OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

October 1, 2024

MEMORANDUM

SUBJECT: Transmittal of Meeting Minutes and Final Report for the Science Advisory Committee on Chemicals Virtual Public Meeting entitled: "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)" held on July 30-August 1, 2024.

FROM: Alaa Kamel, PhD
Chemist, Designated Federal Official
Peer Review and Ethics Branch (PREB)
Mission Support Division (MSD)
Office of Program Support (OPS)

ALAA KAMEL
Digitally signed by ALAA KAMEL
Date: 2024.10.01 16:40:17 -04'00'

THRU: Steven Knott, MS
Chief, Peer Review and Ethics Branch (PREB)
Mission Support Division (MSD)
Office of Program Support (OPS)

Digitally signed by STEVEN KNOTT
Date: 2024.10.02 '07:56:47 -04'00

Steven M. Knott

AND Hayley Hughes, DrPH, MPH, CSP
Director, Office of Program Support (OPS)

HAYLEY HUGHES
Digitally signed by HAYLEY HUGHES
Date: 2024.10.02 09:08:57 -04'00'

TO: Elissa Reaves, PhD
Director, Office of Pollution Prevention and Toxics (OPPT)

Attached, please find the meeting minutes and final report for the Science Advisory Committee on Chemicals virtual public meeting held via Webcast on July 30-August 1, 2024. This report addresses a set of scientific issues being considered by the Environmental Protection Agency and reviewed by the SACC regarding EPA's Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP).

Attachment:
Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)".

cc: Michal Freedhoff, PhD
Mark Hartman, MA
Jeffrey Morris, PhD
Karen Eisenreich, PhD
Yvette Selby-Mohamadu, PhD
Collin Beachum, PhD
Jacqueline Mosby, MPH
Steven Knott, MS
OPPT docket

Scientific Advisory Committee on Chemicals (SACC)

George P. Cobb, PhD, Chair
Udayan Apte, PhD
Marissa Baker, PhD
Christine Chaisson, PhD
Stephanie Eick, PhD
Robinan Gentry, PhD
Cynthia Graham, PhD
Wendy Heiger-Bernays, PhD
Allison Jenkins, MPH
Li Li, DSc
Francheska Merced-Nieves, PhD
Mary Ottinger, PhD
Jennifer Przybyla, PhD
David Reif, PhD

SACC *ad hoc* Peer Reviewers

Raymond M. David, PhD
Elinor Fanning, PhD
Penelope A. Fenner-Crisp, PhD
Kembra L. Howdeshell, PhD
Jeanelle M. Martinez, PhD, DABT
Molly Shuman-Goodier, PhD
Daniel J. Spade, PhD
Douglas C. Wolf, DVM, PhD

Science Advisory Committee on Chemicals

Meeting Minutes and Final Report

No. 2024-2

Docket ID: EPA-HQ-OPPT-2024-0073

For the

Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)

Virtual Meeting via Webcast

Held on

July 30-August 1, 2024

NOTICE

The Science Advisory Committee on Chemicals (SACC) is a Federal Advisory Committee operating in accordance with the Federal Advisory Committee Act (FACA) and established under the provisions of the Toxic Substances Control Act (TSCA) as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act of 2016. The SACC provides advice, information, and recommendations to the US Environmental Protection Agency's ("EPA" or "Agency") Administrator on chemicals and chemical-related issues regarding the impact of regulatory actions on health and the environment. 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 employed on an *ad hoc* basis to assist in reviews conducted by the SACC. The meeting minutes and final report are provided as part of the activities of the SACC.

The meeting minutes and final report represent the views and recommendations of the 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 30-August 1, 2024, SACC meeting represent the SACC's consideration and review of scientific issues associated with the Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP). The SACC carefully considered all information provided and presented by the Agency, as well as information presented by the public.

The Peer Review and Ethics Branch of EPA's Office of Program Support conducted the quality assurance and quality control of the meeting minutes and final report. The SACC Chair, Dr. George Cobb, and SACC meeting Designated Federal Official (DFO), Dr. Alaa Kamel, compiled and certified the minutes and final report, which is publicly available through the e-docket No. EPA-HQ-OPPT-2024-0073 , accessible through the docket portal at Regulations.gov, and the Peer Review of EPA's Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP) web page of the SACC website. Further information about SACC reports and activities can be obtained from its website at TSCA Scientific Peer Review Committees. Interested persons are invited to contact the DFO for this meeting, Dr. Alaa Kamel, via e-mail at kamel.alaa@epa.gov, for questions regarding this peer review.

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CERTIFICATION

We, the undersigned, certify that the minutes in this report are an accurate and complete summary of the SACC's July 30-August 1, 2024, discussions of EPA's "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)" under the Toxic Substances Control Act (TSCA).

George Cobb, PhD
Chair,
Science Advisory Committee on Chemicals

Signature:

George Cobb

Digitally signed by George Cobb
Date: 2024.10.01 15:31:07 -05'00'

Date: 10/01/2024

Alaa Kamel, PhD
Designated Federal Official,
Science Advisory Committee on Chemicals

Signature:

ALAA KAMEL

Digitally signed by ALAA KAMEL
Date: 2024.10.01 16:39:26 -04'00'

Date: 10/01/2024

LIST OF ACRONYMS AND ABBREVIATIONS

ACC	American Chemistry Council
ACS	American Chemical Society
ADR	Acute Dose Rate
AERMOD	American meteorological society/Environmental protection agency Regulatory MODel
AF	Assessment Factor
AhR	Aryl hydrocarbon Receptor
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANKCL	Aggressive Natural Killer Cell Leukemia
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BBP	Butyl Benzyl Phthalate
BMD	Benchmark Dose
BMDL	Benchmark Dose (lower confidence) Limit
BMR	Benchmark Response
CAR	Androstane Receptor
CDR	Chemical Data Repository
CEM	Consumer Exposure Model
CI	Confidence Interval
COC	Contaminants OF Concern
COU	Conditions OF Use
CPSC	Consumer Products Safety Commission
CQ	Charge Question
CRA	Cumulative Risk Assessment
DBP	Dibutyl phthalate
DCHP	Dicyclohexyl phthalate
DDEF	Data-Derived Extrapolation Factor
DEHP	Di(2-ethylhexyl) phthalate
DFO	Designated Federal Official
DIBP	Diisobutyl phthalate
DIDP	Diisodecyl phthalate
DINP	Diisononyl phthalate
DMP	Dimethyl phthalate
DNA	Deoxyribonucleic Acid
EAR	Exposure Activity Ratio
EC	Environment Canada
ECCC	Environment and Climate Change Canada

ECHA	European Chemicals Agency
ECOSAR	Ecological Structure-Activity Relationship
ECRAD	Existing Chemical Risk Assessment Division
EFSA	European Food Safety Authority
EIM	Environmental Information Management
EPA	Environmental Protection Agency
EPI	Estimation Program Interface
EU	European Union
F1	First filial generation
F2	Second filial generation
FACA	Federal Advisory Committee Act
GD	Gestation Day
GLP	Good Laboratory Practice
HC	Health Canada
HCD	Historical Control Data
HEC	Human Equivalent Concentration
HED	Human Equivalent Dose
HESI	Health and Environmental Sciences Institute
HRF	Human Relevance Framework
HSD	Harlan Sprague Dawley
IRIS	Integrated Risk Information System
KC	Key Characteristics
KE	Key Events
K_{OA}	Octanol/Air Partition Coefficient
K_{OC}	Organic Carbon/Water Partition Coefficient
K_{OW}	Octanol/Water Partition Coefficient
LCT	Leydig Cell Tumor
LGL	Large Granular Lymphocyte
LL	from Line X to Line Y
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
MATC	Maximum Acceptable Toxicant Concentration
MCOP	Mono-Carboxy-isoOctyl Phthalate
MIE	Molecular Initiating Event
MINP	Mono-IsoNonyl Phthalate
MNCL	MonoNuclear Cell Leukemia
MOA	Mode Of Action
MOE	Margin Of Exposure
NA	Not Available
NAM	New Approach Methodologies

NAS	National Academy of Sciences
NASEM	National Academies of Sciences, Engineering, and Medicine
NHANES	National Health and Nutrition Examination Survey
NIPH	National Institute of Public Health
NK	Natural Killer
NOAEL	No Observed Adverse Effects Level
NOEC	No Observed Effect Concentration
NR	Nuclear Receptor
NTP	National Toxicology Program
NTTC	National Tribal Toxics Council
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organisation for Economic Co-operation and Development
OES	Occupational Exposure Scenario
OPP	Office of Pesticides Program
OPPT	Office of Pollution Prevention and Toxics
OPPTS	Office of Prevention, Pesticides and Toxic Substances (Office of Chemical Safety and Pollution Prevention- (OCSPP))
OPS	Office of Program Support
PBPK	Physiologically Based PharmacoKinetic
PESS	Potentially Exposed or Susceptible Subpopulation(s)
PFAS	Poly FluoroAlkyl Substances
PND	Postnatal Day
POD	Point Of Departure
PPAR	Peroxisome Proliferator-Activated Receptor
PROTEX	PROduction-To-EXposure
PV	Production Volume
PVC	PolyVinyl chloride
PXR	Pregnane X Receptor
QA	Quality Assurance
QC	Quality Control
QSAR	Quantitative Structure–Activity Relationship
RAGS	Risk Assessment Guidance for Superfund
RAIDAR	Risk Assessment IDentification And Ranking
RCT	Randomized Controlled Trials
RE	Risk Evaluation
RIVM	Dutch National Institute for Public Health and the Environment
RPF	Relative Potency Factor
SACC	Science Advisory Committee on Chemicals
SD	Sprague Dawley
SVOCs	Semi-Volatile Organic Compounds

TG	Test Guidelines
TK	ToxicoKinetics
TRI	Toxics Release Inventory
TRV	Toxicity Reference Value
TSCA	Toxic Substances Control Act
TSS	Total Suspended Solid
UF	Uncertainty Factor
USFDA	United States Food and Drug Administration
USCPSC	United States Consumer Products Safety Commission
VVWM	Variable Volume Water Model
WHO	World Health Organization
WOE	Weight Of Evidence
WWT	WasteWater Treatment
WWTP	Wastewater Treatment Plants

SCIENCE ADVISORY COMMITTEE ON CHEMICALS (SACC)

Review of the Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and the Draft Hazard Assessments for Di-isononyl Phthalate (DINP)

PARTICIPANTS

SACC Chair

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

Designated Federal Official

Alaa Kamel, PhD
Office of Program Support
Office of Chemical Safety and Pollution Prevention
US Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460
Phone: 202-564-5336
Email: kamel.alaa@epa.gov

Science Advisory Committee on Chemicals Members

Udayan Apte, PhD
Department of Pharmacology, Toxicology, and Therapeutics
KU Medical Center
University of Kansas
Kansas City, Kansas

Marissa Baker, PhD
Department of Environmental & Occupational Health Sciences
School of Public Health
University of Washington
Seattle, Washington

Christine Chaisson, PhD
The LifeLine Group
Annandale, Virginia

Stephanie Eick, PhD
Rollins School of Public Health
Emory University
Atlanta, Georgia

Robinan Gentry, PhD
Ramboll US Corporation
Monroe, Louisiana

Cynthia Graham, PhD
Independent Toxicology Consultant
Denver, Colorado

Wendy Heiger-Bernays, PhD
Research Division
Office of Research and Standard
Massachusetts Department of Environmental Protection (MDEP)
Boston, Massachusetts

