrogate data or model results.
- Document the level of effort used to acquire the original and complete data from the European studies.

Question 6: Environmental, General Population, and Consumer Exposure (Sections 2.3 and 2.4.2 of the Draft Risk Evaluation)

> Given the identified conditions of use, both monitoring and modeled data were used for estimating environmental, general population, and consumer exposures. Key sources were identified for integrating relevant monitoring data and three tools were used to estimate HBCD in surface water, sediment, soil, and exposures to wildlife. These tools include the Exposure – Fate Assessment Screening Tool (E-FAST), Variable Volume Water Model - Point Source Calculator (VVWM-PSC), and Integrated Indoor-Outdoor Air Calculator (IIOAC). Key inputs for these exposure modeling tools come from scenario-specific processing data as well as receptor-specific exposure factors and human activity patterns.

Preface to Committee Response:

Each of the models used in this Evaluation are complex in construction and incorporate multiple assumptions. Only modeling experts can truly assess the impact on model outputs when reality deviates from modeled assumptions. The Committee expressed additional experts were needed to assess the adequacy and appropriateness of use for each model. *The Committee recommended that once EPA has utilized these models for the evaluation of several chemicals under TSCA, that a panel of modeling experts be convened to assess the conservativeness of model estimates.* That said, the Committee commented on the role of models in a tiered method used in identifying and prioritizing exposure scenarios. In addition, the Committee identified several statements in these sections of the Evaluation that require clarification and/or further justification. These are listed next:

Section 2.3.7 Sensitivity Analysis – Environmental Exposure

On Page 171: "Reported mean (67%), median (81%), minimum (-29%) and maximum (99%) values for total suspended solids (TSS) removal were reported for 39 observations. EPA considered these reported values and uncertainty in extrapolating from performance of the treatment systems surveyed in the Effluent Guidelines document to those facilities using HBCD. EPA also considered uncertainty associated with the use of TSS removal as a surrogate for HBCD removal. EPA selected 75% removal of HBCD in onsite wastewater treatment for direct dischargers. EPA is confident that some removal of HBCD will occur in onsite wastewater treatment. Higher or lower removal of HBC could occur based on the type of treatment employed and its performance optimization."

The Committee concluded that further justification is needed to support the assumption of 75% removal in onsite wastewater treatment.

Section 2.3.8 Assumptions and key sources of uncertainty in environmental exposure assessment

Page 173: "When modeling the HBCD concentrations in water and sediment, EPA did not consider the potential impact of persistence and longer-term sinks in lake and estuary environments." The Committee found this statement in direct contradiction to the understanding

that HBCD is persistent and bioaccumulative. A rationale for not including persistence and longer-term sinks in the modeling of HBCD concentrations in water and sediment should be provided in the Evaluation. *The Committee considered accumulation and long-term release of HBCD would clearly be the most directly applicable to obtaining good estimates of exposure*.

Section 2.4.2.1 Approach and methodology

On Page 221: "In this evaluation, general population is considered to be individuals who are not expected to live close to point sources (far-field) and are not expected to have HBCD-containing articles in their home, although data on the prevalence of articles containing HBCD in homes throughout the United States is not well characterized." Given the absence of data from the U.S., and the long-term wide-spread use of HBCD in household use materials, *the Committee recommended EPA provide a rationale for this assumption*.

On page 221: EPA describes exposure to the general population as "more homogenous as this group is exposed primarily to background levels of HBCD" yet page 226 states "HBCD exposures to the general population are highly variable and are influenced by both sources into the environment and degradation and removal from the environment." *The Committee recommended EPA consider re-wording one or the other to be consistent.*

Section 2.4.2.2 General population exposures from environmental monitoring and exposure factors and from human biomonitoring and reverse dosimetry

On Page 226: The 64-day half-life attributed to Aylward and Hays (2011) is a secondary citation to Geyer et al. (2004). Geyer et al. estimated a range of 23-219 days. *The Committee recommended incorporating the uncertainty of the primary reference into the risk evaluation.*

On pages 229, 237, 238, the X-axes in figures 2-2 through 2-5 require labels.

Section 2.4.2.3 Dietary exposure

Page 231: "The levels of HBCD present in these food groups are typically lower than levels detected in wild animals and in plants." *How does this finding impact the dietary exposure analyses performed?*

Page 233: The dietary exposure analysis should include consideration of dietary consumption of bottom feeding fish (e.g., catfish) which are likely to accumulate higher levels of HBCD from sifting through sediment and therefore present higher exposure risk to humans who consume them.

Page 233: EPA chose a BAF value at the lower end of the reported range. The rationale given was that the model-based dissolved surface water estimates were "generally larger" than reported values, so choosing a higher BAF with a higher water estimate would give "unreasonably high estimated fish-tissue concentrations. *Is there any data to support this assumption?*

Page 234: "EPA compared the range of reported fish-tissue concentrations from monitoring data and found the modeled fish tissue concentrations (range of modeled dissolved surface water and low-end lipid normalized upper trophic level fish BAF) to be of a similar order of magnitude.

Provide actual ranges of orders of magnitude rather than use the subjective modifier "similar."

Page 234: "Across all samples, mean HBCD concentrations ranged from ND to 22 g/kg lw in 1999-2002 samples and increased to 13 to 4,640 g/kg lw. Assuming 10% lipid, this converts to $1.3e^{-6}$ µg/mg ww to $4.64e^{-4}$ µg/mg ww." This suggests that ww concentrations may not be declining as use is declining. *How is this justified with the assumption that environmental concentrations are decreasing? This should also be factored into the discussion on uncertainties.*

Page 235, Table 2-78 and Table 2-93 on page 259: Estimated concentrations in water appear to be an order of magnitude lower than reported in Table 2-54 on page 160. *This should be checked, and differences justified if found to be correct.*

Page 242: In Table 2-80 it appears that the concentration in fish captured near the point source are lower than the high range concentration values in fish captured far from the point sources. On page 234 EPA cites Chen et al. (2011) as finding concentrations in fish captured near point sources were generally 1 to 2 orders of magnitude higher than fish captured further away from sources. *These two pieces of information need to be rectified and discussed. Further explanation of Table 2-80 needs to be added to the text.*

Section 2.4.2.4 Dust and soil ingestion

Page 246: The summary of soil concentration ranges provided in Table 2-84 appear to be different from the environmental assessment summary ranges provided in Table 2-56 on page 167. *These differences need to be explained. The references in the two sections are the same, that is Tang 2014a and Tang 2014b refer to the same paper.*

Section 2.4.2.7 qualitative exposure scenarios

Page 257: In the section labeled *HBCD sent to Landfill Across the Lifecycle*, the Evaluation implies that total releases are expected to be large for years to come. Spreading the total tonnage out over the total number of landfills likely to accept these materials brings the concentration down to the central tendency estimates derived for extracted soil monitoring data. Also assumed is that landfill releases are mitigated by coverings, liners and treatment. As mentioned in public comments,[11] this may be an overconfident assumption. For this reason, *additional uncertainty factors should be considered.*

11 Comments submitted by the Environmental Defense Fund, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0024; in oral and written comments submitted to the committee by the National Tribal Toxics Council (no docket number yet available); and the Arctic Monitoring and Assessment Programme assessment of 2016: Chemicals of Emerging Arctic Concern.

Q 6.1	**Exposure modeling tools may have different levels of screening capacity such that one might be more conservative than another given the scenario and inputs. Please comment on EPA's approach to use a tiered method for identifying and prioritizing exposure scenarios to be subjected to higher screening level modeling tools, based on their potential for risk by first using a lower screening level tool.**

Response:

Several Committee members agreed that the concept of using progressively more informative/conservative screening tools makes sense in terms of efficiency, especially in this case where the chemical is likely to partition out of the aqueous phase (the first-tier model assumes total chemical is in the aqueous phase and therefore in this case overestimates the concentration). EPA applied the more complete partitioning Variable Volume Water Model-Point Source Calculator (VVWM-PSC) only for scenarios where the Exposure Fate Assessment and Screening Tool (E-FAST) predicted exposure value that exceeded an acute or chronic hazard value. Interestingly in this case, most of them did exceed the hazard value. It is important to ground-truth these predictions with monitoring data.

The Committee found Table 2-48 helpful in understanding what data and modeling information were used.

The comments and suggestions to Charge Question 4 are also relevant to this question.

Q 6.2	**Please comment on EPA's approach to use receptor-specific exposure factors and activity patterns to estimate doses.**

Response:

In general, the Committee agreed that the approaches used are appropriate, if conservative, including the use of receptor-specific exposure factors and activity patterns in the estimation of doses.

The Committee was unable to determine if the sensitivity analysis for infant exposures by consideration of varying percentiles is valid (Figure 2-6 p. 273). *The Committee recommended that this analysis be reviewed by a statistician familiar with population exposure modeling.*

Table 2-83 on page 245: As with most exposure evaluations carried out for regulatory purposes, this Evaluation excludes soil ingestion rates by children exhibiting soil pica – a relevant susceptibility. *The Evaluation should make this explicit in the text.*

The discussion and associated recommendations related to modeling of dermal absorption for estimating Occupational Exposures also apply to General Population exposures.

Q 6.3	**Surveys have identified fish consumption rates far above those used in this draft risk evaluation to estimate dietary exposure for subsistence fishing populations. Please comment on the use of such information in estimating the contribution of fish and other aquatic life to dietary exposure to HBCD.**

Response:

The Committee concluded that to be protective and account for susceptible population, the Evaluation should consider the use of consumption rates on the high end when estimating exposures. *One Committee member recommended the EPA look at three papers by Lee et al. (2019), Cao et al. (2018), and Fromme et al. (2016) that address dietary exposure and risk management.*

Based on the physical-chemical properties of HBCD, exposure to fish by HBCD in suspended particles could represent a substantial source of exposure, particularly for bottom-feeding fish. *This exposure pathway should be acknowledged and discussed in the Evaluation.*

The Committee discussed two susceptible populations that are not adequately considered in the Evaluation, namely, high fish consumers and infants consuming breast milk. Because HBCD is a PBT, the fish consumption rates used in the scenarios are too low to protect high fish-consuming populations (Native Americans, Asian/Pacific Islanders, etc.). The breast milk pathway is identified in the Evaluation, but not emphasized and not discussed for high fish-consuming and lactating women. For example, Table 2-79, page 239 states that acute dose rates and average daily doses for fish ingestion excludes infants. *Exposure pathways for both high fish consumers and infants consuming breast milk should be discussed.*

Q 6.4	**Exposure modeling results may rely on various estimated inputs and ranges (e.g., physical-chemical properties) given the available data, which results in variability and uncertainty in the results. Please comment on EPA's approach to qualitatively characterize variability and uncertainty for exposure estimates in Tables 2-111 and 2-112**

Response:

In the Evaluation, the quantitative assessment of uncertainty and variability was presented in Tables 2-109 and 2-110. The Committee found these tables quite helpful in capturing and communicating EPA's thinking regarding contributions to uncertainty. As has been previously mentioned, *the Committee recommended that definitions or descriptions of the "High," "Moderate" and "Low" modifiers of uncertainty and variability must be provided for these tables to be truly useful*.

The Committee responses to other charge questions also addressed *issues of uncertainty and variability* and answers to these questions *may require modifications to Table 2-109 and 2-110*.

Question 7: Environmental Hazard (Section 3.1 of the Draft Risk Evaluation)

The environmental hazard of HBCD has been examined in several publications. The chemical has been categorized as persistent, bioaccumulative, and toxic. This assessment addresses HBCD environmental exposure to aquatic and terrestrial organisms and its trophic transfer potential.

The available data on field studies on HBCD toxicity are limited, as presented in the Risk Evaluation for Cyclic Aliphatic Bromides Cluster (HBCD), Systematic Review Supplemental File: Data Extraction Tables for Environmental Hazard.

Q 7.1	**Please comment on the methodologies used to evaluate potential HBCD trophic transfer in aquatic and terrestrial ecosystems.**

Response:

Models and methods used to estimate exposures and hazards to wildlife must be clear and well supported. In the Evaluation, exposures to birds and mammals are apparently based on actual, though limited environmental monitoring data. However, precise criteria and the use of models are not specifically delineated to understand whether oral dose is compared with oral dose estimates using assumptions modeled from environmental media concentrations ***or*** if environmental media concentrations are compared to modeled exposure assumptions to derive a media-screening level similarly to the process used by EPA in the development of EcoSoil Screening Levels. *The Committee suggested that the EPA provide a transparent process (an algorithm) for estimating oral dose/exposures from media concentrations and provide the process used to develop toxicity reference values for mammals and birds.*

Additionally, the process for choosing toxicity benchmarks for wildlife is not provided. It appears that a critical study approach is based on the NOAEL; however, the basis for selecting the study is not provided. The Committee recommended not to necessarily use the most sensitive study, but to employ an evidence integration procedure where studies of highest quality and relevance are utilized and fit a benchmark dose to those data, if possible, to derive a Toxicity Reference Value (TRV) (as what is done for human health). It would also help to provide a scatter diagram to help reviewers see the spread of the toxicity endpoints to ascertain corroboration of the reported outcomes.

There are many examples where concentrations in exposure media are provided. Other cases report dose. These inconsistencies in reporting exposure increases the uncertainty of the Agency's assessment. There are also many inconsistencies in units for toxicity data (ng/g-d, mg/kg-d). The Committee recommended these all be normalized to mg/kg-d. Inconsistences also

exist in the toxic endpoint being used. For example, from the Ema et al. 2008 study, it is not clear whether the thyroid or reproductive endpoint is being used. The latter would be more practical in terms of the potential for a population-level effect.