Allison Jenkins, MPH
Toxicology, Risk Assessment, and Research Division
Texas Commission on Environmental Quality (TCEQ)
Austin, Texas

Li Li, DSc
School of Public Health
University of Nevada
Reno, Nevada

Francheska Merced-Nieves, PhD
Icahn School of Medicine at Mount Sinai
New York, New York

Mary Ottinger, PhD
Department of Biology and Biochemistry
University of Houston
Houston, Texas

Jennifer Przybyla, PhD
Agency for Toxic Substances and Disease Registry (ATSDR)
Centers for Disease Control and Prevention (CDC)
Atlanta, Georgia

David Reif, PhD
Predictive Toxicology Branch (PTB)
National Institute of Environmental Health Sciences
Durham, North Carolina

SACC *ad hoc* Peer Reviewers

Raymond M. David, PhD
David Tox. LLC
Sarasota, Florida

Elinor Fanning, PhD
Office of Environmental Health Sciences
Washington State Department of Health
Tumwater, Washington

Penelope A. Fenner-Crisp, PhD
Independent Consultant
Charlottesville, Virginia

Kembra L. Howdeshell, PhD
Integrated Health Assessment Branch
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

Jeanelle M. Martinez, PhD, DABT
B. Braun Medical, Inc.
Irvine, California

Molly Shuman-Goodier, PhD
Toxics Biological Observation System (TBiOS)
Washington Department of Fish and Wildlife
Olympia, Washington

Daniel J. Spade, PhD
Department of Pathology & Laboratory Medicine
Brown University
Providence, Rhode Island

Douglas C. Wolf, DVM, PhD (retired. US EPA and Syngenta)
Independent Consultant
Pittsboro, North Carolina

INTRODUCTION

The Science Advisory Committee on Chemicals (SACC or Committee), established pursuant to the Toxic Substances Control Act (TSCA) of 1976, as amended by The Frank R. Lautenberg Chemical Safety for the 21st Century Act in 2016, completed its review of the set of scientific issues being considered by the United States Environmental Protection Agency (US EPA, or Agency) regarding the review of the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and the Draft Hazard Assessments for Di-isononyl Phthalate (DINP)" under the Toxic Substances Control Act.

Advance notice of the meeting and request for nominations of *ad hoc* experts was published in the Federal Register on February 29, 2024, followed by a notice published in the Federal Register on May 20, 2024, of the SACC meeting and request for comments on the documents. The review was conducted in an open meeting held virtually via Zoom and streamed live on YouTube (see Meeting Viewing Information) from July 30 – August 1, 2024. The draft risk evaluation of DIDP and draft hazard assessments for DINP, supplemental files, and related documents supporting the SACC meeting are posted in the public e-docket at Regulations.gov, Docket No. EPA-HQ-OPPT-2024-0073. Dr. George Cobb chaired the meeting and Dr. Alaa Kamel served as the Designated Federal Official (DFO).

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

During the SACC meeting, the DFO, SACC Chair and US EPA personnel provided the following presentations in the order listed below:

Opening of Meeting – Alaa Kamel, PhD, Designated Federal Official, Office of Program Support (OPS), Office of Chemical Safety and Pollution Prevention (OCSPP), EPA

Introduction and Identification of Panel Members – George Cobb, PhD, Chair, Science Advisory Committee on Chemicals (SACC)

Introduction and Welcome – Elissa Reeves, PhD, Director, Office of Pollution Prevention and Toxics (OPPT), OCSPP, EPA

Welcome and Introductory Comments – Michal Freedhoff, PhD, Assistant Administrator, OCSPP, EPA

Overview of the 2024 Draft Risk Evaluation for DIDP & Draft Hazard Assessment for DINP

Part 1: Introduction to TSCA, DIDP, and DINP

Collin Beachum, Anthony Luz, Existing Chemicals Risk Assessment Division (ECRAD), OPPT, OCSPP, EPA

Overview of the 2024 Draft Risk Evaluation for DIDP & Draft Hazard Assessment for DINP

Part 2: DIDP Human Health Hazard and Exposure

Anthony Luz, Maiko Arashiro, Yashfin Mahid, Laura Krnavek, Existing Chemicals Risk Assessment Division (ECRAD), OPPT, OCSPP, EPA

Overview of the 2024 Draft Risk Evaluation for DIDP & Draft Hazard Assessment for DINP

Part 3: DINP Human Health Hazard

Anthony Luz, Existing Chemicals Risk Assessment Division (ECRAD), OPPT, OCSPP, EPA.

Overview of the 2024 Draft Risk Evaluation for DIDP & Draft Hazard Assessment for DINP

Part 4: DIDP Environmental Hazard and Exposure, and DINP Environmental Hazard

Jennifer Brennan, Chris Green, Existing Chemicals Risk Assessment Division (ECRAD), OPPT, OCSPP, EPA.

Questions from the SACC on EPA presentations

PUBLIC COMMENTERS

Oral Presentations

Oral statements from the public were presented during the SACC meeting as follows:

#	Name	Organization	Location	Written version of presentation
1	Amanda Buerger, PhD, DABT	ToxStrategies, LLC	Cincinnati, Ohio	EPA-HQ-OPPT-2024-0073-0083
2	Paul DeLeo, PhD	American Chemistry Council	Washington, District of Columbia	EPA-HQ-OPPT-2024-0073-0090
3	Jennifer Foreman, DABT, PhD	ACC High Phthalates Panel	Spring, Texas	EPA-HQ-OPPT-2024-0073-0078
4	Suzanne Hartigan, PhD	American Chemistry Council	Washington, District of Columbia	EPA-HQ-OPPT-2024-0073-0079
5	Thomas Hmiel	Teknor Apex Company	Pawtucket, Rhode Island	EPA-HQ-OPPT-2024-0073-0082
6	Rashmi Joglekar, PhD	University of California, San Francisco	San Francisco, California	EPA-HQ-OPPT-2024-0073-0085
7	Kelly Lester	Earthjustice	New York, New York	EPA-HQ-OPPT-2024-0073-0091
8	Silvia Maberti, PhD	ExxonMobil Biomedical Sciences	Spring, Texas	EPA-HQ-OPPT-2024-0073-0080
9	Hua Qian, PhD	ExxonMobil Biomedical Sciences	Annandale, New Jersey	EPA-HQ-OPPT-2024-0073-0081
10	Nigel Sarginson	Sarginson Consulting SRL	Lasne, Belgium	EPA-HQ-OPPT-2024-0073-0093
11	Chad Thompson, PhD, MBA	ToxStrategies, LLC	Katy, Texas	EPA-HQ-OPPT-2024-0073-0084
12	Paige Varner, PhD	Environmental Defense Fund	Durham, North Carolina	EPA-HQ-OPPT-2024-0073-0092

Written comments

Written comments were submitted in response to the SACC meeting on the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and the Draft Hazard Assessments for Di-isononyl Phthalate (DINP)" under the Toxic Substances Control Act as follows:

#	Name	Organization	Location	Written version of presentation
1	Catherine Palin	Alliance for Automotive Innovation	Washington, District of Columbia	EPA-HQ-OPPT-2024-0073-0065
2	Scientists, Academics, and Clinicians	University of California, San Francisco, *et al*.	San Francisco, California	EPA-HQ-OPPT-2024-0073-0063
3	Hannah Cook	NA	NA	EPA-HQ-OPPT-2024-0073-0064
4	Dianne Barton, PhD	National Tribal Toxics Council	Anchorage, Alaska	EPA-HQ-OPPT-2024-0073-0070
5	Eileen Conneely	American Chemical Council	Washington, District of Columbia	EPA-HQ-OPPT-2024-0073-0069
6	NA	European Plasticizers	Brussels, Belgium	EPA-HQ-OPPT-2024-0073-0067
7	André Algazi	California Department of Toxic Substances Control	Sacramento, California	EPA-HQ-OPPT-2024-0073-0068
8	Anonymous	NA	NA	EPA-HQ-OPPT-2024-0073-0058
9	Katherine O'Brien and Paige Varner	Alaska Community Action on Toxics	NA	EPA-HQ-OPPT-2024-0073-0062
Attachments at: EPA-HQ-OPPT-2024-0073-0071, EPA-HQ-OPPT-2024-0073-0072 and EPA-HQ-OPPT-2024-0073-0073				
10	Anonymous	NA	NA	EPA-HQ-OPPT-2024-0073-0066
11	Earl Gray	NA	NA	EPA-HQ-OPPT-2024-0073-0056
12	Peter Boylan	NA	NA	EPA-HQ-OPPT-2024-0073-0061
13	Jennifer Foreman, DABT, PhD*	ACC High Phthalates Panel	Spring, Texas	EPA-HQ-OPPT-2024-0073-0086

NA=Not available

*Presented as "chat to everyone" in Zoom during SACC meeting on July 30, 2024.

EXECUTIVE SUMMARY

1. DIDP Risk Evaluation

The Committee commends the Environmental Protection Agency (EPA) for their professionalism in creating and presenting the phthalate assessment and recognizes their effort to consider perspectives of the public commentors and those of previous SACC recommendations. Dr. Freedhoff's introductory message strengthens our resolve to provide our best constructive advice to these scientists and the EPA leadership.

The Committee noted that DIDP is relatively data-poor in comparison to the other high priority phthalates, and offered suggestions on a range of issues, including overall concepts of exposure scenarios (e.g., additional Conditions of Use (COUs)), factors and dynamics to be considered in methods of exposure and toxicity assessments, additional information to be considered, and utilization of data in exposure models. The comparison of EPA approaches and assessment "answers" for di-isodecyl phthalate (DIDP) with those of other reputable risk assessment organizations is important as it expands the understanding and application of data in addition to clarifying the assumptions and functionality of the models that EPA utilized. Concurrence in answers and approaches may improve confidence in EPA assessments, but explanation for those elements that appear quite different are also important to highlight and discuss.

The Committee agreed that perhaps the most significant issue with the current DIDP and DINP assessments is omission of likely exposure scenarios. In particular, the overall construct of the review severely limits the scope of the evaluation. EPA only considered: a) environmental scenarios consequential to industrial emissions but failed to included monitoring data for discharges to the environment; b) residential exposures (rather than all indoor scenarios); and c) limited vehicle interior scenarios (or other public transportation options). Total exposure to phthalates is much more complex and involves many exposure sources, including those beyond the regulatory authority of Toxic Substances Control Act (TSCA). However, those exposures should be included as "background" or some other designation, rather than being invisible in the risk assessment. The science should not be redacted because of legislative compartmentalization of the contributors to real risk.

The Committee noted calculation issues (as with the ingestion route) and omissions of exposure pathways, including dermal exposure routes, in the Consumer Exposure Model (CEM) calculations. The Committee raised concern about the ability of the CEM to model all relevant contributions of DIDP, and by extension other phthalates, from products into air and indoor dust compartments. Again, consequences of the limits of the CEM to handle distributions of data, rather than point estimates were noted by the Committee, especially for short-term (acute) calculations which will be necessary for other phthalates. To partially compensate for that method limitation, the Committee suggested adding a discussion and statistical "examination" of all the monitoring data, taken together, with a focus on how the distributions are characterized and what variabilities, and sentinel scenarios are revealed.

In general, the Committee accepted the EPA approach and assumptions for mouthing values and migration to saliva, with some advisory comments regarding use of statistical metrics in different situations and expansion of product definition.

The Committee was hesitant to endorse the conclusions of EPA's assessments of consumer and indoor dust. Approaches were suggested to enhance the clarity and transparency of the data and overall evaluation. Concerns of the Committee ranged from significant omissions of exposure scenarios to technical and methodological issues used in these evaluations. The Committee's suggestions for improving clarity and transparency could be applied in practice to other parts of the phthalate documents as well.

Risk assessments for each of the additional phthalates should reflect their unique hazard and exposure characteristics which should be carefully aligned, particularly in terms of how metrics are chosen for utility in the CEM. CEM use for combining (not aggregating) exposures across products or scenarios can be problematic and would require careful consideration of the applied metrics and potential overestimation of exposure and risk. The model functionality needed for true aggregation of multiple exposure sources and routes cannot be achieved with the CEM, nor can the cumulative assessment as envisioned by the Committee for this family of chemicals. These assessments are further constrained by some significant data gaps which could be filled by the review petitioner.

The Committee noted omissions and underestimation of exposure scenarios resulting from multiple concept issues. For example, new realities of product distribution have created massive warehouse centers, existing in clusters, where workers and nearby residents may be exposed to phthalates. Additional exposure scenarios and pathways exist from waterborne phthalates on particles in water and in sediments. Sentinel exposure values seem to underestimate exposures to those scenarios discussed in the assessment. The Committee offered alternative methods to calculate exposure for those situations and also noted the contributions from public comments.

The Committee appreciates EPA's efforts to integrate both model predictions and environmental monitoring evidence for assessing surface water contamination and the resulting exposure of the general human population. However, it is unfortunate that all water monitoring data came from water bodies outside the US The Committee also raised concerns about the modeled DIDP concentrations in water and sediment. Modeled concentrations in water exceeded DIDP's water solubility by nearly 60,000 times. Should EPA determine if they have high confidence in these high concentrations, significant risks to aquatic ecological receptors will be needed. The Committee understands that ecological risks were not included in the question asked by EPA. Regardless, ecological risks are important and require full consideration by the EPA, and the Committee has provided specific comments to that effect.

The Committee supports the Agency's conclusion regarding the confidence of the estimated exposures and that there were no exposure pathways of concern for the General Population based on modeling data comparison to the National Health and Nutrition Examination Survey (NHANES) biomonitoring data.

Key issues included expansion of the COUs, especially noting "complex consumer products" with vehicles being a major example. Those exposure scenarios require aggregation of the exposures consequential to individual components of the products, and over multiple phthalates likely used in the products. For multiple environmental media considerations, use of models based on principles of mass balance may offer a better approach. Models that consider multiple sources of exposure (and multiple products and environments) for a given exposure event to yield a true aggregation of the exposure to populations would be an improvement over the models used in the DIDP exposure assessments. Use of models to estimate exposures to ecological receptors without having monitoring data to verify results were again

an issue concerning the Committee. The Committee provided recommendations to EPA to improve the assessments of release, volatilization, migration, biomagnification, and organism access.

The EPA investigated potential concerns associated with dietary exposure of ecologically relevant terrestrial and riparian species using models and the available, although somewhat limited, exposure and toxicity information. The EPA conducted a screening level analysis using "representative" species; it also explained the choice of ecological species, exposure factors, and the relevance of these decisions in a transparent manner. Overall, the Committee believes the methods and data used by the EPA for estimating dietary exposures are reasonable, effective, and relevant, reflecting a conservative approach to estimation. The methods and data are clearly presented, with Figure 5-1 being particularly helpful. However, there is a major concern regarding the use of DIDP concentrations in sediment. It appears that the DIDP concentrations might be overestimated to an unknown degree, as noted above. Given the uncertainties in deriving these toxicity thresholds, these exposure data suggest the potential for reproductive and developmental effects.

The Committee recommended that future assessments consider the cooccurrence of multiple phthalates and/or their primary metabolites as "mixtures" in the environment. In the meantime, certain phthalates should be prioritized based on their environmental occurrence, release, chemical properties, and/or toxicity. Other sources of data should also be considered and laboratory data from studies that expose more closely related species to one or more of these compounds should be used to gain a more accurate estimate of potential risk to various classes of organisms. The DINP exposure assessment should be reviewed by the SACC. The Committee is concerned that issues are likely to arise with the DINP review and with other phthalates which have not drawn attention during the DIDP review**.**

The development of a Toxicity Reference Value (TRV) for terrestrial wildlife exposed to DIDP by using laboratory studies with more human relevant species is suboptimal, but this approach was deemed acceptable by the Committee. There are uncertainties and refinements that the EPA might consider in further evaluation of hazard and risk as well as for approaches to evaluate the hazard and risk associated with exposures to other high priority phthalates. Two of the studies used to develop the DIDP TRV used concentrations higher than solubility, raising a question of true bioactive levels.

The Committee found that the EPA appropriately selected DINP as a suitable analog for DIDP based on very similar structural, chemical, and physical characteristics between the two phthalates, and comparable environmental fate and transport. The EPA approach is reasonable and appropriate for protection of terrestrial invertebrate health given that DINP was a phthalate for which environmental hazard assessment was conducted and a risk assessment is ongoing.

The Draft Human Health Hazard Assessment for DIDP presents a Human Equivalent Dose (HED) of 9.0 mg (No Observed Adverse Effect Level (NOAEL) of 38 mg/kg-day), supported by data collected in a two-generation Good Laboratory Practice (GLP) study conducted in Sprague Dawley rats that demonstrated primarily developmental effects. Although some reproductive effects were observed, measures did not include hormone measurements or sperm viability and other more sensitive indicators of adverse effects. Additionally, the primary mechanism of action of DIDP appears to be peroxisome proliferator-activated receptor alpha (PPARα) activation, thereby emphasizing effects on biotransformation processes. Given the information available, it may be possible to develop a common point of departure (POD) for DINP and DIDP that would be protective of both carcinogenic and noncarcinogenic responses.

There are several issues pertinent to many of the charge questions. These issues are largely due to the lack of available data for deriving the TRVs and estimating Exposure and Risk Assessments, particularly for wildlife and as discussed below, occupational exposure. Notably, the use of laboratory studies provides some insight into the potential adverse effects of exposures to phthalates in wildlife, particularly small mammals. In addition, there were data collected in earthworms that provided information on potential adverse effects from exposure for soil exposed organisms. The study with daphnia provided some toxicity information, but adverse effects were not considered even though toxicant concentrations in test systems were below measured concentrations in municipal wastewater treatment plant (WWT) effluents. These risks need to be quantitatively assessed. No studies on birds, larger mammals, and wildlife were included in development of the TRV due to apparent lack of availability. However, there are laboratory studies in birds that could provide information on adverse effects from exposure (see references) and these data could enhance the accuracy of TRVs developed for wildlife and potential adverse effects from exposure to environmental phthalates.

Another potential source of phthalate exposure, to humans, domestic species and wildlife is from plastics. EPA allowed zero contribution of plastic products/articles to the concentrations of phthalates in environmental media. Yet, phthalate release presumably proceeds through some of the same pathways as indoors, i.e., some limited volatilization from outdoor uses with subsequent partitioning to soil and air particles, but also degradation of plastics that can carry the phthalates into environmental media. In addition, microplastics may emerge as part of the indoor dust associated with abrasion and degradation of phthalate-containing products during their use lifetimes. In terms of environmental exposures, there is growing evidence for the ubiquitous presence of microplastics (see Grace *et al*., 2023).

No Charge Question on Occupational Exposure Assessment was posed by the EPA. As plasticized products move through commerce and retail, there are likely additional releases and opportunities for exposure that are not mentioned, such as at large department stores. However, the Agency determined that one occupational exposure scenario to DIDP posed an unreasonable risk. For occupational exposures, central tendency and 95 centile exposures were evaluated, but only the central tendency conditions were carried through to the risk characterization. EPA should justify why the pivot from past practice, when it is noted that the benchmark was exceeded for some COUs using the 95th centile exposure conditions.

2. DINP Hazard Assessment

Long-term oral studies in rats and mice have shown that administration of DINP increases incidences of kidney tumors and mononuclear cell leukemia (MNCL) in rats and liver tumors in both rats and mice. Given the lack of human relevance of the observed kidney tumors due to their association with a male rat specific urinary protein, and questionable usefulness and human relevance of the MNCL observations, the agency decided to focus on a more detailed mode of action (MOA) analysis of the liver tumors, which was appropriate. A number of MOAs were considered but excluded, with the focus shifting to determining whether, given that DINP is a PPARα receptor activator, that this could be the MOA. DINP-specific data were available to identify PPARα activation as the molecular-initiating event (MIE), Key Events #1 and #3 in the adverse outcome pathway and liver tumors as the adverse outcome. While DINP-specific data were not available for all key events in the current analysis, the use of quantitative structure–activity relationship (QSAR), read-across and possibly some newer studies provided by a public commenter are sufficient to provide additional support for the MOA. The Agency

summarized the information in a manner consistent with the WHO IPCS Mode-of-action/human relevance framework to illustrate that this was the MOA for the DINP-induced liver tumors and their likely lack of human relevance.

EPA's preliminary determination of DINP's human carcinogenic potential was "*Not Likely to be Carcinogenic to Humans* below levels that do not induce PPARα activation (KE1)." To be more accurate and follow the guidance from the 2005 Cancer Guidelines, the majority of the Committee members support a revision of the cancer classification to just "Not Likely to be Carcinogenic to Humans" due to the lack of human relevance of the PPARα activation MOA for liver tumors. In addition, the lack of relevance of the kidney tumors and MNCL also support this conclusion.

DETAILED COMMITTEE DISCUSSIONS AND RECOMMENDATIONS

DIDP Risk Evaluation

Charge Question 1 – Exposure Analysis

Charge Question 1.a

EPA relied on data from several sources to derive consumer exposure estimates that include products representative of the conditions of use, as described in Sections 1, 2, and 3 of the "Draft Consumer and Indoor Dust Exposure Assessment" for DIDP. EPA anticipates that the exposure methodologies demonstrated in the Draft Risk Evaluation for DIDP will be applicable to DINP exposure scenarios.

Charge Question 1.a.i

Please comment on the strengths and uncertainties of the selected data and methods used in consumer products and indoor air exposure analyses.

Strengths

The Committee was pleased to see EPA calculated ranges (low, medium, high) of exposure related values. The Committee notes that while this is preferable to considering only a single value for exposure factors, full distributions of values, showing the shape and key metrics of the distributions would be far better, and consistent with contemporary scientific practice. The Committee recognized that the current deterministic exposure model, CEM, being utilized cannot consider distributions in its computation, but those parameters could be presented in the discussion with statistical discussions including description of the distribution and its metrics. Additionally, until such time as a probabilistic exposure assessment model is available to the EPA scientists, data for such values should also consider the mode values to represent the "most common" value anticipated across the population group being considered. This is most important when considering parameters that are likely to be skewed, different from one population to another, "front loaded exposure dynamics" or other common exposure assessment factors. Averages (assuming that is EPA's meaning of "medium") could be quite different than the mode or median for many of these factors, and could cause under-or over-estimation, especially for use in the deterministic CEM. In any case, without robust empirical data to inform probabilistic assessments high centile values should be used for exposure assessment and low centile values used for toxic responses. Any

refinements that do not selection of high centile values should be fully justified, not a simple reversion to the mean. Also, see Section 4.4: issues of assumptions, deterministic methods (using only single values to represent a distribution of plausible values) and other issues show the limitations of estimates from CEM. The Committee appreciated EPA's transparency in presenting this analysis with discussion of the possible sources of differences (1-2 orders of magnitude). This example illustrates the importance of using modeled distributions for each value (highly skewed distributions that are realistic for life changes or venue changes or even activity level differences) and the need of person-oriented modeling for these assessments.