The Committee recommended the Evaluation specifically acknowledge that selection of endpoints for receptors is critical and in many cases taxon specific. For example, in earthworms, based on Shi *et al.* 2018 (listed incorrectly as Shi et al. 2015 in the Evaluation), growth was not significantly reduced, but an upregulation of superoxide dismutase (SOD) and heat shock protein (Hsp70) gene expression was observed. This suggests that a longer exposure to HBCD may result in organism-level toxicological effects. The question of how much longer an exposure would be needed remains unanswered.

The Committee reiterated that relevance of a statistically significant finding is not equivalent to a biological significant finding. The Committee wondered if significant elevation in either of these two biomarkers (SOD or Hsp70) is sufficient to produce organism-level effects. Typically, without validation, biomarkers of exposure are not equivalent to adverse effects that are relevant to the organism or population.

The Committee noted that a lack of data regarding HBCD residues in prey and predators limits the reliability of mathematically-derived predictions/estimates. Indeed, eggs from terrestrial-feeding peregrine falcons collected near Montreal, Canada were observed to contain high HBCD burdens (14,617 ug/kg/ww; Guerra et al. 2012). Similar observations of unexpectedly high levels of hydrophobic decabromodiphenyl ether (another brominated polymer flame retardant) have been observed in other terrestrial birds of prey (Chen et al. 2010).

Although clear from the published field data that HBCD may accumulate to substantial levels in some organisms, HBCD has been more rarely sought than other contaminants and the pathways of exposure remain uncertain. As noted by EPA, the diets of higher trophic level organisms are not known with adequate certainty. Compounding the issue is the fact that HBCD burdens in those prey items are also uncertain.

Further, on page 286, the Evaluation states: “Despite HBCD being found predominantly in aquatic media (e.g., sediments) … HBCD source fluxes between aquatic and terrestrial ecosystems” … emphasizing the movement of HBCD from the former to the latter. However, HBCD-containing products (wherein most HBCD resides) are used and disposed of disproportionately in the terrestrial compartment. Thus, the previous assumption may be subject to question. It may arise from the lack of sampling in the terrestrial compartment. As mentioned above, eggs from terrestrial-feeding peregrine contained high HBCD burdens (Guerra *et al*. 2012). Similar observations of unexpectedly high levels of hydrophobic decabromodiphenyl ether, another brominated polymer flame retardant, have been observed in other terrestrial birds of prey (Chen et al. 2010). These observations suggest alternative sources of terrestrial exposure, perhaps direct consumption or other contact with polymer products containing high levels of flame-retardant additive.

Some insights may be gleaned from comparisons from studies on other hydrophobic flame retardants. However, a basic premise of EPA is that HBCD release is predominantly water-borne and that manufacturing processes are largely responsible for this contamination. As HBCD manufacturing has ceased, this premise would no longer seem to be the case, if indeed it was correct to begin with. Hence more emphasis on products in use and end of life fate appears to be in order when evaluating exposures.

Specific Comments and Recommendations:

- Amphibians are an important interface between terrestrial and aquatic ecosystems. Amphibians are currently not mentioned in the Evaluation but should be discussed and justification for exclusion provided.

- Thyroid hormones are critical to an amphibian during thyroid hormone driven metamorphosis. HBCD has been shown to potentiate T-3-induced tail tip regression, the starting process of metamorphosis. The Committee recommended referring to the paper by Schriks et al. (2006).

- Sex-specific transfer of HBCD. In amphibian reproduction, fat is remobilized to be part of eggs. For instance, up to 23% of injected PCB126 can be transferred to eggs. This has gender-specific and trans-generational implication (Huang et al. 2000). HBCD is a lipophilic compound and may act like lipophilic planar PCBs. The Agency probably has limited information regarding amphibians. However, the Committee suggested that the Evaluation should discuss studies on fish and other aquatic or terrestrial species that can infer sex-specific transfer of HBCD to the offspring and its consequential effects.

- Page 279, Table 3-1: The Evaluation should list test organism species, provide greater detail on the "population" endpoints considered, and resolve issues with units on the avian MOEJ 2009 study. The MOEJ 2009 study protocol reports dosing in ppm but Table 3-1 reports dosing in µg/L where one expects to see µg/kg-day or similar units.

- Page 283 suggests exposure is based on mixed diet, but usually mass/mass not mass/vol. Paper not available in the Agency's HERO literature database.

- Page 283 Crump et al. 2010: What is the exposure pathway (units mg/L; drinking water? What was the dose mg/kg-d?)? The Committee asked that EPA provide all toxicity information in terms of oral dose The Committee asked that EPA provide all toxicity information in terms of oral dose; otherwise use the information only in a qualitative manner.

- Page 287, Table 3-2 – About 32% of the kestrel's diets in trophic transfer analysis is assumed to be Peromyscus (deer mouse). The other 68% of its diet is not discussed. The Evaluation should be specific that the remainder of dietary items are assumed to be uncontaminated and highlight this as an uncertainty for wildlife receptors.

- Page 290, Table 3-3 – The "Effect Concentration" reported in this table is not well defined, and it is unclear how the values reported would be used in assessing toxicity in birds and mammals. If these values are intended to be used as TRVs (i.e. risk based media concentrations), they should be reported as oral units of exposure (mg/kg-d). Current values seem to require a PBPK model and estimated egg loadings to be useful. Values discussed in Section 3.1.6 make more sense.

- Page 292, Table 3-5 – various concentrations are provided as concentrations of concern for birds and mammals, but it is not clear to what these concentrations refer. A column is needed to describe media and exposure regime or provide a TRV and the endpoint on which it is based. References should be included as in previous tables.

- Page 340 – The Evaluation should be specific on the endpoint that defines impaired reproduction in the female American kestrel when exposed to 3.27 ng/g ww. Comparisons are difficult if not impossible when oral doses are not universally reported in mg/kg-d as is typical for reproductive toxicity studies.

- Page 510-512, Tables G.3.1 and G3.2: In the KABAM output, the numbers of significant digits reported imply a false level of precision. Consider using two digits below the decimal for all values.

Q7.2	**What other information can be incorporated into the evaluation?**

Recommendations:

- The Committee requested the Agency to be specific showing exposure calculations, toxicity dose/benchmark evaluation and how effects concentrations are compared to environmental concentrations. This can be done in two columns in a table also integrating other receptors.
- Display derivation for TRVs, the endpoint on which they are based, and utilize diagrams (scatterplots) demonstrating variability for species within a class, when sufficient data exist to do so.
- Consider including amphibian and reptilian receptors and address the uncertainties with doing so.

Q7.3	**Please comment on the use of mammalian studies, which were evaluated using human health metrics through the Systematic Review process, in the evaluation of HBCD risk to wildlife mammals.**

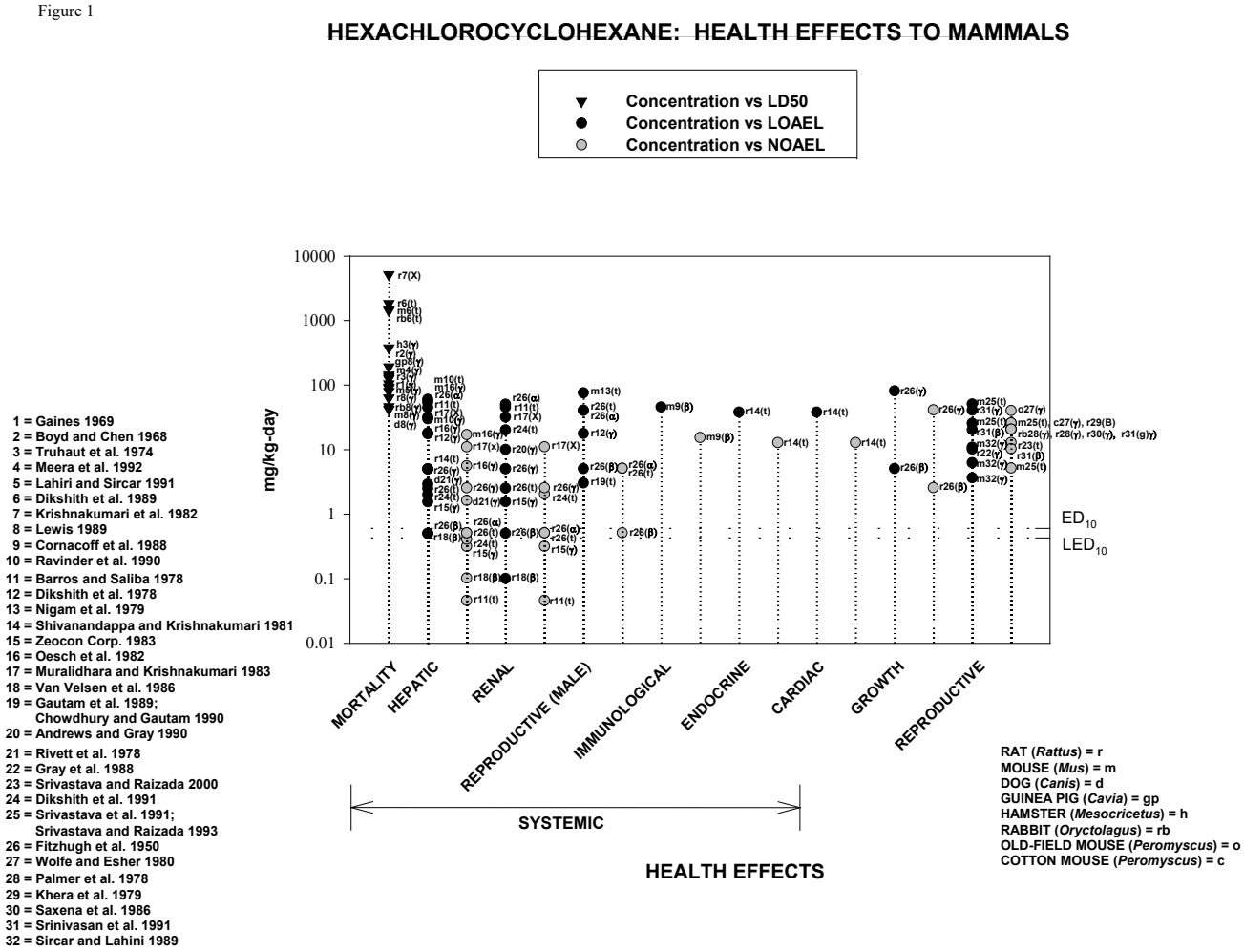
Because of the general lack of wildlife models for mammals and the abundance of rodent data for human health extrapolation, it is reasonable and not uncommon to use rodent data in assessing wildlife risks. However, the effects generally seen in syngeneic rodent models typically

occur at lower exposures than those seen in wildlife species of the same taxonomic order. This logic can be used to support the decision to not use additional uncertainty factors to extrapolate to other species within the class. The rodent models typically used in toxicity studies and those used as receptors to make decisions are often sufficiently different physiologically to potentially affect kinetics from exposure. This is the case in this Evaluation, where rodents are being used to extrapolate to mustelids (otter; mink) and quail used to extrapolate to osprey or kestrels. Differences in how gut physiology and trophic position can affect inferences on toxicity and exposure should be discussed.

The study uses, as the TRV for mammals, a NOAEL for reproductive effects, not thyroid based as mentioned in Table 4.2. Issues remain throughout the Evaluation where exposure units reported from toxicity studies are inconsistent with risk assessment requirements. As mentioned previously, units for exposure should be presented as mg/kg-d when possible. The method for choosing a TRV may be enhanced by using benchmark dose analysis to develop a POD as a TRV.

Figure 1: Example Scatter Diagram showing variation in effects for multiple species relative to oral dose and endpoint (USACHPPM. 2009. Wildlife Toxicity Assessment for Hexachlorocyclohexane. Report Number: 87-MA02T6-05C. U.S. Army Center for Health Promotion and Preventive Medicine, Aberdeen Proving Ground, MD. (Prepared by C.J. Salice, G. Holdsworth, C.A. Arenal, B.E. Sample, and W.S. Eck).

Figure 1



Question 8: Human Health Hazard (Section 3.2 of the Draft Risk Evaluation)

EPA considered the adverse human health effects for HBCD across organ systems and prioritized those that are relevant, sensitive, and found in multiple studies. The HBCD human health hazard systematic review process screened 1,890 studies and obtained 53 studies that were relevant and applicable to the PECO statement. Only two of these studies were unacceptable based on data evaluation criteria. The remaining database of 51 studies included epidemiological studies that examined associations between HBCD exposure and endpoints related to effects on the thyroid, nervous system, and female reproductive system as well as repeated-dose experimental animal studies. EPA examined dose-responses for the endpoints of thyroid effects, liver effects, male and female reproductive effects, developmental toxicity, neurotoxicity, and immunotoxicity. Data on toxicity following acute exposures, irritation, sensitization, genotoxicity, and carcinogenicity were also considered. From these effects, EPA selected endpoints supported by the weight-of-evidence for non-cancer that were amenable to quantitative analysis for dose-response assessment and identified the appropriate toxicological studies to be used for acute and chronic exposure scenarios.

In the systematic review of key studies, numerous studies were identified as ranking high in the quality review. EPA selected PODs for critical effects from two key studies: (WIL Research 2001) and (Ema et al. 2008), to carry forward for dose-response analysis and risk estimations.