The Committee was pleased to see EPA's consideration of children's exposure from dust in the "Draft Consumer and Indoor Dust Exposure Assessment for Diisodecyl Phthalate (DIDP)" document. More discussion of this is presented below.

In Section 5, p 115-116, discussion of rat versus human dermal absorption: The Committee noted EPA's discussion of elements of variability, and adds that variability in human dermal absorption also exists across different areas of the body under different conditions of temperatures, age of humans, etc. EPA used conservative estimates which the Committee considers reasonable under these circumstances.

The Committee was pleased that EPA considered inhalation and oral exposure from indoor dust, but notes that dermal contact is also important. This is discussed again in later sections. The Committee does have caveats to this strength, namely some concerns about the ability of the CEM to conservatively estimate all pathways of DIDP entry into dust that may result in indoor exposure through inhalation, ingestion, and dermal contact. These concerns are addressed under DIDP charge question 1.a.ii.

Values used in the calculations and framework for the dose rate calculations were reasonable for time-integrated doses, given model limitations to utilize the data. The Committee noted that the professional judgements seemed reasonable. The exposure routes presented are likely representative, assuming:

- all the COUs are actually considered and
- groupings of products into each COU scenario did not "disguise" a sentinel COU scenario.

The Committee noted that the current EPA approach does not provide actual distributions of likely exposures, or aggregate exposures, where all routes are considered.

The Committee could not support all assumptions made by EPA, as discussed below.

Uncertainties:

The Committee identified significant omissions of probable exposure scenarios included in this assessment because the scenarios and pathways and even progenitor sources do not seem to reflect all conditions listed in the regulatory mandate. For example:

- There was no mention of exposure related to product transportation, current and emerging market dynamics for product delivery to consumers—including handling of massive quantities of the products (newly minted and wrapped in phthalate-rich materials to contain and stabilize products on slabs) in distribution centers. Thousands of workers in these centers are touching the materials, breathing the dust, taking the dust home (track-back issues), and experiencing long durations of exposure daily. Detailed discussion of this and the potential exposure scenarios

are presented in Charge Question 1.b.i, and similar scenarios were discussed in the SACC's review of cumulative risk assessment for phthalates.

Phthalates are used in electronics, printers, some inks, etc. At least two scenarios of exposure may be relevant: large office areas and computing centers, including the air evacuation systems (operating to vacate working areas covering about a million square feet) for dust removal and cooling systems for those massive centers. The Committee considers this to be an important topic, worthy of at least a qualitative discussion with recognition of the need for data in these major, new exposure scenarios across the country. These new realities in our computing grid and consumer product market systems (Sutapa, I and Wullur, M, 2020 and Rodrigue, J-P., 2024) impose new environmental challenges to both rural and urban areas and are so massive that they deserve attention in regulatory science and representations in the regulations covering transportation and distribution activities.

The Committee noted the absence of consideration of other exposure pathways/scenarios which have the potential to provide durable periods of exposure to subpopulations who may be considered Potentially Exposed or Susceptible Subpopulations (PESS). The following considerations on product/article section for exposure assessment were raised by Committee members:

- Automotive products, other than fluids: EPA dropped automotive interiors from the consumer exposure analysis without clear rationale. Vehicle interiors represent a significant use of DIDP, pose a potential high exposure scenario, and are not necessarily comparable to interior synthetic leather seating as suggested in Table 2-1, p.12. The Committee advised EPA to evaluate and document data for this COU. All interior materials such as seat covers, dashboard and door trim, mats, and other relevant materials should be included in the vehicle scenario. Further, the Committee recommends aggregating exposure across inhalation of dust, dermal contact, and hand to mouth transfer for a young child passenger.

- Adhesives, sealants, and related products are intended to be left in place for long durations after application. The cured products have the potential to wear and abrade, thereby contributing to dusts as well as emitting low concentrations of DIDP to air. EPA's consumer modeling appears to have considered only the exposure contributions that occur during application of these products (Table 2-1, p.12)

- Products selected for modeling in some COU subcategories such as arts/crafts/hobby materials and playground/sports equipment seem limited. EPA did not include a product for arts/crafts/hobby, for example. The plastisol resins that are sold for hobbyists to make fishing lures are one type of hobby product that can contain DIDP. For sports equipment the use of a single fitness ball in a residence does not seem adequate to capture exposures that may occur, for example, in a gym setting where many items can be used simultaneously, by receptor populations with increased respiration rate.

- Occupational exposures to phthalates occur through phthalate containing products, not only through primary production and manufacturing. For example, retail and distribution workers who spend long durations in indoor environments where DIDP-containing products are sold, stored, or transferred may have elevated exposure. Spa/nail salon workers use nail color and conditioning products for long periods daily.

- Occupational exposures involving workers who remove and relocate wastewater treatment sludge for use on fields and other landscaping areas.

The Committee also advised inclusion of pet (dog, cat, etc.) toys as products contributing exposure to young children who would handle those in the same manner as they'd handle "kid toys". Phthalate concentrations or release dynamics may be quite different between pet and children's toys. This type of exposure also underscores the importance of understanding and including release dynamics in the exposure calculations. That issue is discussed in more detail below.

- At Line 351, EPA stated that the "CEM model has been peer reviewed", inferring a level of confidence in its functionality and data relevance that seems to extend beyond the scope of that peer review. That publicly available review (EPA, 2016) focused only on (1) equations and defaults used in the model, (2) features of the user interface, and (3) documentation and utility of the user guide. There were neither discussions by EPA nor the five reviewers related to the capacity of the CEM (in terms of design, mathematics, or concepts) for aggregated exposures across multiple exposure scenarios or multiple products or contact with multiple media. The same is true for cumulative exposure assessment. Also, there were no discussions related to probability product uses, exposure opportunities, or interactions with media or other related factors. During discussions of the adequacy of data and assumptions, EPA did not request that the reviewers discuss the use of distributions of values or guidance for choosing appropriate single metrics for application to the array of different exposure conditions and subpopulations with different exposure patterns. The peer review did not evaluate the Exposure Factors handbook or issues of age or completeness of data included in the Handbook. Because of the narrow scope of the peer review and small panel of experts, EPA's citation of the review (with intention to confer confidence in the CEM capacity) is also constrained to the scope and replies of that 2016 review.

- A similar inference of credibility is made by reference to the Exposure Factors Handbook. The Committee remains very complimentary of the Handbook and encourages EPA to continue support of its updates and expansions. However, it does have limitations and outdated information, as EPA acknowledges in this DIDP assessment when it notes the probability that the Handbook's citation of people's weights was likely to be an underestimation given contemporary facts on US obesity prevalence. The same is likely for other issues such as portion size of fish consumption. The point here is that citation of the source of data is obviously important, but it should not be inferred that the values in the Exposure Factors Handbook are necessarily more "true" than other contemporary or population-focused data.

Non-TSCA uses of DIDP and other phthalates:

There was frequent discussion in the Committee regarding the use of phthalates in/with medical, food and cosmetic products. The Committee recognizes these products are under the regulatory authority of FDA, at least for their intended use. The Committee asked EPA if FDA regulatory reviews consider the exposure scenarios equivalent to those mandated for EPA's TSCA reviews? For example, for food uses, would the exposure/risk scenarios of manufacturing, distribution, transportation, disposal be considered in the same way as EPA would do under TSCA? Is PESS identification part of the FDA regulatory consideration? If not, can EPA assess the scenarios not covered by FDA? In another example DEHP is

used in a range of medical equipment. Are the non-patient risks, for example to bystanders and health care professionals, considered as they would be under TSCA requirements? If FDA does not consider such exposure scenarios, could EPA consider those exposure pathways in the TSCA review? And could all of the medical, cosmetic, food-related exposures be considered part of cumulative and/or mixture exposures, even if not under TSCA regulatory authority? These questions were posed to EPA by the Committee, but EPA representatives were not able to answer. The Committee endorsed the concept of reflecting these exposures in the overall, aggregated exposure and risk assessment and addressing the exposure pathways not assessed and regulated by FDA. The Committee provides some further discussion of these considerations under DIDP charge question 1.a.v.

Notably, models for probabilistic exposure and risk assessment for residues in food are available to TSCA scientists from the Pesticides Office of EPA. These models have been used for decades and will easily accommodate residue data (Giuliani *et al*., 2020) or estimated parametric distributions of potential residues of phthalates in foods. Such models also exist at EPA for the same assessments for non-commercial foods in subsistence communities. These models present true aggregated exposure assessments with distributions of possible exposures across different durations of exposure, ages, and subpopulations of concern.

As with previous SACC reviews, the Committee appreciates the efforts EPA scientists make with CEM's deterministic, spreadsheet approach to these assessments, but we implore EPA leadership to provide state-of-the-art statistical and modeling tools which can utilize full distributions of data, any exposure duration appropriate to the hazard metrics, and provide truly aggregated exposure estimates reporting relative contributions from different exposure opportunities over different conditions of exposure and to different subpopulations. The Committee recognized this cannot be completed for the phthalate regulatory assessment and decisions but recommended that the EPA leadership seriously consider this issue, as raised before.

The Committee noted that EPA did not clearly define PESS groups based on exposure as part of building exposure scenarios. EPA articulated exposure parameters for young children as a high exposure group for some articles and products, which was well-received by the Committee. However, a section of the Exposure Assessment should be dedicated to defining PESS based on both exposure patterns due to consumer patterns of use, and biological susceptibility considerations.

Comments on specific areas of the report: Note that these comments may often overlap or also be relevant to responses for Charge Questions 1.b. They are highly relevant for the overall risk assessment. The Committee pointed out several times during the public meetings that the general population and consumer exposures should not be considered completely separately, as was done in this report.

As previously stated, the exposure estimates are likely representative of the general population, assuming all of the COUs and resulting exposure scenarios are actually considered and groupings of products into each COU scenario did not "disguise" a sentinel COU exposure scenario. This may be an issue for exposures via water (both drinking and full body (swimming, showering) from water contamination (down the drain releases to environmental media and into water sources)). The exposures consequential to the contamination of particles and sediment of water bodies were addressed by the Committee in the response to Charge Questions 1.b.i. The Committee noted issues of PESS community diets and other exposure scenarios such as fishing/crabbing/oyster consumption, consumption and/or contact with other biota. This was discussed in more detail by Dr. Diane Barton's public comment

submission for the National Tribal Toxics Committee (NTTC). While fish consumed by Native Americans may indeed be worthy of a separate consideration, other subsistence populations derive a significant amount of their food from shallow surface water bodies, brackish water sources. Consider the coastal regions of the Gulf of Mexico. PESS communities utilize local resources including all types of coastal birds, shrimp, fish and other aquatic animals, as well as alligator for food. Consider the coastal communities of the Chesapeake Bay and equivalent communities of the northwest and northern eastern coasts where consumption of bivalves is constant and significant as are a range of fish and other aquatic organisms that filter and live in potentially contaminated waters. Although bioaccumulation is not expected, the residue in these foods could be estimated using representative residue values computed from the ecological studies for representative animals. The Committee considers that theoretical, representative exposure calculation would be preferable having no quantitative estimate for an important sentinel exposure. Theoretical sentinel exposure estimates could be developed for scenarios where people and animals (especially those hunted or fished (including bottom-dweller shellfish, etc.) are exposed. These assessments can be constructed with factors derived from tissue residue values in ecological representatives of aquatic and terrestrial species, along with PESS consumption values (see Barton comments) as representative exposures.

Committee members found the pathways for chemicals to enter the three dust compartments of CEM to be poorly described especially for abraded particles. It does not appear that modeled products contribute any mass to dust, e.g., through abrasion. The generation of dust particles comes from tracking in outdoor dust, dander, smoking, and cooking in the model. These comments may reflect limited CEM capabilities more than the assessment approach. The related issue is the apparent absence in the calculations of factors representing the changes and dynamics of phthalate release in different plastics or other polymers (cellulose will be a matrix of relevance for other phthalates), and the effect of age, abrasion, torsion, or other physical challenges on the release rate of the phthalate from the matrix. (Panthi *et al*., 2024 and Yan *et al*., 2021). The release rate dynamics may follow skewed distributions for different variables, and description of those dynamics are important to understand. Note that this comment is also relevant to CQ a.ii.

Product and Article selection: EPA should explain and substantiate how consumer products or articles containing DIDP were selected to represent each COU. The brief explanation given in lines 275-278, “selected for large surface area” is not sufficient for COUs with large numbers of possible products and articles. Please provide clear rationale that the products and articles moved forward for quantitative exposure modeling are those best suited to capture and quantify the upper range of potential consumer exposures and result in a health protective evaluation. This will apply to DINP and other high priority phthalates.

It does not appear that the assessment includes any measured concentrations of airborne DIDP or DINP, even in occupational settings. It is not clear whether the vapor phase of DIDP and DINP is considered. Clarification of the data used, assumptions about data distributions, and data application will help determine the extent of data gaps, especially if the manufacturing community that petitioned to have this DIDP review has or is likely to have such information.

LL275 Change to many indoor spaces including residential settings. This statement suggests that only residential settings were considered. Eliminating indoor dust monitoring because the spaces were not residential leaves open the potential for significant exposures for those who spend time in these

environments. Schools, places of worship, and hotels come to mind as examples of spaces where individuals can spend significant time and thereby potentially experience phthalate exposure. This creates a significant gap in the exposure profile that is not protective, and relevant information for those venues may be available to EPA.

LL1418-1425: There are no data from US residences within the cited studies. A single study from Canada is used for this assessment. Moreover, this study relied on dust collection through vacuuming by individuals residing in the dwellings being studied. This approach does not evaluate airborne particulates indoors. This lack of information is inconsistent with a manufacturer-requested review, and such data from US residences are needed if a requested review can include sufficient exposure and effect data to allow appropriate Environmental and Human Health Protections.

LL385-386: The documents state that CEM 3.2 models inhalation of gas-phase semi-volatile organic compounds (SVOCs). Later (LL400-401) CEM is characterized as modeling both gas and particle phase exposures. However, later text related to the Indoor assessment (~LL1418), states that only suspended dust was considered for inhalation exposure. There is a disconnect that needs to be resolved.

L419: In section 2.1.1 it is unclear if both gas and particle phase exposures were modeled or if only particle. The modeled phases should be explicitly stated in LL 421-422. This specification needs to be repeated at the beginning of subsequent sections where it could be misconstrued whether both vapor and particle phase DIDP were evaluated. In fact, if only particle phase DIDP is considered, then a search replace of inhalation with particle inhalation would be appropriate in areas of the text after it is relayed EARLY in the document that only particulate exposures are being considered.

A contaminant that becomes sequestered into sediments of a water body cannot be considered to be inconsequential to human or environmental risk or that it is permanently sequestered. This is discussed in detail in the Committee response to Charge Question 1.b.i. Today's realities may pose additional issues, including for some areas daily freshwater flooding throughout the US interior, displacing sediment into new locations within the environment that may alter exposure venues and routes such as food (biota and all forms of animal). Microplastics can act as carriers of phthalates (Ye, X., *et al*. 2020), and the Committee notes that this increasingly important exposure pathway can be recognized and discussed in the report, even if quantitative assessments are not possible at this time.

EPA did not perform quantitative assessments of the COU summarized in Table 2-2 due to "lack of reasonably available information, monitoring data, and modeling tools" (line 315, 316). The Committee suggests there is a likelihood for widespread and significant exposure via dermal and ingestion (water, water foods, secondary washing of clothes, swimming, bathing, etc.) and representative sentinel exposure estimates could be derived.

The Committee was pleased that the Dutch National Institute for Public Health and the Environment (RIVM), European Union, Netherlands, the National Institute of Public Health (NIPH) and the European Chemical Agency (ECHA) evaluations were considered as comparisons for some values. However, an overall comparison of the exposure assessment conclusions for product groupings across these regulatory authorities was not provided, making it difficult to interpret the comparison. In a related issue, data quality (as function of possible differences between US and Canada) was cited as a potential problem with monitoring data for DIDP in residential indoor dust (page 126, lines 2181-2190), but no perspective given about why EPA suspects the problem denigrates use of the information. Were there

regulatory positions on use of the phthalates over that time period, as compared to US regulation of these phthalates? Which information (not assumptions) led to the concerns about US/Canadian product use or phthalate content? It could be assumed that these products and uses are very similar, some products even provided by the same manufacturers. Why the downgrade? The Committee would also appreciate discussions on how product groupings were done by these other authorities.

Methodological issues

Lines 1131 to 1141 on Page 45 and Section 3.1: The EPA calculated the dermal absorption of DIDP in consumer products and articles by making the following two assumptions. (1) DIDP in consumer products or articles first migrates into a layer of aqueous phase on the product or article surface to form a saturated solution and (2) the human skin absorbs DIDP from this saturated solution. This is the reason that the EPA used Equation 2-24, which was originally designed to calculate dermal exposure to chemicals in water by the EPA's "Risk Assessment Guidance for Superfund (RAGS), Volume I: Human Health Evaluation Manual."

However, this calculation has two main methodological problems:

1. When using Equation 2-24, the EPA assumed the DIDP concentration is equal to its water solubility. That means, the EPA assumed the migration of DIDP into the surface aqueous phase is so fast that it cannot be a rate-limiting step. In other words, there is a continuous, sufficient supply of DIDP from the product or article material (usually polymers) to sustain the saturation of DIDP in this surface aqueous phase. If this is not the case in reality, then the current estimate of dermal absorption may have substantially overestimated DIDP concentrations in this aqueous phase, and so, overestimated dermal exposure.

However, this assumption cannot be made without comparing the mass transfer of DIDP in the polymer material (i.e., the solid product or article) and in the water phase. The Committee suggests EPA compares the mass transfer of DIDP in the polymer material and in the water phase to determine the rate-limiting step.

When reviewing the EPA report, one Committee Member did some preliminary calculations using the built-in equations in the CEM model's user guide. If one applies DIDP's molar mass and vapor pressure to Equations 58 and 59 in the CEM model's user guide, we can calculate that DIDP's diffusivity in solid product material is $2x10^{-12}$ m^2/h, and DIDP's partition coefficient between solid product material and air is $6x10^{8}$. Given DIDP has a small air-water partition coefficient of $1.6x10^{-3}$, DIDP's partition coefficient between solid product material and water is calculated to be around $1x10^{6}$. So now we have the diffusivity ($2x10^{-12}$ m^2/h), the material-water partition coefficient ($1x10^{6}$), and if we assume the product has a thickness of 0.1 m, then the mass transfer coefficient is at a level of $4x10^{-5}$ m/h in solid material. This number is orders of magnitude lower than a chemical's mass transfer coefficient in water (0.1 m/h). Therefore, it does not support EPA's assumption. EPA may wish to revisit this calculation to compare the mass transfer of DIDP in the polymer material and in the water phase to see if this approximates actual phthalate behavior.

2. This calculation considers only that the human skin absorbs DIDP from a saturated solution on the surface of products or articles. This calculation does not consider dermal absorption of DIDP found in dust adhered to the hand surface. Recent studies have shown (Abdallah *et al*., 2015)

that chemicals bound to dust may also lead to dermal absorption. Those researchers highlighted the important contribution of dust-bound chemicals to human dermal exposure. If the EPA does not want to consider this exposure pathway, the Committee suggests that the EPA articulates the omission with technical explanation as to why dust-associated DIDP is not readily available for dermal absorption.

The Committee noted (Line 1253 on Page 48) notation of a water solubility of 0.33 mg/L, which is 2000 times higher than the water solubility of 0.17 ug/L as used in environmental media modeling (Section 4.2.1 of "Draft Environmental Media and General Population Exposure for Diisodecyl Phthalate"). However, 0.17 ug/L also appears as a "selected value" in the Excel spreadsheet "DIDP. Draft Consumer Risk Calculator. Public Release. May 2024". This inconsistency is significant. The Committee hopes EPA can clarify that selection of values or resolve the inconsistency with explanation. This comment can also be considered relevant for issues discussed in CQ 1.b

The Committee suggested that EPA's discussion of potential biodegradation was insufficient (Section 3.1: Biodegradation). A more thorough explanation of half-life is needed. Half-life does not indicate a time to decrease toxicity by 50%. The Committee suggested EPA address the relevant issues: To what extent has transformation of DIDP to mono-isodecyl phthalate been assessed in the context of the toxicological relevance of half-lives, and the influence of this half-life on availability of toxic transformation products.

The Committee is concerned that there are no use data upon which to base environmental releases for DIDP. The Committee frequently voiced the opinion that SACC review of any chemical deserving to be moved ahead of high priority chemicals through manufacturer request should have ample supporting data in the publicly available domain. This lack of basic information is inconsistent with the manufacturer request for review of these two compounds, and the users/producers/trade organizations should be required to provide needed data. This Committee perspective was expressed for other data uncertainties and gaps as well, questioning the scientific validity of proceeding with manufacturer requested reviews if the requestor does not provide pertinent and necessary information. Additionally, it is critical to have environmental monitoring and effects data relevant to the US, beyond laboratory studies. In the absence of such information, the Committee noted that EPA scientists face a quandary regarding what assumptions should be made without data to support their decisions.

The evaluation of phthalate releases to water lists two studies of phthalates, one to a watershed in China and another to a river in France. Neither of these systems represent industrial effluents. This is insufficient information upon which to make any reasonable assessment of the environmental exposures that would be expected for people or non-human organisms. If there are more data describing DIDP releases to water, they need to be documented in this report. There is a study from 2023 that would add some breadth to this evaluation (Baloyi, Tekere *et al*., 2023).

Generally, the Committee agreed that the Exposure Assessment needs to more clearly articulate how DIDP is considered to enter dust compartments in the modeling. It is difficult to tell whether volatilization to air is the only route for chemical migration from these products and articles. Is direct migration to a dust layer considered? Do articles contribute to the mass of dust through degradation or abrasion?