Q 8.1	**Please provide comment on whether there are other comparable high-quality studies that might be recommended for further consideration for dose-response for additional critical effects and for acute or chronic exposure scenario consideration.**

Response (*Recommendations in Italics*):

The Committee identified a recent study by Rasinger et al. (2018), not cited in the Evaluation, as one that merited additional review. In this study, low dose exposure to HBCD, CD-153 or TCDD induces histopathological and hormonal effects and changes in brain protein and gene expression in juvenile female BALB/c mice. In this study, exposure was to juvenile mice for 28 days of exposure to HBCD, concentrations that are considered relevant to human dietary exposure. While not a conventional developmental toxicity study, this study demonstrates effects from short-term HBCD exposure on a susceptible life stage and the Evaluation should discuss it.

The Evaluation considers both developmental toxicity endpoints, such as reduced pup weight, and mortality (offspring loss) when estimating risks following acute oral exposures to HBCD and in subsequent estimates of risk to the general population. Offspring loss in rodents was shown to be the most sensitive endpoint.

The Evaluation states that while neonatal effects are not traditionally associated with acute exposures, the long half-life of HBCD suggests that a single exposure may result in retained body burdens for extended periods of time. Additionally, evidence from other thyroid disruptors suggests that acute or short-term exposure can result in thyroid hormone effects (Paul et al. 2010; Hedge et al., 2009; Zhou et al., 2001), including in weanling rodents, and this may result in downstream effects on developmental endpoints. The Evaluation considers both endpoints relevant for estimating risks following acute general population exposures. *The Committee agreed with this appraisal*.

Ema et al. (2008) reports on a two-generation reproduction study in Sprague-Dawley CD rats with HBCD given at 0, 150, 1500, and 15,000 ppm in diet. F0 and F1 follicle size decreased, and T4 was increased in F0 females at 1500 and 15,000 ppm; thyroid weight was reduced at these doses and liver weights increased. In F2 offspring, viability was reduced at 15,000 ppm. Body weight was initially increased then decreased in F1 progeny at 1500 and 15,000 ppm. There was delayed eye opening in the F1 at 1500 ppm (in males and females) but not at 15,000 ppm. In F2 offspring, eye opening was delayed in males and females at 1500 and 15,000 ppm. In addition, F1 male progeny had faster righting times, whereas females had longer times at 15,000 ppm. These opposite effects at the same dose are not likely to be reliable. No effects were found on 1-hour open-field activity. In the Biel water maze, 1500 and 15,000 ppm HBCD exposed males had shorter latencies, and at 15,000 ppm made fewer errors on the third test day (out of 3 days of testing when given 3 trials/day).

Ema et al. (2008) used multiple one-way ANOVAs done separately on males and females. A better approach would include a 'Dose x Sex' interaction term in a two-way ANOVA. This approach allows testing for a possible treatment 'x' sex interaction effect, and results in more sensitive statistical tests overall. The mid-dose female-only "air right effect" was not dose-dependent and unlikely to be reliable. Shorter Biel maze latencies and errors on day-3 of the test in the 15,000 ppm group may represent a sporadic effect and should not be relied upon. When behavioral data are dose-dependent, they are more credible. This is also the case if they occur in both sexes (although sex-specific effects are known for some compounds), and convergent across tests measuring related behaviors. This is not the case for effects reported in Ema et al. (2008). Moreover, shorter latencies and fewer errors in the Biel maze suggest improved learning, rather than impairment. However, notwithstanding these concerns, *Ema et al. (2008) did find several effects in both the 1500 and 15,000 ppm HBCD groups, therefore, it is recommended that 1500 be used as the NOAEL.*

Maranghi et al. (2013) found increased liver weight in juvenile BALB/c mice after dietary HBCD exposure.

Saegusa et al. (2009) gave HBCD in diet to Sprague-Dawley rats from E10-P20 and found increased thyroid weight and thyroid stimulating hormone (TSH), and reduced T3 at 10,000 ppm at P29 and the same at 1000 ppm in adult offspring. HBCD at 10,000 ppm also reduced the density of oligodendrocytes by ~33% in cingulate, with no significant changes in CA1 or corpus callosum.

Van der Ven et al. (2009) used Wistar rats exposed to HBCD prior to mating and throughout

gestation and lactation by dietary exposure to doses resulting in exposures of approximately 0, 0.1, 0.3, 1, 3, 10, 30, and 100 mg/kg. They report finding markers of immunity changed and reduced testicular weight suggesting endocrine disruption. *A limitation of the study is small group sizes.*

Lilienthal et al. (2009) use the same rats as van der Ven et al. (2009) and report changes in haloperidol induced catalepsy recovery and brainstem auditory evoked potentials. At HBCD exposures of 1 to 10 mg/kg the authors report shorter movement latencies after haloperidol in females but not males. They also report increased auditory evoked potential thresholds and longer early wave latencies at these same doses. The catalepsy test used 0.25 mg/kg of haloperidol with observations at 30 and 60 minutes after being placed in different positions and timing latency to move, but only 60-minute results are reported. Data are based on 5 males and 5 males per group from an unspecified number of litters plus additional females from other litters from the 0.3 mg/kg group, and additional rats from one other litter from the 20 mg/kg HBCD group. The authors report shorter movement latencies in the 30 and 100 mg/kg females. P-values are reported, not F-ratios or degrees of freedom (DF), making aspects of the analysis difficult to determine. For brainstem auditory evoked potentials, effects are reported in males using a benchmark analysis, although the ANOVA was (apparently) not statistically significant. Evoked potential thresholds are increased at 30 and 100 mg/kg HBCD based on a linear trend analysis. No pairwise comparisons between exposed groups and controls were conducted. The linear trend was heavily influenced by the highest dose group, and in some cases supported by data from the second highest group. It is unclear why these data are analyzed by trend analysis, when other data are analyzed by ANOVA. This study has methodological deficiencies, including small group sizes, no control for litter effects, and inconsistent and poorly explained statistical methods. *The Committee indicated EPA should not rely on this study for neuro effects.*

Miller-Rhodes et al. (2014) from E0 to parturition gavaged Long-Evan rats with 0, 3, 10, or 30 mg/kg HBCD dissolved in corn oil. Offspring were given a Functional Observation Battery, but no effects were found. Adults were tested in open-field locomotor activity and in an operant go/no-go procedure for food reinforcement. Young rats had increased tail-pinch reactivity, decreased forelimb grip strength, and later impaired go/no-go performance when nearly one year old, and increased mortality as they aged out to 17 months. At 3 mg/kg HBCD the authors report hind-limb paralysis in the oldest age groups (17 months). The operant test was done at 11 or 17 months of age. In this test, one color light signaled that a lever press was reinforced with a food pellet; whereas a different color was reinforced with food for not pressing the lever. The main findings are reduced forelimb grip strength in the 10 and 30 mg/kg groups and reduced hits (successfully obtained reinforcements) in go/no-go operant test in the 3 mg/kg group, but no effects were observed on this test in the 10 or 30 mg/kg HBCD groups. Authors report that litter was the unit of analysis, but the number of litters used was not provided, nor was the food restriction schedule. The operant finding at the 3 mg/kg HBCD dose, with no effect at higher doses makes the low dose effect difficult to interpret. The forelimb grip strength reductions at 10 and 30 mg/kg, however, appear reliable. The Evaluation reported on this study but did not rely on it.

The Committee regarded the discussions in the Evaluation on the chosen adult neurological

studies as generally appropriate with a few exceptions as noted below.

Genskow et al. (2015) tested HBCD in cell culture in SK-N-SH cells (a catecholaminergic cell line). HBCD at up to 25 micro-molar concentrations for 24 hours caused cell death. In primary neuronal culture HBCD reduced growth and survival of tyrosine hydroxylate-positive cells at 72 hours at concentrations up to 10 micromolar. In C57BL/6J mice, gavaged with 25 mg/kg/day HBCD dissolved in corn oil for 30 consecutive days and striatum analyzed 24 hours after the last dose, found significantly reduced DAT (dopamine transporter) and VMAT2 (vesicular monoamine transporter-2) where found by western blot with no change in tyrosine hydroxylate protein expression. *It was not clear to the Committee why the in vivo data from this study is not used in the Evaluation and a justification for this exclusion is needed*.

Page 309: "In the absence of adequate human data, animal toxicity studies were used for dose-response analysis." The basis of this decision is appropriate and is adequately explained.

The Evaluation reported on six epidemiological studies that examine associations between HBCD exposure and endpoints related to effects on thyroid, nervous system, and the male reproductive system. The Evaluation concludes that the epidemiological database is insufficient for dose-response assessment. The limitations of studies in experimental animals is thoughtfully described and the Agency concludes that two studies could be used for dose-response assessment (Ema et al. 2008, WIL Research 2001). *As noted in the response to previous Questions, there is vagueness and potential inconsistency with how qualitative statements as "High," "Medium," and "Low" are used in the assessment of studies. Their meaning is not entirely clear in all cases and should be clarified*.

The WIL Research (2001) study is available in the Agency HERO database, but the study's peer review status was unclear. *At the meeting of the Committee, EPA clarified that this study was reviewed by Agency staff and found acceptable. This should be noted in the Evaluation along with a description of how the review was performed.*

EPA considered both developmental toxicity endpoints of reduced pup weight and offspring loss for estimating risks following acute oral exposures to HBCD in the general population. Risk estimates were shown for the most sensitive endpoint of offspring loss. While these neonatal effects are not traditionally associated with acute exposures, the long half-life of HBCD suggests that even a single exposure may result in a retained body burden for an extended period. Additionally, evidence from other thyroid disruptors suggests that acute or short-term exposure can result in thyroid hormone effects (Paul et al. 2010, Hedge et al. 2009, Zhou et al. 2001), including in weanlings, and presumably resulting in downstream effects on developmental endpoints. The Evaluation reported both endpoints as relevant for estimating risks following acute general population exposures. The Committee concurred.

Q 8.2	**Please comment on EPA's justification in the document for consideration of developmental toxicity risks following acute exposures.**

Response (*Recommendations in Italics*):

The developmental toxicity endpoints may only be relevant to child-bearing age groups in the general population. The endpoint of offspring loss is only observed in the F2 generation in a two-generation reproduction toxicity study (Ema et al. 2008), suggesting a multigenerational effect, possibly due to increasing bioaccumulation over repeated/chronic exposures. *However, while developmental effects would not be expected to present in younger lifestages, the bioaccumulation and persistence of HBCD in tissues suggests that initial exposure at an earlier age could result in effects later in life. Additionally, it is unknown whether developmental effects on neonates (i.e. decreased weight) could also present in young exposed children*.

One of the outcomes in the Ema et al. (2008) study is loss of litters. The Evaluation combines the litters lost data from two generations within the study in its analysis. When combined, a significant HBCD effect is obtained. *The Committee expressed concern over how these data are combined and an alternate approach was suggested. One Committee member suggested that at a minimum the analysis model should estimate a generation effect (one degree of freedom) prior to examining the HBCD dose-response effect. The decision to combine data requires more justification.*

The definition of what is an adult human use in the Evaluation seems to be different than that used in cited articles. The Evaluation uses as cutoff ages of 16 or 21 years whereas most literature uses 18 years of age as the first adult age group. *Justification of the different threshold age for an adult is required. Consideration should be given to standardizing the first adult age as 18 years.*

The Committee discussed, in the context of developmental effects, the extent to which the same MOA could be used for both humans and rodents. *How rodent data is used to extrapolate to humans requires more discussion and more justification on why rodent developmental endpoints chosen are relevant to humans.*

The Committee recognized the significance of the identified thyroid effects from HBCD exposure, but also noted significant uncertainty around the different thyroid endpoints. *The Committee expressed that the Evaluation did not discuss the range of this uncertainty adequately*.

The Committee suggested that justification for not considering a developmental MOA for liver effects be included in the Evaluation.

The Evaluation notes that effects were found on the thymus. *The Evaluation should discuss how thymus effects have the potential to cause significant effects, including long-term effects, on the immune system.*

Q 8.3	**Please comment on EPA's justification in the document for consideration of developmental toxicity risks in all age groups.**

Response (*Recommendations in Italics*):

The justification in the Evaluation for using developmental toxicity in all age groups is adequate.

The rationale for applying developmental outcomes to all age groups relates to the fact that HBCD has a long half-life and presumably bioaccumulates. However, without hard data to support this, application to all age groups is a protective approach that likely overestimates risk.

The Evaluation notes that developmental effects would not be expected to manifest at younger life stages (page 365). The fact that HBCD does bioaccumulate means that early life exposure could result in later-life effects. *Nevertheless, the Committee was not certain that these conclusions are self-evident and thus requires more discussion in the Evaluation*.

Relatively short-term developmental or early life exposure in rodents to HBCD is associated with alterations in body weight and skeleton formation (Ema et al. (2008), Maranghi et al. (2013), Saegusa et al. (2009), and van der Ven et al. (2009); neurodevelopment parameters (Miller-Rhodes et al. (2004), Eriksson et al. (2006), Lilienthal et al. (2009)); thyroid function (Ema et al. (2008)); thymus (Maranghi et al. (2013), and antibody production (van der Ven et al. (2009) and Hachisuka et al. (2010). Each of these endpoints can have multiple effects in both early and adult animals.