The Committee discussed the issue of age of data sources for several of the study types utilized in the EPA report. For example, EPA based confidence in weight fractions for different products on the number

and age of data sources that were used, and the difference between moderate and low confidence was based on the age of the sources (Lines 987-88). Particularly given that DIDP is a replacement for DEHP in some products, the Committee was concerned about how EPA assigned values of "more current" or "less current" as a factor of confidence in the data quality. The Committee noted that such studies are generally “older” and unlikely to be regularly updated with more contemporary study standards or using more sensitive equipment and methods. None-the-less, the studies are valuable and certainly better than an absence of data. The Committee suggested EPA provide this perspective unless some definitive utility and standards for “current/not current” is defined and deemed useful here. Further, The Committee suggested EPA discuss any generalizable trend in the rate of DINP use across product categories that could be used to reduce uncertainty.

The Committee offered these specific comments on routes of exposure and products/articles in Table 2-1:

- Automotive products, other than fluids: automotive interiors were dropped from analysis without clear rationale. Vehicle interiors are a significant use of DIDP and represent a potential high exposure scenario. The Committee advised EPA to evaluate and document data for this COU.
- Adhesives, sealants, and related products are intended to be left in place for long durations after application. The cured products have the potential to wear and abrade and contribute to dusts as well as to emit low levels of DIDP to air. The modeling only included exposure contributions during application of these products.
- Products selected for modeling in some COU subcategories such as arts/crafts/hobby materials and playground/sports equipment seem limited. EPA did not include a product for arts/crafts/hobby, and use of a single fitness ball in a residence does not seem adequate to capture exposures that may occur, for example, in a gym for the sports equipment COU.

Minor/Editorial comments

- Equation 2.7 includes a term, TSP_{floor_max}, that is not defined in the list of terms below the equation.
- There are several typos in the same format: prE-populated and timE-varying,

Recommendations

The Committee recommended that:

- EPA expand the scenarios and venues of exposure, especially to include vehicles, all interior spaces and other scenarios as discussed here.
- EPA should obtain from the requestors of this review additional information for critical data gaps, and expand their access to monitoring data from community facilities for residues in water and foods, etc. Not just for DIDP but for all chemicals being evaluated.

- EPA Should obtain and utilize established methods and models to utilize the data including dietary assessments utilizing the available probabilistic models at EPA for these non-pesticide residues.
- EPA should model additional products for some COUs that have the potential for high exposure to PESS groups. Examples of products and scenarios are provided above.
- EPA should clearly define high exposure PESS in a new section of the document.
- EPA should consider exposures that are consequential to products regulated by FDA, via pathways not included in FDA review.
- EPA should revisit the dermal exposure work to include sorption from products not just from dusts.
- EPA should revisit exposure scenarios and calculations for dust exposure and water exposure to ensure that partitioning behaviors are within the bounds of model parameters.
- EPA should expand the scenarios, pathways and progenitors of exposure and risk, as described above with emphasis on PESS situations. The Committee recommended expansion of mapping COUs to other paradigms in addition to Occupational Exposure Scenario (OES) so that a much broader scope of exposure scenarios and pathways can be considered, many of which are likely to affect at least as many people and exposure scenarios as now considered in the document.
- EPA should include an assessment, or at least a discussion of what is known about phthalate release rates and dynamics affecting release, as well as phthalate mobility and availability on microplastics.
- EPA should expand the explanation of decisions taken by other authorities, including in the discussion on the approaches, regulatory authority and mandate, statistical and modeling utilized, and other perspectives that clarify the comparisons of "the answers" while also educating the reader as to the different regulatory philosophies imposed on the assessment approach, differences in the products and exposure pathways, etc. With such information, similar answers will be viewed as supportive, while understanding why there are differences in the answers can lessen the apparent disagreement.
- EPA should use caution in its referral to the 2016 CEM peer review to confer confidence about its capacity or utility in multiple products, multiple scenarios, aggregate or cumulative exposure assessment.
- EPA scientists should consider the background information from which exposure factors are derived to be sure they are using the most current information which aligns with the hazard profile for the assessment, even if those values are derived from the EPA Exposure Factors Handbook. More appropriate data now may be available in the general literature.

Charge Question 1.a.ii

Please include a consideration of the Consumer Exposure Model assumptions for analysis of suspended and surface dust through inhalation and ingestion routes of exposure.

Discussion

Specific issues regarding factors involved with quantitative aspects of dust exposure, as well as the absence of dermal exposure considerations are addressed in detail in the response to Charge Question 1.a.i. Those are not repeated here, but additional issues noted by the Committee are discussed here. The issues raised could result in both increases and decreases in resulting exposure and risk estimates.

The Committee noted that EPA's modeled results of exposure through dust ingestion are 50 times to 700 times higher than estimates based on monitoring data. The EPA wrote, "the sum of DIDP intakes from dust in CEM modeled scenarios were, in all cases, considerably higher than those predicted by the monitoring approach. The difference between the two approaches ranged from 50 times in infants less than 1 year old, to a high of 704 times in teenagers 16 to 20 years old." (Section 4.4 on Page 112). However, the Committee also noted (summarized in comments on DIDP CQ 1.a.iv) that the monitoring data available for DIDP may not reflect the distribution of DIDP concentrations in dust for US consumers at the present time.

The Committee suspects that the method used by CEM may have overestimated the DIDP concentration in dust by a factor of 100. CEM assumes DIDP first enters the air phase from product/article material and then partitions into dust, with the latter process characterized by DIDP's partition coefficient between dust and air. The CEM model uses an equation (see Equation 56 of the CEM model's user guide) that expresses a chemical's dust-air partition coefficient as being proportional to a chemical's *equilibrium* octanol-air partition coefficient (K_{OA}). The underlying assumption is that the model treats dust as being equivalent to 40% octanol and assumes equilibrium partitioning between dust and air. However, increasing evidence shows that this equilibrium partitioning assumption is not valid for low volatility chemicals, especially for chemicals with a K_{OA} greater than 10^{10} (Weschler and Nazaroff, 2010). This is because low volatility chemicals need an extremely long time to reach equilibrium between air and dust, which is often orders of magnitude longer than the residence time (typically days to months) of dust within the indoor environment. In other words, dust disappears before a chemical reaches equilibrium between air and dust. Therefore, concentrations of low volatility chemicals, predicted to occur in dust by equilibrium models may always be higher than those measured in reality, which further overestimates of DIDP concentration in dust and human exposure to DIDP through dust ingestion. These equilibrium dynamics would also underpredict DIDP concentrations in air, and lack of monitoring data require that model estimates be protective of human and environmental health.

For example, Weschler and Nazaroff (2010) collected measurements of more than 60 organic chemicals from 19 published studies. Their analysis, summarized in Figure 2 of their publication, showed that equilibrium models may overestimate chemical concentrations in dust by a factor of 5 for a chemical with a KOA of 10^{10}, and by a factor of 100 for a chemical with a KOA of 10^{13}. As we know, DIDP is a low volatility chemical, and the "Draft Physical Chemistry Assessment for Diisodecyl Phthalate (DIDP)" used a KOA of 10^{13} for this chemical. Therefore, it is likely that the DIDP concentration in dust has been overestimated by a factor of 100.

The Committee suggests EPA replace the default CEM method with more realistic estimates that consider non-equilibrium partitioning of DIDP between dust and air, or if this is not feasible, articulate this overestimation in the report and how this consideration influences vapor phase DIDP concentration estimates.

In addition, CEM does not consider the release of DIDP-containing particles as part of settled dust in the indoor environment due to abrasion. In such cases, DIDP-containing particles may have the same concentration of DIDP as found in the product/article material. Indoor residents may also ingest these particles as part of indoor dust ingestion.

Further, the Committee found that the CEM considers that exposure to DIDP in dust resulting from a product or article only occurs when there is contact with the article. It is more realistic for articles and products to contribute chemical mass to respirable particles, settled dust, and larger particles from abraded products that are then distributed throughout the volume of the modeled building for residents to inhale, ingest, or contact dermally. This consideration may be especially important for infants and very young children who can be exposed to dust on floors anywhere in the residence.

The Committee requested clarification as to why the EPA had sought to back-calculate the ingestion rate of "dust" from the ingestion rate of "DIDP" among Canadians (reported by EC/HC) (Lines 1463 to 1467 and Equation 3-1 on Pages 56 and 57). First, this back-calculated ingestion rate of dust was apparently not used in the EPA's own calculation, as the EPA indicated later that the data for their calculations "were taken from Özkaynak *et al*. (2022)." Second, the way EC/HC calculated the ingestion rate of DIDP is by multiplying DIDP chemical concentrations and the ingestion rate of "dust", so the ingestion rate of dust is actually the input, not something that needs to be back calculated.

The CEM addresses a home environment of a "general population," limiting exposure scenarios for the COUs to only this interior space. Absent are considerations of all other interiors where people spend significant proportions of their life. Among those are vehicle interiors, gyms, businesses, schools and other work-related interiors such as distribution centers, where DIDP could also be used in plastic materials that fall under the specified COUs. That issue was discussed in Charge Question 1.a.i and 1.b. as a major omission in the overall logic of defining exposure pathways emanating only from industrial emissions as well as a major indoor worker exposure opportunity. Vehicles are complex products containing many components that contain one or more phthalates. People of all ages and vulnerabilities may spend significant portions of their day, repeatedly, in these closed interior spaces multi-route exposure opportunities. The Committee strongly urges EPA to include vehicles and other interior venues in the assessment. Additionally, consideration of each COU or physical process (volatilization, dust resuspension, etc.) separately within a single space is likely to underestimate concentrations of DIDP and other phthalates present in the indoor environment.

As noted before, a major shortcoming of the CEM capability is its inability to consider full distributions of essential factor's values. Hence, deterministic values were selected for each input into the exposure algorithms. The Committee did not perform a QA/QC check on these many values for their relevance to the calculations at hand, but again wishes to emphasize some key points around this issue:

- Appropriate value related to short term versus longer duration periods for the objective of the assessment.
- Utilization of average/mean/"middle" values instead of median values…especially as the full distribution, with its characteristic skew, cannot be visualized. Mean values may not be representative of the issue or population factors employed in the calculation.

There are unique difficulties to represent short term exposures (acute) with deterministic models. Because the short-term hazard may be triggered with single (or short term) exposure, mean or median values for exposure parameters are not appropriate. There is a tendency to employ the maximum or high centile values for such parameters, noting that those may be more relevant and appropriate to the hazard characteristics. However, employment of high-end values for a collection of parameters in the algorithm could easily overestimate the exposure (High end value x high end value x high end value, etc.). The appropriate way to do this is to utilize the full distribution of values for each factor in the algorithm and employ the probabilistic method of multiple calculation runs to generate one distribution of answers from that collection of parameters. Then, the upper end of the "answer distribution" represents the answer appropriate for the acute exposure value—avoiding the overestimation produced by use only of the deterministic high-end calculations. The Committee is concerned about the absence of consideration of carpeting in interior spaces and the effect carpeting has on the probable exposure to different ages and in different locations. The presence of carpet may alter dust fate and chemical loading of dusts and should be considered as a unique "medium" with its own dynamics for loading, retention and unloading of chemicals, or at least recognized as a source of variability/uncertainty in the modeling.

The Committee appreciated the overview of equations and Tables 2-7 through 2-12. However, some additional information on dust size fractions, and fate pathways into dust is needed.

The Committee noted the apparent absence of a dermal to oral pathway (hand-to-mouth) for DIDP (Section 2.2 Dermal modeling). This may be important for articles for some PESS and the Committee recommends adding this exposure scenario for DIDP and for the other phthalates as well. Example: a young child using synthetic leather furnishing while sucking a thumb or eating a snack with unwashed hands.