The Evaluation is not clear on how the multi-generational bioaccumulation of HBCD, as noted by Ema et al. (2008), works given that this was a continuous, two-generation feeding study in which the body burden of HBCD may increase with each generation. The use of multi-generational effects is reasonable, likely due to the accumulation and persistence of HBCD. While using such data is reasonable, it may be an overly conservative approach. One Committee member believed this to be justified due to the severity of some of the observed effects

On Page 313: "From a statistical standpoint, most reproductive and developmental studies with nested study designs typically support a BMR of 5% extra risk (ER) (U.S. EPA, 2012). A BMR of 1% ER was used in this case to address the severity of this endpoint (i.e., offspring loss), in accordance with EPA Benchmark Dose Guidance (U.S. EPA, 2012), which supports use of smaller BMRs for more severe or "frank" effects." *Considering some of the uncertainties in the database, the Committee questioned whether the use of a smaller BMR is justified. Perhaps more explanation would help support this choice.*

Q 8.4	**Please comment on whether EPA should consider thyroid hormone effects as an acute endpoint.**

Response (*Recommendations in Italics*):

The Evaluation estimates risks for effects on thyroid hormones only following chronic exposure.

However, evidence from other thyroid disruptors suggests that acute or short-term exposure can potentially result in thyroid hormone effects (Paul et al. 2010; Hedge et al. 2009; Zhou et al. 2001).

Page 299: "In humans, (Eggesbø et al. 2011) reported elevated but non-statistically significant odds ratios for increased thyroid stimulating hormone (TSH) in relation to increased HBCD levels in human breast milk, but confidence intervals (CIs) around point estimates were wide and a dose-response was not observed." *If the odds ratio change is not statistically significant, the Evaluation should report this as a no effect finding rather than imply inconclusive evidence.*

Page 304: "Additionally, a review of the hypothalamic-pituitary-thyroid (HPT) axis across species published more recently than the NAS review (Zoeller et al. 2007) states that there is minimal evidence linking biochemical and metabolic differences in thyroid hormones (due primarily to reduced serum binding proteins in rodents) to differences in sensitivity among rodents and humans except on a MOA-specific basis." *This statement is unclear and seems to imply a different MOA may be responsible for effects in humans compared to effects in rodents.*

Page 304: "Therefore, overall the weight-of-evidence indicates that rodents are an adequate model for assessment of thyroid disruption by HBCD, however it is possible that quantitative extrapolation may overestimate the adversity of effects in humans." *No evidence is presented to support the adequacy of rodents for this response. Significant questions are raised that are not addressed, primarily because few experimental data address this question.* Developmental exposure also led to alterations in thyroid hormones in both sexes and across studies of different exposure durations. This is notable given female rats are considered less sensitive to thyroid effects than male rats (Choksi, et al. 2003). *However, it is not clear that the concentrations of HBCD that generated these changes are relevant to human exposures and further discussion is needed on this issue.*

The evidence supporting the proposed MOA for thyroid seems weak and non-specific. The Evaluation seems to down weight the differential role of thyroid hormone glucuronidation in humans versus rodents (noted on page 304). The existence of inconsistencies in the literature and the poorly characterized interspecies differences regarding MOA, adds uncertainty to the use of thyroid effects as an acute exposure endpoint. *Better justification for the use of thyroid effects is needed and the Evaluation should clearly state the limitations with using thyroid effects.*

The Committee discussed the potential for hormone effects, including those related to thyroid hormones, to display a non-monotonic (either U-shaped and inverted U-shaped) dose-response form. Such non-monotonic responses have been documented for exposures to endocrine

disrupting chemicals, which may include HBCD. *The Committee suggested that the Evaluation might wish to discuss this possibility*.

Saegusa et al. (2009) and WIL Research (2001) reported follicular cell hypertrophy as a result of exposure to HBCD. *The Committee suggested that further clarification is needed in the Evaluation as to whether this effect is adverse or recoverable.* WIL Research (2001) reports effects at 1000 mg/kg, but these effects are reported as not significant (NS) with reductions of greater than 20%. *This finding requires further discussion.*

After an acute exposure, thyroid hormones should be measured 1-2 weeks after a perturbation and not at 24 hours Thyroid hormones are best evaluated in a sub-chronic study at 1, 2, or 4 weeks. Acute changes (<48 hours) do not accurately reflect the effects of chemicals on thyroid hormone economy. The half-life of thyroxine in rats is 1-2 days. It is feasible to see an increase in TSH with depressed T4 at one week. If a chemical disrupts T4 protein binding (TBG, TTR, albumin) then the amounts of free and bound T4 can be measured acutely at 24 hours

Many of the developmental effects of altered T4 levels occur *in utero* (Forhead and Fowden. 2014). Rawn et al. (2014) found HBCD in placental tissue in Canadian women, and in fetuses from as early as 6.5 weeks. This shows that HBCD crosses the placenta as well as being transferred through lactation after birth. Thus, alterations in thyroid hormone may occur quickly, and after short exposure. This suggests that HBCD may impact the fetus during a developmental period that is sensitive to chemical exposure.

Additional acute or short-term studies on thyroid hormone effects should be included in assessing human health hazards. The Committee provided two reasons for asking for these studies: a) lipophilic chemicals that possess some chemical properties that are similar to those of HBCD have been found to be thyroid disruptors in laboratory animals, and b) perturbation of thyroid hormones by PCBs, PCDDs, and PCDFs have been identified in field species such as birds, amphibians, and other terrestrial mammalian species in acute or short-term studies.

In the study by Ema et al. (2008) the increased incidence of non-pregnancy in HBCD-exposed F0 or F1 rats alone is not statistically significant with either a pairwise test (as reported by authors) or the Cochran-Armitage trend test (as conducted by EPA). Dose-response curves were shallow and never reached a high response percentage. The results of several statistical tests indicate that F0 and F1 datasets are compatible for combining. Therefore, the Evaluation reported this change to be biologically relevant and a log-logistic model fit to the combined response data (which only demonstrated adequate fit after dropping the highest dose) was used to derive the BMDL for this chronic endpoint. *In a previous Question, the Committee recommended the Evaluation revisit this model fit and account better for potential F0 and F1 differences.*

The Committee discussed the available information on thyroid markers but was divided on the utility of these data as surrogates for adverse health effects. More information and more study are needed to demonstrate that changes in thyroid markers translates to changes in health.

Q 8.5	**Please comment on the evaluation of human health hazards and weight-of-evidence characterization.**

Response (*Recommendations in Italics*):

The weight-of-evidence characterization of the four health effect domains (thyroid, liver, female reproductive and developmental toxicity), the acute and chronic exposure effects, and the use of rodents to model of HBCD thyroid effects seem appropriate, if conservative, given the available literature. However, *better documentation of the HBCD concentration information associated with these studies in the Evaluation would make it easier for readers to assess how the same endpoints are likely to be altered by human exposure.*

The Evaluation needs to better justify why the 1500 ppm LOAEL from Ema et al. (2008) is not used in the risk assessment.

Page 303: "A pattern of increased TSH, a sensitive early indicator of decreased thyroid hormone reserve…" One Committee member suggested *prefacing this statement with: "Increased TSH is a sensitive early indicator of disruption of the thyroid hormone economy, including decreased thyroid hormone synthesis or secretion, decreased serum concentrations of T4, or decreased deiodination of T4 to T3 in peripheral tissues." The phrase "a sensitive early indicator of decreased thyroid hormone reserve" can then be dropped.*

Page 303: "A few studies demonstrate that HBCD may induce human health hazards downstream of thyroid hormone dysregulation through activation of the DNA-binding thyroid receptor." *The Evaluation should provide more detail on what expected downstream effects of activation of the thyroid hormone receptor might be. It is possible that activation of the thyroid receptor could reduce TSH secretion from pituitary thyrotropes.*

Page 315: "Although the adversity of increased liver weight was ambiguous in some studies, it serves as an effective and sensitive toxicological indicator for liver toxicity, especially within a susceptible population. Increased liver weight was therefore selected as the representative endpoint for dose-response analysis of liver effects based on being the most consistently observed toxicological effect." The characteristics of "ambiguity" and "sensitivity" appear contradictory. *The Committee recommended that this statement be modified to clarify the contradiction, restate the weight of evidence argument for liver weight as the appropriate toxicity endpoint, and remove the suggestion of subjectivity in choice of adverse effects for the risk assessment.*

Page 317: The Evaluation provides a rationale for using a 5% ER rather than a 10% ER for assessing risk for female reproductive toxicity and pregnancy incidence. The justification for this is unclear and creates a sense of bias. Using a smaller BMR for developmental effects because of severity of endpoint seems contrived. *This discussion should be reviewed and revised to improve the justification and remove the suggestion of bias in ER selection.*

Page 319: The Committee discussed the rationale given in the Evaluation for employing an interspecies uncertainty factor (UF_A) of 3. *The Committee suggested using the default of 10 can*

be better justified in this case.

Q 8.6	**Are there any additional HBCD specific data and/or information that should be considered?**

Response:

The Committee identified the following studies on HBCD exposure as relevant and not included in the Evaluation.

- Lee CC, Chang WH, Chen HL. 2019. *Environmental Pollution* 249. pp 728-734. doi: 10.1016/j.envpol.2019.03.040. Epub 2019 Mar 14. - Dietary exposure and risk assessment of exposure to hexabromocyclododecanes in a Taiwan population. Used to estimate an MOE.
- Cao X, Lu Y, Zhang Y, Khan K, Wang C, Baninla Y. 2018. *Environmental Pollution*. 236. pp:283-295. doi: 10.1016/j.envpol.2018.01.040. - A review of hexabromocyclododecanes (HBCDs) in environmental media with focus on their potential risk and management in China.
- Fromme H, Hilger B, Albrecht M, Gries W, Leng G, Völkel W. 2016. *Int J Hyg Environ Health*. 219(4-5). pp380-8. doi: 10.1016/j.ijheh.2016.03.003. - Occurrence of chlorinated and brominated dioxins/furans, PCBs, and brominated flame retardants in blood of German adults

Q 8.7	**Please comment on any other aspect of the human health hazard assessment that has not been mentioned above.**

Response (*Recommendations in Italics*):

The Evaluation should make clear those endpoints that have been identified but deemed not amenable to quantitative risk analysis. *When data on these endpoints are available, justifications for exclusion of these endpoints from the risk assessment should be clearly stated.*

The summary of liver effects (Section 3.2.4.1.2) in the Evaluation is adequate but does not discuss that exposure to HBCD may have additive or synergistic effects when combined with a high fat diet. Also, for liver effects, there is no discussion on potential modes of action (MOA). There are numerous studies which could be useful in identifying potential liver MOAs.

There is no discussion of dose-response relationships with human health effects in general or specifically in case of liver effects.

There are six studies considered for the liver effects, but only one is used for POD analysis. One study (van Der Ven et al. 2006) which includes the highest dose groups is not used, without adequate justification. The Committee concluded that this is an acceptable study, with 7 doses,

BMD calculations and analysis in multiple organs. Justification for giving it no weight in the final analysis should be provided.

Page 305: The location of the Wheater and Burkit (1996) reference suggests it provides mechanistic information on HBCD-induced liver lipid transport changes. This citation is a book chapter discussing basic histopathology. *Its inclusion here should be justified*.

Information on Absorption, Distribution, Metabolism, and Excretion (ADME) is typically found in the body of a risk assessment not relegated to an appendix as is done in this Evaluation. The text provided in Appendix H is better suited to Section 3.2.2 Toxicokinetics. In reading the document, reviewers had to go back and forth between the main document and Appendix H. Neither discussion is comprehensive, but *by merging Appendix H back into Section 3.2.2, the information flow is better than before, and redundancy is minimized.*

One Committee member asked if the study by Yu and Atalla (1980) cited in Section 3.2.2 and Appendix H has been peer-reviewed.

The immune effects examined in a developmental study by van der Ven et al. (2009) demonstrated that developmental/early life exposure to HBCD resulted in bioaccumulation in offspring liver, as well as an increase in antibody production when the adaptive immune response was challenged.

Several *in vitro* studies using human lymphocytes reported increases in immune parameters that can promote inflammation (e.g., increase in IFN-γ, IL-1γ, IL-6, and TNF-γ, as well as increased expression of the co-stimulatory molecule CD80. Cumulatively, these studies suggest that HBCD may be immunotoxic.

Question 9: Environmental Risk Characterization (Section 4.1 of the Draft Risk Evaluation)

EPA considered use of different model assumptions and ecological considerations in its establishment of risk quotients (RQs) (e.g., flow rate, partitioning in environmental media, percentage of HBCD removal from direct releases, etc.).

Q 9.1	**Please comment on the appropriateness of EPA's selections for deriving RQs**.

EPA considered the use of Kow (based) Aquatic BioAccumulation Model (KABAM) (U.S. EPA. 2009), a model used by the Office of Pesticide Programs, to estimate potential bioaccumulation of HBCD in freshwater aquatic food webs to provide information regarding HBCD trophic transfer using predicted surface water and sediment concentrations (E-FAST and PSC), in order to relate HBCD exposure to specific conditions of use.

Q 9.2	**Please comment on the appropriateness of using this methodology for characterizing risk.**

Response (*Recommendations in Italics*):

Using estimated water, sediment and soil concentrations, appropriate risk quotients (RQs) are made using thresholds and safety factors from the literature for these media. Acute and chronic toxicity thresholds are appropriate for plants, invertebrates and vertebrates for water, sediment and soil media. However, there are uncertainties, and these are primarily discussed in Question 7.

The Evaluation should include a rationale and justification for using the 50th percentile for biota concentrations from the Kow Based Aquatic Bio Accumulation Model (KABAM) (page 341) to characterize the exposure in fish tissues. It was unclear why a more probabilistic approach with Monte Carlo analyses was not used for the exposure assessment. A 90th percentile could also be used for comparison to the 50th percentile. While it is clear the Evaluation uses a 90th percentile in river water dilution models, an additional 90th percentile should be included in the overall predicted environmental concentration assessment.

The threshold concentration established for soil may not be relevant. To assess risk in soil, a 200 mg/kg threshold for worm toxicity is used in the RQ. A change in superoxide dismutase and HSP70 is used as an endpoint for toxicity. In the absence of validation and verification, use of biochemical sublethal endpoints is highly uncertain. Some Committee members thought these endpoints could be used in a screening capacity. However, if the accuracy of true exposure and bioaccumulation/biomagnification are low, then the estimation of risk in the face of inadequate data on toxicological consequences is suspect and can increase uncertainty. *It is recommended that apical endpoints of survival, growth or reproduction be used for hazard threshold*

derivation. A Predicted No Effect Concentration (PNEC) of 59 mg/kg is suggested by Arnot et al. 2009.

In general, the Committee expressed concerns over estimating water or sediment concentrations and then using those estimates to calculate bioaccumulation in food webs. Furthermore, dietary compositions of the predators in those webs are often not adequately understood.

Considering HBCD is a PBT, the Committee thought that *E-FAST and KABAM models can be linked and used to predict critical body-burden tissue levels in fish, and these values can be divided by HBCD PNECs for fish health (4 mg/kg) (Arnot et al. 2009; European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC), 2011).* Methods for using critical body burdens in risk assessments can be found at ECETOC, (2011).

The Committee expressed concern that fish-eating birds are not considered in the assessment of avian receptors. Kestrel data are not used to assess impacts in fish-eating birds because kestrels do not consume fish. Concentrations of HBCD in seabirds are at levels similar to those found in kestrels that cause reproductive impairment (AMAP 2017, Guigueno and Fernie 2017). If the seabird HBCD tissue residue data are consistent with that seen in wild falcons and in the reproduction toxicity study with kestrels, then it can be concluded the reproduction toxicity seen in the controlled HBCD feeding study will predict effects to seabird raptors. The AMAP (2017) lists several seabird species. *The Committee concluded that Kestrel data can be used to assess seabird body burden, but with some uncertainty.*

Page 329: "Specifically, environmental monitoring data cannot provide HBCD release information that can be attributed to a specific COU or COU-specific parameter, nor can it be used to determine HBCD releases from a specific time period." *Some Committee members suggested that passive sampling for waterborne hydrophobic contaminants can be conducted relatively inexpensively. The Committee also thought that the presence of HBCD within plastics/fragments is a major factor affecting HBCD fate and bioavailability but is not discussed adequately in the document.*

On page 330: "There are many potential sources of uncertainty in all of the parameters involved in environmental exposure estimates…. the greatest influence on exposure estimates given the associated uncertainty and sensitivity (effect on the final values) stems from the selection of emission factor and days of release… . EPA believes that these sub-scenarios sufficiently capture the range of risk estimates for all reasonably expected environmental exposures, with minimal remaining unaccounted-for uncertainty. Therefore, EPA has high confidence in the range of risk estimates for the highly exposed aquatic and terrestrial organisms." With these uncertainties, knowing little about behavior of microplastics or the HBCD therein and the uncertainties regarding the role of discarded polystyrene debris, *some of the Committee disagreed that categorizing risk estimates as "high confidence" is merited. The Committee suggested comparing model estimates for HBCD levels in Canadian falcons. The Committee indicated similar tissue concentration anomalies in terrestrial birds of prey for Decabromodiphenyl ether (DecaBDE), an extremely hydrophobic brominated flame-retardant additive that does not appear to substantially accumulate in fish (Potter et al. 2009).*

Page 334, Table 4.3: The "Near General Population" sites are from the Great Lakes. One

Committee member expected substantial dilution in the Great Lakes versus living just downstream of a WWTP, suggesting that the risk characterization may be less protective than indicated.

Page 337, Table 4-6: The Committee expressed concern that the threshold of 200,000 µg/kg was chosen based on very limited data.

Page 340: "Table 3-2 suggests that American kestrel are exposed to 64.4 ng HBCD per day through the consumption of small mammals (i.e., mice), however mice only comprise approximately a third of American kestrel diet; it is likely that these calculations vastly underestimate HBCD uptake through diet." One Committee member observed that field data for birds of prey suggest high tissue concentrations occur occasionally for unknown reasons, thus demonstrating underlying uncertainty in relation to routes of exposure.

Recommendations:

- *Critical body burden analyses should be carried out with PBT compounds such as HBCD.*
- *Risk characterization for birds should be included with discussions of uncertainty between fish consuming birds relative to non-fish consuming birds*
- *Probabilistic assessments of* Predicted Environmental Concentration (*PEC) of HBCD should be included with discussions of uncertainty.*
- *Hazard assessments should use thresholds that evaluate endpoints of growth, survival and reproduction (not biomarkers of oxidative stress as used in soil organisms).*

Question 10: Human Health Risk Characterization (Section 4.2 of the Draft Risk Evaluation)

> EPA evaluated integrated risk estimates for the general population in order to account for individuals who are chronically exposed across multiple lifestages. Exposure scenarios include central tendency (13 year) and higher end (33 year) periods of residential mobility, based on the Exposure Factors Handbook values. MOEs were integrated across each lifestage as a weighted average.

Q 10.1	**Please comment on EPA's approach.**

Response (*Recommendations in italics*):

The Committee generally found that EPA's approach to evaluating risk estimates for the general population with chronic exposures to HBCD across multiple lifestages follow standard EPA policy. All the exposure groups are clearly coupled to the different exposure scenarios. Furthermore, each of these exposure scenarios are clearly described and the nature of potential exposures are mostly clearly justified. A concern was noted, however, about the decision of no unreasonable risk for installation and demolition conditions of use. *The Committee noted both a lack of consistency throughout the document and with the Department of Health and Human Services (DHHS) standard of age 18 years as the division between children and adults: The document uses age 16 years in some places and ages 18 or 21 years in other places*.

Inasmuch as regulations for the use of appropriate personal protective equipment (PPE) are in place for occupational exposures, the Committee agreed that it is appropriate for the EPA to calculate MOEs based on the diminished exposure anticipated from use of the PPE. However, some members on the Committee also noted that some workers may not use PPE at all times, even when instructed or required to do so. *Accordingly, calculation of MOEs without use of PPE should be done for all routes of exposure. The EPA did this for the use of respiratory protection with regard to inhalation exposures but chose not to do this for the use of gloves with regard to dermal exposures.*

The Committee generally agreed that the use of health effects, including developmental, thyroid, liver and reproduction seems appropriate, with perhaps additional consideration of immunotoxicity as an endpoint. Concerns were expressed by some members of the Committee, however, regarding the use of thyroid effects as the most sensitive hazard endpoint following acute HBCD exposures. These concerns relate to the lack of clear effects on thyroid hormone status or function in exposed humans and the high degree of uncertainty with this endpoint due to potential physiological differences between humans and rodents with respect to regulation of thyroid function. Much of the supporting, mechanistic information from the published literature is not included in the main document but is provided in multiple supplemental documents. It was noted, however, that no or little direct reference is made to this supporting information in the

main document.

A Committee member also noted that the EPA used industrial exposures for HBCD and particulate matter (PM) from the European Union (EU). Because there is a lower limit for occupational exposures to PNOR in the EU (i.e., 10 mg/m^3 8-hour TWA) than OSHA's PEL (i.e., 15 mg/m^3 8-hour TWA), exposures are controlled to a lower level in the EU, so that use of these data might underestimate U.S. worker exposure. This issue is further discussed in the response to Question 5. It was also noted that while fish consumption as a source of exposure to HBCD is explained and described, the document does not consider certain populations whose consumption of fish is especially high due to cultural practices (e.g., Native American subsistence fishers).

In describing lifestage susceptibilities and chronic exposures to HBCD, the EPA made assumptions based on population mobility. A Committee member noted a concern that *individuals from lower socioeconomic groups will likely have lower mobility, thus prolonging their exposure to HBCD. Besides socioeconomic status, a Committee member also noted the absence of consideration of specific preexisting conditions, such as obesity, metabolic disease, hypercholesterolemia, non-alcoholic fatty liver disease, alcoholic liver disease, and Hepatitis C and B viral infections that may result in increases in liver fat content. Such conditions could impact HBCD retention and thus increase effective exposure and risk.*

Finally, although it is recognized that little knowledge is available about the MOA for HBCD, it was noted that HBCD is structurally/chemically similar to PCBs. Recently reported effects of PCBs on brain signaling and calcuim (Ca), zinc (Zn) ions, and oxidative stress as these effects for PCBs could have relevance to HBCD. Such effects could contribute to neurodevelopmental effects.

Recommendations from Committee to Improve the HBCD Evaluation:

- *The EPA should calculate MOEs both with and without the use of appropriate PPE. This includes the use of personal protection face masks (i.e., respiratory protection) for inhalation exposures and the wearing of gloves for dermal exposures.*
- *In considering different lifestages, the EPA should follow the DHHS guidelines and consider adults as those age 18 years and higher.*
- *The EPA should clearly cross-reference information provided in supplemental documents in the main document when they provide explanation, justification or other experimental support for a key choice of hazard endpoint or critical study.*
- *The EPA should ensure that exposure estimates incorporate the differences in Permissible Exposure Limits (PELs) for HBCD and for PNOC in the occupational scenarios. Thus, reference to EU PEL for PNOC should be added.*
- *The EPA should perform additional sensitivity analysis based on differences in mobility in subpopulations with varying socioeconomic status.*

- *The EPA should more carefully evaluate the levels of risk for installation and demolition conditions of use.*
- *The EPA should add consideration of the impact of specific preexisting conditions that result in increases in liver fat content, as these could impact HBCD retention and thus change biologically effective exposure and the risk.*
- *The EPA should give special consideration to specific populations (e.g., tribal, arctic inhabitants, etc.) who depend on fish as a major source of food because of cultural considerations and provide some quantitative sense of how much extra risk exists for these populations.*
- *The EPA should consider immunotoxicity as an additional health endpoint of HBCD exposure.*
- *The EPA should consider adding a discussion of known effects of PCBs on brain signaling, Ca and Zn status, and oxidative stress, as they may have relevance to HBCD.*

Physiologically based pharmacokinetic (PBPK) models would be needed in order to be able to accurately estimate bioaccumulation of HBCD in human tissue for different exposure durations over time. Some simplistic models for HBCD exist (empirical two-compartment open kinetic model; and a simple first-order elimination model to estimate the steady-state lipid concentration); however, these models introduce significant uncertainties that reduce the value of their use. Based on the absence of a robust peer-reviewed PBPK model for HBCD, EPA relied on the application of default uncertainty factors for interspecies, intraspecies uncertainty factor and subchronic-to-chronic from subchronic exposure studies.

Q 10.2	**Please comment on EPA's approach.**

Response:

The Committee did not comment on the potential use of PBPK models, even simplistic ones, in informing uncertainty factors. Comments on the setting of levels for uncertainty factors can be found in the Committee's responses to other charge questions.

Question 11: ***General Risk Characterization (Sections 4.1 and 4.2 of the Draft Risk Evaluation)***

> After consideration of all information identified by EPA that pertains to HBCD, EPA concluded that HBCD does not present an unreasonable risk of injury to health or the environment for the conditions of use identified in this draft risk evaluation. EPA made these determinations considering risk to potentially exposed and susceptible subpopulations identified as relevant, under the conditions of use without considering costs or other non-risk factors.

Q 11.1	**Please comment on the objectivity of the underlying data used to support the risk determinations and the sensitivity of the Agency's conclusions to analytic assumptions made.**

Response (*Recommendations in Italics*):

There was general agreement among Committee members that EPA did a very good job in assembling, organizing and presenting a vast amount of information on HBCD in their Draft Risk Evaluation and Characterization (the Evaluation). Committee members that served on the recent review of Pigment Violet 29 (PV 29) praised EPA for improving the clarity, organization and effectiveness of their written and oral presentations on HBCD. Particularly helpful was the slide presentation summarizing EPA's overall strategy for assessing risk evaluation and characterization. *The Committee suggested that for future reviews that EPA make available their summarizing PowerPoint presentations prior to the meeting.* Committee members would greatly benefit from having access to the summary slide presentation to help guide them through the corresponding Evaluation and supplemental files. This will be especially helpful given the very tight timeline anticipated for completing reviews. Characterization of EPA's confidence at various stages of the evaluation, such as for exposure assessment, summarized in Section 2.4.1, was useful in that it gave the Committee a sense of EPA's own assessment of where the strengths, uncertainties and assumptions were in the data EPA used, and this provided a framework for Committee discussions.

Despite the overall improvements stated above, the Committee raised several concerns with the approach used by the EPA to screen and evaluate the relevant research literature on HBCD. In particular, the initial data search strategy was viewed by many Committee members as too restrictive and resulted in exclusion of a large body of relevant information that EPA did not consider in the initial data search. For example, there exists an extensive peer-reviewed literature on "respirator use industry"[12] that can be readily accessed through a PubMed search that would likely have served to better inform and guide EPA on the potential effects of exposure controls using reliable data rather than relying on many assumptions.

12 See for example: www.ncbi.nlm.nih.gov/pubmed/?term='respirator+use+industr'

The Committee expressed grave concerns that subjective rather than empirical criteria were used during the data and information collection phase (Section 1.5). It was unclear whether a set of objective inclusion/exclusion criteria were set out prior to selecting 71 of 1,796 references to assess environmental fate and transport (Figure 1-6), 26 of 1847 references to assess environmental releases and occupational exposure (Figure 1-7), 345 of 11,208 references to assess general population, consumer and environmental exposures (Figure 1-8), 48 of 630 sources to assess environmental hazard (Figure 1-9), and 51 of 1890 studies to assess human health hazard (Figure 1-10).