The Committee notes that production and use of DIDP has increased since the Canadian House Dust study was performed and this 2013 publication on dust in Canadian homes may underestimate current exposures of phthalates from dust in the US. It is also worth noting that the maximum concentration of DIDP in house dust was 14-fold higher than the median, indicating substantial variability in this key factor. However, the significance of that difference cannot be understood without seeing the full distribution of the data, noting that if the distribution is highly skewed, the maximum concentration may be regarded as an outlier rather than indicating a large variability. Regarding other phthalates, there are considerably more dust monitoring studies for lower molecular weight phthalates which the Committee recommends that EPA fully utilize these distributions, with statistical rigor to characterize the contamination and potential exposure to this family of chemicals.

The Committee thanks EPA for providing a 2016 peer review of the CEM (US EPA (2016)), conducted by a third party. On pages 6-7 of the peer review comments, Dr. Gary Ginsberg pointed out that under certain model conditions, the CEM overpredicted DINP and DEHP concentrations in air relative to measured data, but underpredicted measured dust concentrations. From the limited monitoring data for DIDP discussed above, it appears that the reverse may be true for DIDP. However, EPA must address the peer review comments before applying the modeling methods developed for DIDP to other phthalates in the TSCA review.

It should be noted that the focus of the 2016 Peer Review, as stated in the introduction and reflected by the Charge Questions was for evaluation of (1) equations and defaults used in the model, (2) features of the user interface, and (3) documentation and utility of the user guide. There were no discussions by EPA

nor the five reviewers related to the capacity of the CEM (in terms of design, mathematics, or concepts) for aggregated exposures across multiple exposure scenarios or multiple products or contact with multiple media. The same is true for cumulative exposure assessment. Also, there were no discussions related to probability of use of the products, exposure opportunities, interactions with media or other related factors, and during discussions of the adequacy of data and assumptions, EPA did not request discussion of the use of distributions of values or guidance for choosing appropriate single metrics for application to the array of different exposure conditions and subpopulations with different exposure patterns. Because of the narrow scope of the peer review and small panel of experts, EPA's citation of the review (with intention to confer confidence in the CEM capacity) is also limited to the scope and replies of that 2016 review.

As noted previously in the Committee's comments on DIDP CQ1.a.i, exposure to products such as caulks, sealants and lacquers is not adequately captured by emission model E1 and near-field inhalation as indicated in Table 2-6. These products also contribute to air and dust emissions for the duration of their use and should be additionally modeled in a way comparable to articles and their usage throughout their lifetime. A somewhat related scenario to illustrate this concern are legacy uses of polychlorinated biphenyls in caulks and sealants that contribute to indoor exposures over long periods of time.

There is some evidence for direct transfer of phthalates into settled dust, this pathway of release from articles should be included in the modeling (Bi *et al*, 2021).

EPA's use of the CEM was limited to residential exposure scenarios. People may experience high exposure to products and articles within the considered COUs in other settings. Either the CEM needs to be adapted to model those settings, or another modeling approach is needed to ensure that high exposure scenarios are captured in the exposure assessment.

Recommendations

- The Committee recommends that EPA reconsider the calculation of DIDP concentration in dust and address the confusion with the ingestion rate of dust, as per the discussion above, or explain why they choose to use the concentration in dust, which the Committee estimates to be a large overestimation.
- All releases of DIDP from products and articles into indoor dust should be considered, not only evaporative emission to air followed by partitioning into dust. Both abrasion and direct transfer into dust should be considered for the exposure assessment.
- The EPA should fully utilize a broader spectrum of the phthalate monitoring studies with contemporary statistical tools to create a thorough understanding of the potential contamination of indoor and outdoor (and vehicle) venues, and the probable acute and longer duration exposures to different subpopulations. Regarding other phthalates, there are considerably more dust monitoring studies for lower molecular weight phthalates which should be fully utilized, with statistical rigor to characterize the contamination and potential exposure to this family of chemicals. The Committee looks forward to a robust discussion of the data, used in combination to inform that "picture" before applying the metrics to the CEM or other exposure model.

- When addressing cumulative phthalate risks or risks from any single phthalate, EPA should address the detailed points discussed above and also discussed in related responses to CQ 1.a.i and CQ 1.b.
- EPA should be cautious in its referral to the 2016 CEM peer review to confer confidence about its capacity or utility in multiple products, multiple scenarios, aggregate or cumulative exposure assessment.

Charge Question 1.a.iii

Please also comment on mouthing behavior input parameters related to estimating chemical migration to saliva for infants and toddlers.

Discussion

The Committee accepted, in general, the EPA approach and assumptions utilized in the exposure assessment for the conclusions to be representative of the subpopulations. However, the Committee reminds EPA that this approach (described at line 851+ and in table 2-10) may be appropriate only as "representative" values for non-acute exposure assessment durations. To set high, medium, and low exposure scenario mouthing values, EPA used mean mouthing times from the Exposure Factor Manual for ages 1-3, 3-6, 6-9, and 9-12 months, without descriptions of the distribution curves and metrics for those factors. Thus, one could question the calculation for the high exposure scenario mouthing time as the longest *mean* time from those four subgroups. Obviously, the model is missing approximately the upper 50% of the distribution for that highest subset, and without showing the characteristics of those data, one could effectively argue that this underestimates exposure. When calculating this exposure scenario for other phthalates with acute hazard concerns, or considering a hypothetical sentinel exposure, the mean values are inappropriate for the exposure algorithm as it may yield an underestimation of the risk. The Committee acknowledges use only of the upper end values for the parameters of the algorithm may yield an overestimation of acute exposure risk; however, the lack of actual exposure data requires a conservative estimation. Thus, a discussion of the data distribution for each metric should be provided as the risk assessors choose single values for use in the deterministic model. This statistical conundrum is further discussed in the response to Charge Question 1.a.ii. In general, the Committee often noted a lack of discussion of the data, relying only on the fact that values were taken from the Exposure Factors Handbook. Though that is, indeed, a great tool and honestly presents the citations and logic for all selected values, use of those values without consideration of the genesis of the value and overall statistics can lead to unintended consequences.

The Committee appreciated the utility of the Danish report on migration of phthalates and agreed that DINP migration rate is a reasonable surrogate for DIDP calculations.

The Committee urged EPA to expand its consideration of the objects representing the "toys" of children to include pet toys (i.e., dog, cat, etc.). Such young children cannot differentiate between kid toys and pet toys, both being attractive and providing opportunity for the same mouthing behavior. Thus, these belong in the children's risk assessment, with the key issue being one of phthalate content. EPA should determine if pet toys' ingredients are similar to children's toys and adjust the exposure metrics accordingly.

Recommendations

The Committee makes the following recommendations:

- Pet toys be included as objects available for mouthing exposure to young children, noting the phthalate content in these products as compared to those manufactured specifically for use by young children.
- Especially since the exposure models operate only on single value parameters for each algorithm's calculation, choice of those input values from the originating distribution of values should be discussed in detail, especially when considering the application of mean versus median, mean versus high-end calculations and the potential cumulative impact of multiple factors within each algorithm using those choices. Those decisions may have more impact on the integrity of the exposure answer than any other "uncertainty" concerns which are discussed in the document.

Charge Question 1.a.iv

In light of comments on charge questions 1.a.i through 1.a.iii, please comment on the weight of scientific evidence and its conclusions for the consumer and indoor dust assessment (Section 5 of Draft Consumer and Indoor Dust Exposure Assessment). Please include in these comments a discussion of the clarity and transparency of the data used, and EPA's interpretation of the exposure results.

Discussion

Overall, the clarity and transparency of EPA's reports are impressive for a regulatory assessment across such broad, necessary sciences. The Committee can recognize areas where previous SACC recommendations have been adopted and commends the scientists for their openness to these advisories and their professionalism. Committee comments in this review are intended to assist for additional improvements.

The Committee has discussed issues related to the inability to understand the distribution of data used throughout the review process. Hence, it is difficult for the Committee to determine the confidence in data use and sees this omission as a significant transparency problem. Discussion of this has been presented in the responses to Charge Questions 1.a.i, and 1.a. ii.

Use of Canadian data and data from other countries:

This issue drew a range of comments from Committee members. For example, some Committee members favored downgrading of the study as summarized by:

- Regarding Section 5-2, Confidence in the estimates derived from the Canadian House Dust Study monitoring should be reduced from moderate to slight. There are numerous uncertainties in comparing the modeled to measured estimates, many are noted in the subsections of this section. Especially important is increased production volume of DIDP since the Canadian House Dust Study, the variability between homes, and the absence of dust studies at important non-residential locations like schools, medical facilities, and in-vehicle environments.

- The Canadian Household Dust Study also relied upon residents for sampling. This introduces error in methodology, consistency, and timing of sampling.

Yet, other members favored upgrading the confidence score for this study, as summarized by:

- Unless there are reasons to expect COUs and/or other significant factors of manufacturing, environmental conditions, use, populations involved or such, the jurisdiction in which a study was conducted does not seem relevant for a downgrading. This is especially true for information from Canada and the EU countries where the scientific and regulatory "attitudes" about research, monitoring, data quality, regulatory use of information, etc. are at least equal to those of US regulatory and research bodies. Also, many consumer products are produced by one manufacturer and used in both countries.

The Committee's discussion about the Canadian data was emblematic of "reviewer confusion and interpretation," sparked because of vague discussion and seemingly arbitrary decision factors used in the EPA assessment. Differences in opinions presented by the Committee members likely portend a similar reaction from any other group who reads the document. But that can be corrected with some additional narrative and perhaps some updated "policies of practice" in writing for some of these complex assessment situations. The factors driving these different determinations by committee members can, and should be, addressed. They are all valid factors playing into any person's evaluation criteria for "trust." Similar issues arise in other parts of EPA's phthalates review, such as "Are older studies really of lesser quality and imparting less reliable information than would be in contemporary ones? Is there really a need for newer studies? Are monitoring studies of better or lesser quality or graded on a different scale? Are studies from other countries or evaluations from other authorities mentioned only when we have a void, or when the other authorities agree with us? If not mentioned, should we assume other authorities did not agree with us?" The Committee acknowledges that older studies may not capture newer use or market dynamics. The factor driving the EPA scoring is not really "age", rather market dynamics or some other factor and should be discussed in that way.

Comparing regulatory science reviews of EPA to those of other authorities is an important contribution to virtually any regulatory review. This is important for a variety of reasons, including comparisons of data use, approaches, and ultimate exposure assessment (and/or risk assessment) metrics. In such comparisons the details about options and utility of data, approaches, methods, and models can be understood, by EPA scientists, SACC reviewers, stakeholders and the public. This practice of comparison can show areas of agreement in the scientific community, or honestly disclose differences (which at least shows EPA awareness of the situation). Further, discussions about these comparisons can serve to educate the reader and increase public confidence in the EPA professionals who create the evaluation.

Without broad comparisons, EPA evaluations can seem to be isolated reviews on an international level, although most people know that the products and chemicals are often internationally distributed, used and regulated.

Conversations about reviews by other authorities can offer scientific perspective on more than just "the answers." For example, contextual factors such as:

- Are the products grouped in the same way for review…yes or why not?

- Are other data/information used by other authorities,

- What computational models are used throughout the review and assessments?
- Age of the reviewed information, resolution of issues such as data gaps, assumptions,
- Are aggregated exposure/risk assessments used…either to assess multiple scenarios OR to highlight relative contributions of different exposure scenarios and products to the aggregated risk?
- What are the differences among the answers (exposure, populations exposed, etc.)