The Committee was encouraged that EPA considered key and supporting studies from existing assessments (e.g., EPA IRIS assessments, ATSDR assessments, ECHA dossier), however, there is a lack of clarity about when and to what extent data contained within these key reports were included or excluded in the HBCD assessment. Concerns were expressed that a more empirical approach to data screening and evaluation would have resulted in the inclusion of a larger number of high-quality studies that may have impacted EPA's general risk characterization of both environmental and human receptors. Although the Committee appreciated the focus of TSCA mandates, which targets primary occupational exposures scenarios, the Committee strongly felt that HBCD secondary exposures (post-manufacturing situations, subsequent environmental disposition and risks to the general population) should be more transparently and rigorously assessed throughout the evaluation. In this regard, several members expressed that the Evaluation did not accurately characterize risk through environmental exposures, especially to highly susceptible populations exemplified by but not limited to women during pregnancy, children during the prenatal periods, and populations with traditional cultural practices that would results in significantly higher dietary exposures rates.

Although discussed at several points during the Committee's deliberation, it remained unclear the extent to which the scoring system used to include or exclude data and data sources impacted the initial evaluation and risk characterization. This lack of clarity increased the Committee's concern that relevant studies of high-quality may have been excluded. The Committee was not confident that the review faithfully followed the protocols and metrics described in the TSCA systematic review document. The Committee and public commenters questioned the objectivity of the TSCA systematic review protocol, considering it still too subjective, not based on clearly defined study quality parameters, and in general not empirical. Some Committee members felt that the approach used in the Evaluation increases uncertainty across several components of the overall risk characterization for HBCD, and likely contributes to underestimates of risk.

As it has done in previous TSCA chemical reviews, *the Committee recommended EPA revise its TSCA systematic review (SR) protocol/practice and take a more systematic and more complete approach to reviewing the available information sources and data.* EPA is encouraged to move forward with adopting a review protocol that is more explicit, more systematic and more objective than the current TSCA SR protocol. An overview of current SR best practices was presented during the public comments[13]. The empirical approach proposed by Woodruff and Sutton (2009) forms the basis for the approach adapted by the National Toxicology Program's

13 Public comment docket ID: EPA-HQ-OPPT-2019-0237-0044

Office of Health Assessment and Translation (OHAT) in 2013, reviewed by the National Academies, and adopted by EPA's Integrated Risk Information System's Review (IRIS). Recently, Singla et al. (2019) identified several best practices for systematic review that TSCA should adopt. It is expected that the identified practices will be consistent with EPA's TSCA evaluation needs. Should TSCA mandates necessitate specific modification to current best practices, for example the IRIS SR protocol, these modifications should undergo peer-review and then clearly explained to the SACC.

A shared concern of many Committee members was that there are no data to support the key assumption that potentially exposed workers would necessarily wear protective equipment and use PPE. Assumptions of appropriate PPE use in the primary manufacturing workplace, and more significantly, in post-manufacturing situations (demolition, disposal, recycling) are unrealistic and would lead to an overall underestimation of exposure for human receptors. This was viewed as a weakness of the risk evaluation that contributed significant uncertainty to the overall risk characterization.

Another weakness of the risk characterization is that the estimates of HBCD half-life in several environmental compartments, including the built environment, relies heavily on unsubstantiated assumptions. No attempt is made to draw from the rich data that exists for related persistent organic pollutants with similar physicochemical properties and use patterns (e.g., polybrominated diphenylethers, polychlorinated biphenyls), whose half-lives have been accurately measured to be on the order of years, rather than weeks as suggested for HBCD. Such omissions of high-quality data are likely to influence the HBCD Evaluation and in turn weaken several of the conclusions about general risk characterization.

Q 11.2	**Please comment on the characterization of uncertainties and assumptions including whether EPA has presented a clear explanation of underlying assumptions, accurate contextualization of uncertainties and, as appropriate, the probabilities associated with both optimistic and pessimistic projections, including best-case and worst-case scenarios.**

Response (*Recommendations in italics*):

There was extensive discussion among Committee members in Question 8 (*Human Health Hazard - Section 3.2 of the Draft Risk Evaluation)* as to the appropriateness and validity of using 15,000 ppm (high dose exposure group) as the point of departure (POD) for the thyroid hormone (TH) effects from Ema et al. (2008). *Committee members strongly recommended that EPA reconsider using the 1500 ppm dose (e.g., delay in eye opening) as the POD for risk characterization.* Perhaps both analyses should be included by amending the appropriate tables and text in the main report. *At the very least, a stronger, more convincing, rationale should be offered to justify use the 15,000 ppm data as a POD.* Since several classes of chemically related persistent organic pollutants (POPs) can elicit non-monotonic ("inverted U") dose relationships in both *in vivo* and *in vitro* animal models of developmental neurotoxicity (Frank et al. 2018; Chen et al. 2017; Dach et al. 2017; Kim et al. 2011), the analysis and rationale should include

discussion of this potential response for outcomes related to changes in TH signaling (Sethi et al. 2019).

The Evaluation acknowledges that alternative adverse outcome pathways affecting neurogenesis and differentiation, calcium homeostasis, and neurotransmitter release could be contributing to HBCD adverse outcomes, however, these alternative adverse outcome pathways are afforded one short paragraph within the Evaluation (page 307), only regarding a primary TH mechanism. This underlying assumption may not be accurate, and two Committee members referred to relevant publications not considered by EPA that indicate low-dose HBCD elicits reproductive and neurodevelopmental toxicity both *in vivo* and *in vitro* mediated by alternative mechanisms. These mechanisms are elicited at much lower concentrations/doses than those reported for TH-related effects reported by Ema et al. 2008 (see Shi et al. 2019, Rasinger et al. 2018; Reflatto et al. 2018, Rasinger et al. 2014). For example, similar *in vivo* and *in vitro* mechanisms of HBCD neurotoxicity have been implicated using both transcriptomic profiling in brains of female mice exposed through their diet to HBCD (199 mg/kg body weight per day) for 28 days and compared with those of neuronal N2A and NSC-19 cell lines exposed to 1 or 2 µM HBCD. Similar pathways and functions were affected both *in vivo* and *in vitro*, including Ca^{2+} and Zn^{2+}signalling, glutamatergic neuron activity, apoptosis, and oxidative stress. *Although most of these data were published after preparation of the EPA risk evaluation, they should be used to provide context for the limitations of the underlying assumptions and the uncertainties that arise from using the high-dose data from Ema et al. 2008 as the POD.*

TH measurements and reductions produced by HBCD from the Ema et al. (2008) study should also be considered in the context of the available human epidemiology data indicating the quantitative reductions of T4 and/or increases in TSH needed to observe cognitive and behavioral impairments. This would better place the TH effects on which the developmental POD is based in the context of the human literature on hypothyroidism.

There was significant discussion and concern about the objectivity of the analysis used in the developmental POD for risk characterization. Particularly concerning was the potential weaknesses of combining of F0 and F1 data from Ema et al. 2008 in order to generate a statistically significant result. The potential pitfalls of the experimental design that uses continuous dosing across F0 and F1 generations without accounting for influences of HBCD bioaccumulation across generations deserves additional discussion.

Throughout the draft Evaluation, characterization of uncertainties is qualitative and only minor efforts are made to demonstrate uncertainties quantitatively. In many incidences EPA might not have sufficient data to conduct quantitative (probabilistic) assessment of uncertainties; but in some cases EPA appeared to have a range of values (e.g., estimated environmental release, half-life time, dermal absorption rate, etc. see for example Table_Apx F-3 and Table_Apx F-4) that allow for quantitative assessment of the impact of the assumptions or choice (e.g., mean vs 90^{th} percentile) on associated estimation, and also assessment of how the uncertainties might propagate downstream to further affect the final risk value. Taking mouthing as an example of exposure route, EPA has a reasonable estimate of the distribution of exposure and could have

conducted a sensitivity analysis by using multiple values along this distribution as an estimated exposure level. Table 4-13 displays only central tendency estimates, but no high-end estimate. The Committee encouraged EPA to develop a practical and sensible process whereby uncertainties are quantified systematically and consistently. The present Evaluation of HBCD presents such an opportunity to do so.

Q11.3	**Please provide information on additional uncertainties and assumptions that EPA has not adequately presented.**

Response (*Recommendations in italics*):

The decision to exclude from consideration nearly all complete or potentially complete exposure pathways other than the very limited workplace exposures—currently limited to one operation (Indium Corporation) with perhaps no more than about10 to 25 total employees engaged in HBCD solder flux production—reduces the utility and value of this Evaluation. Given the partial international ban on HBCD export and decisions by U.S. firms to voluntarily cease HBCD production, there are few HBCD primary receptors (primary occupational/occupational non-users) as currently defined by TSCA.

EPA made several assumptions regarding "recycle dust" associated with HBCD-containing construction demolition debris. Many of these assumptions were viewed as speculative by Committee members, given no area or personal breathing zone or particle size(s) data on these dusts are available. As a result, there is a great degree of uncertainty about the disposition of the inhaled material within the airways and lungs and how efficiently it is transferred to systemic targets.

EPA's designation of "legacy" environmental HBCD contamination only briefly mentions potential ecological risk (primarily benthic or fish species) and excludes avian raptors whose primary prey are aquatic. There is a considerable volume of data on exposure patterns and bioaccumulation of highly lipophilic persistent organic pollutants and the adverse outcomes they produce on high trophic level species. *The Committee concluded that although HBCD in occupational scenarios may not pose an unreasonable risk, risks associated with HBCD releases and migration into the environment and its high bioaccumulation potential across trophic levels should represent a major driver of risk characterization.* The estimates of HBCD half-life in various environmental scenarios (weeks to months) reported in the Evaluation are considered unrealistic and are likely large underestimates. This is due to chemical stability issues, but also more importantly to releases into the environment from degradation of XPS and EPS into microparticles (nanoparticles) that will likely persist for many decades.

Q11.4	**Please comment on whether the information presented supports the findings outlined in the draft risk characterization section. If not, please suggest alternative approaches or information that could be used to develop a risk finding in the context of the requirements of the EPA's Final Rule, Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act (82 FR 33726).**

Response (*Recommendations in italics*):

One Committee member suggested that the risk assessment document needs a table and associated text at the end of Section 4 to inform the reader of which scenarios discussed are associated (linked) to which combinations of life stage by category and sub-category of condition of use identified in Table 5-1. It was mentioned during the meeting that the risk determination for each combination of life stage by category and sub-category of condition of use can involve up to 32 different scenarios. As currently presented, readers are unable to determine which among the 32 scenarios drive the final risk characterization.

The Committee expressed concerns that the HBCD half-life estimates used by EPA which are measured in weeks, are likely to be unrealistically short. The Committee concluded that the values presented represents a gross underestimation of the true half-life, which is likely to be measured in years if not decades. This degree of underestimation is likely to influence several aspects of risk characterization and lead to underestimation of related uncertainty.

Potential reductions in uncertainty are possible through estimation of dermal absorption via the newer more sophisticated methods measuring dermal flux parameters rather than the fraction absorbed method.

In considering special and susceptible population exposures, more consideration needs to be given to populations with specific preexisting conditions, such as metabolic disease and obesity, as well as to tribal, ethnic and other subpopulations that depend heavily on potentially contaminated foods, such as Native American subsistence fishers. In this Evaluation, discussion is mostly confined to indicating groups potentially at greater risk, but there is no mention of how much greater these risks might be. Quantification of risk to these susceptible populations was not attempted.

Overall, the Committee would have liked to have seen a more detailed discussion of mode of action (MOA) in this Evaluation. Specifically, the Committee looked for discussion of MOA for thyroid effects, but also to other mechanisms that might contribute to hepatic, reproductive and developmental toxicity endpoints. Lack of a set of acceptable MOAs should be acknowledged and factored into the uncertainty analysis (also refer to Q11.2).

A significant lack of information on toxicokinetics coupled with the fact that HBCD can cross the placenta into the fetus and be secreted in the milk to the newborn and infant both limited discussion on developmental risks to infants and raised concerns that those unassessed risks might be substantial. The final risk determination did not adequately take this into consideration

but should have.

Stated a few times over the course of the meeting, *the Evaluation should provide additional details, clarity, or explanation on how the results of the risk characterization lead to the risk determination*. In some cases, particularly for aquatic environmental risk (Section 4.1.5.2; 4.1.5.3), where multiple COU's scenarios had estimated RQ's greater than one, the process that ultimately produced a determination of "no unreasonable risk" is not clear

The impact of the assumption that PPE will be used universally and appropriately has been raised by the Committee in each of the three assessments reviewed to date. The Committee states that it is unreasonable to assume that all workers will always use PPE, but this assumption is critical to the overall conclusion that there is no unreasonable risk to the workers. *This Evaluation provided RQ value for scenarios where no PPE use is assumed which allows informed comparisons with RQ values when full PPE use is assumed. This should be done consistently in TSCA evaluations*.

The Committee understands that risk mitigation follows risk assessment and is the responsibility of others in EPA, OSHA and State Agencies. But, assessing risk under varying levels and types of risk mitigation practices including use of PPE will help inform others in their risk mitigation practice. *Lacking data to demonstrate that workers actually use PPE to the extent assumed in the Evaluation, a more acceptable alternative is to determine what is reasonable use of PPE and base the assessment on that assumption.* One Committee member suggested a definition of reasonable use being that specified by current occupational enforcement standards—that is, PPE use specified in the current PEL. Referencing material safety data sheet (MSDS) information as the criteria or simply stating current "best practices" is insufficiently precise and represents an unrealistic approach to risk assessment. Another approach suggested would be to ask the authors of the referenced monitoring studies about observed use of PPE during their project. Given this observational information is very subjective and subject to error, many concluded that this information would not be acceptable as "data" for a science-based risk assessment. Published literature and NIOSH might provide some generic data on use of PPE in certain industries such as construction (see discussion in Q1.1). *The section on uncertainties should also include a statement concerning the uncertainty of regular and effective PPE regular use*.

Page 376: "Based on the EPA Development Document for Effluent Limitations, Guidelines and Standards for Organic Chemicals, Plastics and Synthetic Fibers Point Source Category, 75% removal was selected as a reasonable removal estimate." *The Evaluation is unclear as to whether the choice of 75% wastewater treatment (WWT) removal rate is evidence-based or simply an administrative decision. This point is important because as shown in Table Apx-K-1, MOE is proportional to WWT. Sensitivity analysis allowing this fraction to vary down to say 50% or 25% would provide information to better assess the impact of this assumption.*

Page 380: "EPA chose a BAF value at the low-end of the reported range. This was done because the modeled dissolved surface water estimates are generally larger than values reported in the literature. EPA compared the range of reported fish-tissue concentrations from monitoring data and found the modeled fish tissue concentrations (range of modeled dissolved surface water and low-end BAF) to be of a similar order of magnitude. Therefore, while selection of a different

BAF value would have a significant effect on fish ingestion risk estimates, the values for BAF and resulting fish ingestion exposure are well-supported by the data." *Differences in "similar order of magnitude" can be up to 10-fold, which is too big to ignore. The Evaluation should include its analysis in the report to support its choice.*

Page 380: "ADD values representing chronic exposure utilized central-tendency fish ingestion rates, which are expected to be more representative of the most populations over a sustained period. While these assumptions are expected to protect the majority of populations, there is potential for higher risk among subpopulations with consistently elevated fish consumption rates." *The Evaluation recognizes the potential for subpopulations with higher rates of fish consumption to experience higher risks, but this is not adequately discussed in uncertainty section. As mentioned in the response to a previous question, using Monte Carlo techniques, it may be possible to quantify these uncertainties in risk.*

P380: "EPA believes that these sub-scenarios sufficiently capture the range of risk estimates for all reasonably expected general population exposures, with minimal remaining unaccounted-for uncertainty. Consumer article modeling defaults are believed to be highly uncertain and highly sensitive, however estimation of the risk for consumer articles were orders of magnitude above the benchmark MOE. Therefore, EPA has high confidence in the range of risk estimates for the highly exposed general population." *Data and analysis are not provided to support the conclusion of "minimal remaining unaccounted-for uncertainty." The MOE for the exposed general population is being extrapolated to the highly exposed population based on its estimates for exposed general population. This needs discussion and justification.*

REFERENCES — HBCD

Abdallah MA, Pawar G, Harrad S. 2015. Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. Environ Int 84: 64-70. http://dx.doi.org/10.1016/j.envint.2015.07.015.

Arctic Monitoring and Assessment Programme (AMAP). 2017. AMAP Assessment 2016: Chemicals of Emerging Arctic Concern. file:///C:/Users/hale/AppData/Local/Microsoft/Windows/INetCache/Content.Outlook/AL7D7FSL/AMAP%202016%20Contaminants%20of%20Emerging%20Concern.pdf

Arnot J, McCarty L, Armitage J, Toose-Reid L, Wania F, Cousins I. 2009. An evaluation of hexabromocyclododecane (HBCD) for Persistent Organic Pollutant (POP) properties and the potential for adverse effects in the Environment. Submitted to: European Brominated Flame Retardant Industry Panel (EBFRIP). (https://www.unece.org/fileadmin/DAM/env/documents/2009/EB/wg5/wgsr45/Informal%20docs/An%20evaluation%20of%20hexabromocyclododecane_Final%20report.pdf).

Aylward LL, Hays SM. 2011. Biomonitoring-based risk assessment for hexabromocyclododecane (HBCD) [Review]. Int J Hyg Environ Health 214: 179-187. http://dx.doi.org/10.1016/j.ijheh.2011.02.002.

Binational Strategy for Hexabromocyclododecane (HBCD) Risk Management. 2017. U.S. and Canadian Governments. https://binational.net/wp-content/uploads/2018/05/HBCD_Strategy_December_19_2017.pdf

Bowen SH, Gu B, Huang Z. 2006. Diet and Digestion in Chinese Mud Carp Cirrhinus molitorella Compared with Other Ilyophagous Fishes. Transactions of the American Fisheries Society 135: 1383-1388

Cao X, Lu Y, Zhang Y, Khan K, Wang C, Baninla Y. 2018. Environmental Pollution. 236. pp:283-295. doi: 10.1016/j.envpol.2018.01.040. - A review of hexabromocyclododecanes (HBCDs) in environmental media with focus on their potential risk and management in China.

Chapin RE, Adams J, Boekelheide K, Gray LE, Jr., Hayward SW, Lees PS, McIntyre BS, Portier, KM, Schnorr TM, Selevan SG, Vandenberg JG, and Woskie SR. 2008. NTP-CERHR report on the reproductive and developmental toxicity of bisphenol A. Birth Defects Res. B. Dev. Reprod. Toxicol. 83(3): 157-395.

Chen D, Hale RC, La Guardia MJ, Luellen D, Kim S, Geisz HN. 2015. Hexabromocyclododecane flame retardant in Antarctica: Research stations as sources. Environ. Pollut. 206:611-8. doi: 10.1016/j.envpol.2015.08.024.

Chen D, Hale RC, Watts BD, La Guardia MJ, Harvey E, Mojica EK. 2010. Species-specific accumulation of polybrominated diphenyl ether flame retardants in birds of prey from the Chesapeake Bay region, USA. Environ Pollut. 158(5):1883-9. doi: 10.1016/j.envpol.2009.10.042.

Chen D; La Guardia MJ, Luellen DR, Harvey E, Mainor, TM, Hale RC. 2011. Do temporal and geographical patterns of HBCD and PBDE flame retardants in U.S. fish reflect evolving industrial usage? Environ Sci Technol 45: 8254-8261. http://dx.doi.org/10.1021/es201444w.

Choksi NY, Gloria D, Jahnke, St. Hilaire C, Shelby M. 2003. Role of Thyroid Hormones in Human and Laboratory Animal Reproductive Health, Birth Defects Research (Part B) 68 pp 479–491

Crump D, Egloff C, Chiu S, Letcher RJ, Chu S, Kennedy SW. 2010. Pipping success, isomer-specific accumulation, and hepatic mRNA expression in chicken embryos exposed to HBCD. Toxicol Sci 115: 492-500. http://dx.doi.org/10.1093/toxsci/kfq068.

Cumming H, Rucker C. 2017. Octanol-water partition coefficient measurement by a simple NMR method. ACS Omega 2: 6244- 6249. https://pubs.acs.org/doi/pdf/10.1021/acsomega.7b01102

Dach K, Bendt F, Huebenthal U, Giersiefer S, Lein PJ, Heuer H, Fritsche E. 2017. BDE-99 impairs differentiation of human and mouse NPCs into the oligodendroglial lineage by species-specific modes of action. Sci Rep. 2017 Mar 20;7:44861. doi: 10.1038/srep44861.

Davis A, Gift JS, Woodall GM, Narotsky MG, Fourman GL. 2009. The role of developmental toxicity studies in acute exposure assessments: analysis of single-day vs. multiple-day exposure regimens. Regul Toxicol Pharmacol 54: 134-142. http://dx.doi.org/10.1016/j.yrtph.2009.03.006.

Davis JW, Gonsior S, Marty G, Ariano J. 2005. The transformation of hexabromocyclododecane in aerobic and anaerobic soils and aquatic sediments. Water Res 39: 1075-1084. http://dx.doi.org/10.1016/j.watres.2004.11.024.

Davis JW, Gonsior, SJ, Markham DA, Friederich U, Hunziker RW, Ariano JM. (2006. Biodegradation and product identification of [14C]hexabromocyclododecane in wastewater sludge and freshwater aquatic sediment. Environ Sci Technol 40: 5395-5401. http://dx.doi.org/10.1021/es060009m.

Drottar KR, Krueger HO. 2000. Hexabromocyclododecane (HBCD): A flow-through bioconcentration test with the rainbow trout (Oncorhynchus mykiss). Easton, MD: Wildlife International Ltd.

Drottar KR, Krueger HO. 2000. Hexabromocyclododecane (HBCD): A flow-through

bioconcentration test with the rainbow trout (Oncorhynchus mykiss). Easton, MD: Wildlife International Ltd.

Eggesbø M, Thomsen C, Jørgensen JV, Becher G, Odland JØ, Longnecker MP. 2011. Associations between brominated flame retardants in human milk and thyroid-stimulating hormone (TSH) in neonates. Environ Res 111: 737-743. http://dx.doi.org/10.1016/j.envres.2011.05.004.

Ema M, Fujii S, Hirata-Koizumi M, Matsumoto M. 2008. Two-generation reproductive toxicity study of the flame retardant hexabromocyclododecane in rats. Reprod Toxicol 25: 335-351. http://dx.doi.org/10.1016/j.reprotox.2007.12.004.

Eriksson P, Fischer C, Wallin M, Jakobsson, E, Fredriksson A. 2006. Impaired behaviour, learning and memory, in adult mice neonatally exposed to hexabromocyclododecane (HBCDD). Environ Toxicol Pharmacol 21: 317-322. http://dx.doi.org/10.1016/j.etap.2005.10.001.

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). 2011. Refined Approachees for Risk Assessment of PBT/vPvB Chemicals. Technical Report No. 112. ISSN-0773-8072-112.

Forhead AJ, Fowden AL. 2014. Thyroid hormones in fetal growth and prepartum maturation [Review]. J Endocrinol 221: R87-R103. http://dx.doi.org/10.1530/JOE-14-0025.

Frank DF, Brander SM, Hasenbein S, Harvey DJ, Lein PJ, Geist J, Connon RE. 2019. Developmental exposure to environmentally relevant concentrations of bifenthrin alters transcription of mTOR and ryanodine receptor-dependent signaling molecules and impairs predator avoidance behavior across early life stages in inland silversides (Menidia beryllina). Aquat Toxicol. 2019 Jan;206:1-13. doi: 10.1016/j.aquatox.2018.10.014

Fromme H, Hilger B, Albrecht M, Gries W, Leng G, Völkel W. 2016. Int J Hyg Environ Health. 219(4-5). pp380-8. doi: 10.1016/j.ijheh.2016.03.003. - Occurrence of chlorinated and brominated dioxins/furans, PCBs, and brominated flame retardants in blood of German adults

Genskow KR, Bradner JM, Hossain MM, Richardson JR, Caudle WM. 2015. Selective damage to dopaminergic transporters following exposure to the brominated flame retardant, HBCDD. Neurotoxicol Teratol 52: 162-169. http://dx.doi.org/10.1016/j.ntt.2015.06.003.

Geyer HJ, Schramm KW, Darnerud PO, Aune M, Feicht EA, Fried KW, Henkelmann B, Lenoir D, Schmid P, McDonald TA. 2004. Terminal elimination half-lives of the brominated flame retardants TBBPA, HBCD, and lower brominated PBDEs in humans. Organohalogen Compd 66: 3820-3825.

Gouin T, Mackay D, Jones KC, Harner T, Meijer SN 2004. Evidence for the "grasshopper"

effect and fractionation during long-range atmospheric transport of organic contaminants. Environ Pollut. 128(1-2):139-48.

Guerra P, Alaee M, Jiménez B, Pacepavicius G, Marvin C, MacInnis G, Eljarrat E, Barceló D, Champoux L, Fernie K. 2012. Emerging and historical brominated flame retardants in peregrine falcon (Falco peregrinus) eggs from Canada and Spain. Environment International, 40, 179-186, https://doi.org/10.1016/j.envint.2011.07.014

Guigueno MF, Fernie KJ. 2017. Birds and flame retardants: A review of the toxic effects on birds of historical and novel flame retardants Environ Res.154:398-424

Hachisuka A, Nakamura R, Sato Y, Nakamura R, Shibutani M, Teshima R. 2010. Effects of perinatal exposure to the brominated flame-retardant hexabromocyclododecane (HBCD) on the developing immune system in rats [translation]. Kokuritsu Iyakuhin Shokuhin Eisei Kenkyūjo Hōkoku (128): 58-64.

Hansch C, Leo A, Hoekman D. 1995. Exploring QSAR: Hydrophobic, electronic, and steric constants. In C Hansch; A Leo, DH Hoekman (Eds.), Exploring QSAR: Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society.

He MJ, Luo, XJ, Yu, LH, Wu, JP, Chen, SJ, Mai, BX. 2013. Diasteroisomer and enantiomer-specific profiles of hexabromocyclododecane and tetrabromobisphenol A in an aquatic environment in a highly industrialized area, South China: vertical profile, phase partition, and bioaccumulation. Environ Pollut 179: 105-110. http://dx.doi.org/10.1016/j.envpol.2013.04.016.

Hedge JM, Devito MJ, Crofton KM. 2009. In vivo acute exposure to polychlorinated biphenyls: effects on free and total thyroxine in rats. Int J Toxicol 28: 382-391. http://dx.doi.org/10.1177/1091581809344631.

Huang Y-W, Karasov WH. 2000. Oral bioavailability and toxicokinetics of 3,3',4,4',5-pentachlorobiphenyl (PCB 126) in northern leopard frogs, *Rana pipiens*. doi:10.1002/etc.5620190712. Environmental Toxicology and Chemistry, 19(7):1788-1794.

Jang M, Shim WJ, Han GM, Rani M, Song YK, Hong SH. 2016. Styrofoam debris as a source of hazardous additives for marine organisms. Environ. Sci. Technol., 50(10), 4951-4960. http://doi.org/10.1021/acs.est.5b05485

Kajiwara N, Sueoka M, Ohiwa T, Takigami H. 2009. Determination of flame-retardant hexabromocyclododecane diastereomers in textiles. Chemosphere. 74(11):1485-9. doi: 10.1016/j.chemosphere.2008.11.046.

Kiciński M, Viaene MK, Den Hond E, Schoeters G, Covaci A, Dirtu AC, Nelen V, Bruckers L, Croes K, Sioen , Baeyens W, Van Larebeke N, Nawrot TS. 2012. Neurobehavioral function and

low-level exposure to brominated flame retardants in adolescents: A cross-sectional study. Environ Health 11: 86. http://dx.doi.org/10.1186/1476-069X-11-86.

Kim KH, Bose DD, Ghogha A, Riehl J, Zhang R, Barnhart CD, Lein PJ, Pessah IN. 2011. Para- and ortho-substitutions are key determinants of polybrominated diphenyl ether activity toward ryanodine receptors and neurotoxicity. Environ Health Perspect. 2011 Apr;119(4):519-26. doi: 10.1289/ehp.1002728.

Klimisch H-J, Andreae M, Tillmann U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25: 1-5.

Lee CC, Chang WH, Chen HL. 2019. Environmental Pollution 249. pp 728-734. doi: 10.1016/j.envpol.2019.03.040. Epub 2019 Mar 14. - Dietary exposure and risk assessment of exposure to hexabromocyclododecanes in a Taiwan population. Used to estimate an MOE.

Lilienthal H, van der Ven LT; Piersma AH; Vos JG. (2009). Effects of the brominated flame retardant hexabromocyclododecane (HBCD) on dopamine-dependent behavior and brainstem auditory evoked potentials in a one-generation reproduction study in Wistar rats. Toxicol Lett 185: 63-72. http://dx.doi.org/10.1016/j.toxlet.2008.12.002.

Lindberg P, Sellström U, Häggberg L, de Wit CA. 2004. Higher brominated diphenyl ethers and hexabromocyclododecane found in eggs of peregrine falcons (Falco peregrinus) breeding in Sweden. Environ Sci Technol 38: 93-96. http://dx.doi.org/10.1021/es034614q.

Manviri R, Myung HG, Joon SW, Mi J, Hee HS. 2017 Releasing of hexabromocyclododecanes from expanded polystyrenes in seawater -field and laboratory experiments. Chemosphere 185:798-805.

Maranghi F, Tassinari, R, Moracci G, Altieri I, Rasinger JD, Carroll TS, Hogstrand C, Lundebye AK, Mantovani A. 2013. Dietary exposure of juvenile female mice to polyhalogenated seafood contaminants (HBCD, BDE-47, PCB-153, TCDD): comparative assessment of effects in potential target tissues. Food Chem Toxicol 56: 443-449. http://dx.doi.org/10.1016/j.fct.2013.02.056.

Mezin L, Hale RC. 2004a. Effect of humic acids on toxicity of DDT and chlorpyrifos to freshwater and estuarine invertebrates. Environ. Toxicol. Chem. 23:583-590.

Mezin L. Hale RC. 2004b. Combined effects of humic acids and salinity on solid-phase microextraction of DDT and chlorpyrifos, an estimator of their bioavailability. Environ. Toxicol. Chem. 23: 576-582.

Mi J, Joon SW, Kyoung SY, Myung HG, Manviri R, Hee HS. 2017. Widespread detection of a brominated flame retardant, hexabromocyclododecane, in expanded polystyrene marine debris

and microplastics from South Korea and the Asia-Pacific coastal region. Environmental pollution 231:785-794.

Miller-Rhodes P, Popescu M, Goeke C, Tirabassi T, Johnson L, Markowski VP. 2014. Prenatal exposure to the brominated flame retardant hexabromocyclododecane (HBCD) impairs measures of sustained attention and increases age-related morbidity in the Long-Evans rat. Neurotoxicol Teratol 45: 34-43. http://dx.doi.org/10.1016/j.ntt.2014.06.009.

MOEJ. 2009. 6-Week Administration Study of 1,2,5,6,9,10-Hexabromocyclododecane for avian reproduction toxicity under long-day conditions using Japanese Quail. Tokyo, Japan: Ministry of the Environment, Japan.

Paul KB, Hedge JM, Devito MJ, Crofton KM. 2010. Short-term exposure to triclosan decreases thyroxine *in vivo* via upregulation of hepatic catabolism in Young Long-Evans rats. Toxicol Sci 113: 367-379. http://dx.doi.org/10.1093/toxsci/kfp271.

Posner S, Roos S, Olsson E. 2010. Exploration of Management options for HBCD, SWEREA IVF Project report 10/11, Sweden, page 21. https://www.unece.org/fileadmin/DAM/env/lrtap/TaskForce/popsxg/2010/Updated%20documetns_June2010/Exploration%20of%20management%20options%20for%20HBCD.pdf .

Potter KE, Watts BD, La Guardia MJ, Harvey EP, Hale RC. 2009. Polybrominated diphenyl ether flame retardants in Chesapeake Bay region, USA, peregrine falcon (*Falco peregrinus*) eggs: Urban/rural trends. Environ. Toxicol. Chem. 28(5) 973-981.

Rani M, Myung HG, Joon SW, Mi J, Hee HS. 2017. Releasing of hexabromocyclododecanes from expanded polystyrenes in seawater-field and laboratory experiments. Chemosphere 185:798-805.

Rasinger JD, Carroll TS, Lundebye AK, Hogstrand C. 2014. Cross-omics gene and protein expression profiling in juvenile female mice highlights disruption of calcium and zinc signaling in the brain following dietary exposure to CB-153, BDE-47, HBCD or TCDD. Toxicology. 2014 Jul 3;321:1-12. doi: 10.1016/j.tox.2014.03.006.

Rasinger JD, Carroll TS, Maranghi F, Tassinari R, Moracci G, Altieri I, Mantovani A, Lundebye AK, Hogstrand C. 2018. Low dose exposure to HBCD, CB-153 or TCDD induces histopathological and hormonal effects and changes in brain protein and gene expression in juvenile female BALB/c mice. Reprod Toxicol. 2018 Sep;80:105-116. doi: 10.1016/j.reprotox.2018.06.010.

Rawn DF; Gaertner, DW, Weber, D, Curran, IH, Cooke, GM, Goodyer CG. 2014. Hexabromocyclododecane concentrations in Canadian human fetal liver and placental tissues. Sci Total Environ 468-469: 622-629. http://dx.doi.org/10.1016/j.scitotenv.2013.08.014.

Reffatto V, Rasinger JD, Carroll TS, Ganay T, Lundebye AK, Sekler I, Hershfinkel M, Hogstrand C. 2018. Parallel in vivo and in vitro transcriptomics analysis reveals calcium and zinc signalling in the brain as sensitive targets of HBCD neurotoxicity. Arch Toxicol. 2018 Mar;92(3):1189-1203. doi: 10.1007/s00204-017-2119-2.

Roper CS, Madden S, Biesemeier JA, Hoonagel H, Rothenbacker K. 2007. **The *in vitro* percutaneous absorption of radiolabelled hexabromocyclododecane (HBCD) through human skin** Organohalogen Compd. 69: .2094-2095.

Rosen Y. 2013. Wave of Styrofoam from 2011 tsunami threatens Alaska environment. Reuters. January A 30, 2013. https://www.reuters.com/article/us-usa-tsunami-styrofoam-idUSBRE90T06F20130130

Roze E, Meijer L, Bakker A, Van Braeckel KNJ A, Sauer PJJ, Bos AF. 2009. Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. Environ Health Perspect 117: 1953-1958. http://dx.doi.org/10.1289/ehp.0901015.

Saegusa Y, Fujimoto H, Woo GH, Inoue K, Takahashi,M, Mitsumori K, Hirose M, Nishikawa A, Shibutani M. 2009. Developmental toxicity of brominated flame retardants, tetrabromobisphenol A and 1,2,5,6,9,10-hexabromocyclododecane, in rat offspring after maternal exposure from mid-gestation through lactation. Reprod Toxicol 28: 456-467. http://dx.doi.org/10.1016/j.reprotox.2009.06.011.

Schriks M, Zvinavashe E, Furlow JD, Murk AJ. 2006. Disruption of thyroid hormone-mediated Xenopus laevis tadpole tail tip regression by hexabromocyclododecane (HBCD) and 2,2',3,3',4,4',5,5',6-nona brominated diphenyl ether (BDE206). Chemosphere. 65(10):1904-8.

Sethi S, Morgan RK, Feng W, Lin Y, Li X, Luna C, Koch M, Bansal R, Duffel MW, Puschner B, Zoeller RT, Lehmler HJ, Pessah IN, Lein PJ. 2019. Comparative Analyses of the 12 Most Abundant PCB Congeners Detected in Human Maternal Serum for Activity at the Thyroid Hormone Receptor and Ryanodine Receptor. Environ Sci Technol. 2019 Apr 2;53(7):3948-3958. doi: 10.1021/acs.est.9b00535.

Shi Y, Xu X, Chen J, Liang, R, Zheng X, Shi Y, Wang Y. 2018. Antioxidant gene expression and metabolic responses of earthworms (Eisenia fetida) after exposure to various concentrations of hexabromocyclododecane. Environ Pollut 232: 245-251.

Singla VI, Patrice M, Sutton PM, Woodruff TJ. 2019. The Environmental Protection Agency Toxic Substances Control Act Systematic Review Method May Curtail Science Used to Inform Policies, With Profound Implications for Public Health. Am J Public Health. 2019 Jul;109(7):982-984. doi: 10.2105/AJPH.2019.305068.

Tomko G, McDonald, KM. 2013. Environmental fate of hexabromocyclododecane from a new Canadian electronic recycling facility. Journal of Environmental Management 114:324-327.

U.S. EPA. 2009. User's guide and technical documentation: KABAM version 1.0 (Kow (based) Aquatic BioAccumulation Model). https://www.epa.gov/sites/production/files/2015-07/documents/kabam_v1_0_users_guide.pdf.

U.S. EPA. 2012. Benchmark dose technical guidance. (EPA/100/R-12/001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. https://www.epa.gov/risk/benchmark-dose-technical-guidance.

U.S. EPA. 2019. Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster (HBCD), Systematic Review Supplemental File: Data Extraction Tables of Environmental Hazard Studies. . https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2016-0735.

van der Ven, LTM, van de Kuil T, Leonards PEG, Slob W, Lilienthal H, Litens S; Herlin, M; Håkansson, H; Cantón, RF; van den Berg, M; Visser, TJ; van Loveren, H, Vos JG, Piersma AH. 2009. Endocrine effects of hexabromocyclododecane (HBCD) in a one-generation reproduction study in Wistar rats. Toxicol Lett 185: 51-62. http://dx.doi.org/10.1016/j.toxlet.2008.12.003.

Venkatesan A.K, Halden RU. 2014. Brominated flame retardants in U.S. biosolids from the EPA national sewage sludge survey and chemical persistence in outdoor soil mesocosms. Water Res. 55: 133–142.

Wheater PR, Burkitt HG. 1996. Wheater's basic histopathology: a colour atlas and text. New York: Churchill Livingstone.

WIL Research. 2001. 90-Day oral (gavage) toxicity study of HBCD in rats. (WIL-186012). Washington, DC: Chemical Manufacturers Association.

Woodruff TJ, Sutton P. 2009. The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes. Environ Health Perspect. 2014 Oct;122(10):1007-14. doi: 10.1289/ehp.1307175. Epub 2014 Jun 25.

Wu JP, Guan YT, Zhang Y, Luo, XJ, Zhi H, Chen SJ, Mai BX. 2010. Trophodynamics of hexabromocyclododecanes and several other non-PBDE brominated flame retardants in a freshwater food web. Environ Sci Technol 44: 5490-5495. http://dx.doi.org/10.1021/es101300t.

Yi S, Liu JG, Jin J, Zhu J. 2016. Assessment of the occupational and environmental risks of hexabromocyclododecane (HBCD) in China. Chemosphere 150: 431-437.

Yu CC, Atallah YH. 1980. Pharmacokinetics of HBCD in rats [unpublished]. Rosemont, IL: Vesicol Chemical Corporation.

Zhou T, Ross DG, Devito MJ, Crofton KM. 2001. Effects of short-term in vivo exposure to polybrominated diphenyl ethers on thyroid hormones and hepatic enzyme activities in weanling rats. Toxicol Sci 61: 76-82.

Zhu H, Zhang K, Sun H, Wang F, Yao Y. 2017. Spatial and temporal distributions of hexabromocyclododecanes in the vicinity of an expanded polystyrene material manufacturing plant in Tianjin, China. Environ Pollut. 2017; 222:338-347. doi: 10.1016/j.envpol.2016.12.029

Zoeller RT, Tan SW, Tyl RW. 2007. General background on the hypothalamic-pituitary-thyroid (HPT) axis [Review]. Crit Rev Toxicol 37: 11-53. http://dx.doi.org/10.1080/10408440601123446.