Such consideration of other thoughtful evaluations provide context around the answers and highlight areas of significant differences, which when discussed can improve confidence in the EPA assessment's methods, data use, models, etc.

Scientists, stakeholders, and the public can see differences in "conclusions," regulatory differences, etc. from other authorities and regulators. Without such discussion by EPA, these readers will logically wonder what yielded the differences and question the reviews. The Committee discussions reflected common agreement that perhaps the most significant issue is one of apparent "omission." In particular, the overall construct of the review severely limits the scope of the evaluation. Examples include only environmental scenarios consequential to industrial omissions, only residential exposures rather than all indoor scenarios, no meaningful consideration of vehicle scenarios (or other public transportation options), omission of huge new exposure venues like data processing sites, product distribution hubs and non-consumer use exposure pathways from products regulated—for the consumer use—by other regulatory authorities. EPA's review could be structured around the targets defined in the TSCA mandate, (manufacturing, distribution, transportation, consumer use, disposal) EACH of which include elements of source (water, dust, ambient air indoor and outdoor, etc.), different populations of concern, etc. Perhaps that approach could be less likely to "overlook" exposure opportunities and exposure conditions and potential PESS scenarios. That also could comport to the actual law, making explanations of differences with other regulatory authority efforts more understandable.

Committee suggestions for specific issues

Lines 2102 to 2113 on Page 116: The calculation of the aqueous permeability coefficient (Kp) in this assessment may be highly uncertain. The ten Berge approach was used, which considers the resistance to permeation caused by three components in human skin: the lipid medium, proteins in the stratum corneum, and the aqueous boundary layer over the skin (also known as the water layer). Repeating the EPA calculation reveals that since DIDP is highly hydrophobic, the majority of resistance comes predominantly from the aqueous boundary layer. It does not matter how the lipids and proteins are considered or parameterized in the model; the key is ensuring the permeation across the aqueous boundary layer is well-characterized and calculated. However, a chemical's permeability across the aqueous boundary layer is currently understudied for highly hydrophobic chemicals. Because of the lack of data, the calculated Kp may also be highly uncertain, potentially yielding poor estimates of the actual permeability across the aqueous boundary layer. The Committee recommends discussion of this point in the report to improve transparency.

Lines 2114-2115 on Page 116: The sentence reads, "However, EPA is confident that the selected approach represents an upper bound of dermal absorption of DIDP from solid articles." EPA seemingly provides no explanation for why they are so confident. As previously noted, the EPA's estimate of dermal

absorption may have overestimated dermal exposure because it unfortunately does not consider the rate limit by mass transfer within the product material. If this overestimation is considered a sign of "conservativeness" in risk assessment, then the EPA can state that this confidence is based on that principle. Overestimation can be caused by either using inappropriate assumptions in calculation or by selecting the higher-end values for individual variables – The Committee notes this presents a challenge to transparency as the potential for uncertainty in the calculation is followed by a claim of certainty by the EPA which perhaps is more of a policy or bias for conservatism. The Committee suggests this kind of presentation can erode trust in the assessment.

- The Committee noted that because Dermal absorption is an area of high uncertainty in the assessment, that should be highlighted in the risk evaluation chapter. Use of upper bound exposure estimates in risk evaluation for COUs that include dermal exposure may be defensible due to the considerable uncertainty but the discussion about these decisions and uncertainties should be presented thoroughly.

- Tables 5-1 through 5-3: The Committee raised issues about construction products contributing to exposure after use, as they age and wear in indoor environments. EPA may want to consider if such issues would reduce the overall exposure confidence to less than "robust" until this is corrected.

Recommendations

The Committee recommends the following:

- Key aspects of the regulatory science review as well as conclusions and risk-related metrics should be compared to those found in reviews by other authorities, with discussions putting such comparisons into perspective. This practice is more commonly found in discussions of the hazard studies but should apply equally to the exposure and risk sections. In all sections, the comparisons should be as comprehensive as possible, especially when other authorities have settled on decisions that may be (apparently) at odds with EPA's decisions and approaches.

- EPA should reconsider, explain, or standardize in some way its "grading system" on the utility of consumer and worker exposure data generated by other countries.

- Again, as noted in responses to other Charge questions, the Committee strongly suggests that statistical characteristics of data should be comprehensive and transparent to explain how single values are selected and applied appropriately to the assessment algorithms.

- The Committee again suggests that the pathways and scenarios of exposure be expanded, as discussed here and in other Charge Question responses. The Committee sees this as a very important issue for EPA.

- When evaluating DINP, the Committee suggests attention to the specific concerns cited in detail in the discussion section.

Charge Question 1.a.v

For the remaining phthalates (i.e., DEHP, DBP, DIBP, BBP, DCHP, DINP), EPA anticipates potentially needing to refine the exposure assessment for consumer and indoor dust exposure. Please suggest exposure data sources, models, and related methods for estimating dermal, inhalation, and ingestion exposures to chemicals from consumer products that are reasonably available and can be conducted in a timely fashion that allows EPA to meet statutory timelines for TSCA risk evaluations.

Discussion

The risk assessment for these chemicals, individually, rely on exposure and hazard information that carefully align. At least one of the phthalates, DBP, is thought to be acutely potent, which means that exposure scenarios, computational factors and subpopulation emphasis will likely be uniquely important. Such scenario components are different from those designed for chronic exposure scenarios. Attention on the statistical handling of data informing the exposure models must be appropriate for acute exposure scenarios.

DIDP is relatively data-poor in comparison to the other high priority phthalates. As a general comment, EPA should be prepared to thoroughly evaluate products and scenarios to model, to ensure that the selected items and scenarios will provide reasonable assurance of including upper bound exposures to the most highly exposed or most biologically susceptible subpopulations.

EPA should model some scenarios outside the CEM or through adjustment to the CEM, if those scenarios represent high exposures that may be of concern for a COU.

More complete attention to how chemicals can enter household air and dust through generation of dust particles from articles and products will be important for the broader COUs and a number of products and articles for DINP. As suggested for DIDP, degradation of plastic polymer products and articles should be included in dust exposure modeling.

The DINP exposure assessment should be reviewed by the SACC. The Committee is concerned that issues are likely to arise with the DINP review and with other phthalates which have not drawn attention during the DIDP review. Some of those have been articulated in responses to various Charge Questions, and in particular, the assessment of exposure for the acute effects of phthalates could present a challenge. The application of exposure related values into the CEM will require selection of values within a distribution of values for each parameter in the algorithms. Choices of mean values can understate the exposure. Choices of high-end values, when taken together over many parameters can overestimate exposure.

Those types of issues will be compounded when aggregation of multiple exposure pathways for a given chemical are quantified by “adding” which is not true aggregation. Aggregated exposure to an individual by addition of all possible exposure scenarios without modeling the probability of any one of those scenarios’ occurrence will likely overstate exposure. For example, every hour spent in a car is one hour not in the house. Some people spend four hours a day commuting while others are in the car rarely. Adding together high-end exposure estimates for all venues yields an estimate that does not really exist in people’s schedules. Without a probability factor for the exposure “event”, it will be a challenge to coherently estimate daily exposures to pair with acute hazard metrics. It is possible that the time not in a

home or vehicle could be within another indoor work environment. So having a total time exposed to DIDP that approached 24 hours a day may not be an unreasonable estimate from many individuals. Including exposures in schools, offices, and other indoor environments with an upper limit of 24 hours daily exposure would be useful. Indeed, probabilities accruing to total time exposure over a 24-hour period is a key part of probabilistic models and an important function to be examined in model designs.

In the opinion of the Committee, an overstatement of exposure which is the consequence of limitations in the modeling is not the equivalent of a "conservative estimate." It could just be a wrong estimate.

The Committee assumes that the EPA is moving towards a cumulative risk assessment for phthalates. While the Committee applauds that goal for many reasons, they are very concerned that the EPA will need several improvements in data, quantification of phthalate release from polymers under different stresses, quantification of dermal uptake rates, statistical methodology, logic for capturing significant exposure scenarios missing in the DIDP assessment (and perhaps others not yet considered for other phthalates), and an exposure assessment model to competently utilize such information with proper alignment to the metrics of the hazard assessment. As noted in the Committee response to Charge Questions 1.a.i, ii and 1b.i, there are limitations of the CEM model for individual products and scenarios, but a cumulative assessment will require employing a different model concept altogether.

Additional sources of phthalates quantification in airborne and settled particles as well as human exposure to them can easily be produced by the manufacturers who petitioned for this review, otherwise the assessment will have high uncertainty, which will require high centile (90+) exposure values and low centile (10% or less) effect values. This comment cascades into all other aspects of TSCA related Risk Evaluations and Risk Determinations being considered by EPA.

There are a few studies of exposures that have been published in the last couple of years that may be useful in better defining exposure scenarios: (Subedi, Sullivan and Dhungana, 2017; Bastiaensen, Gys *et al*., 2021; Minatoya and Kishi, 2021; Wang, Chen *et al*., 2021; Hwang, Choi and Park, 2022; Mol, Elbers *et al*., 2022; Yu, Lu *et al*., 2022; Govarts, Gilles *et al*., 2023; Sjöström, Hagström *et al*., 2023; Vogel, Schmidt *et al*., 2023).

LL1130-1220: The EPA evaluation of dermal exposure appropriately used the Dermal flux approach based on in vivo rodent models and the framework suggested by Kissel (as referenced in the Draft Consumer and Indoor Dust Exposure Assessment) i. Dermal exposure data in humans is unlikely to be achievable or advisable.

Recommendations

The Committee recommends:

- EPA should reconsider the alignments of the metrics utilized for exposure assessment to align with the hazard assessments—for both human and environmental risk. This should include careful discussion (in the document) detailing the data distribution and logic for selection of metrics for the CEM, especially as to how it comports with the appropriate hazard scenario (including duration of exposure and profile of person's exposed or environmental targets exposed).

- EPA should require that sufficient data to describe ecological and human health exposures and toxicities are available from petitioners for chemical review under the Toxic Substance Control Act. If data to inform these aspects of distributions are not available, assessments cannot be scientifically justified. Alternatively, petitioners could provide a specific plan to collect data that fill information data gaps for any chemicals undergoing this type of review before the request for review is approved. EPA should propose a path to the cumulative assessment so the data, logic, approaches, and models may be reviewed by SACC prior to initiation of the actual assessment. Hopefully this path will be provided to the SACC for review once the cumulative assessment is produced.
- As with several previous SACC reviews, the Committee implores the leadership of EPA to provide to the EPA scientists the statistical tools, expertise and models needed for the state-of-the-art assessments needed for these chemicals.

Charge Question 1.b

As described in Section 2 of the Draft Environmental Media and General Population Exposure for DIDP, EPA used sentinel exposures to conduct a screening approach for the DIDP exposure assessment. EPA anticipates that the exposure methodologies demonstrated in the Draft Risk Evaluation for DIDP will be applicable to DINP exposure scenarios.

Charge Question 1.b.i

Please comment on the strengths and uncertainties of the selected data and methods employed in the use of sentinel exposures in the screening approach.

Discussion

The Committee discussed several issues related to approaches and assumptions utilized in choosing and describing sentinel exposures, estimating the exposure resulting from those sentinel constructs and likely incompleteness of the considerations. Those are summarized below.

- The concept of the use of sentinel exposures to test for exposure scenarios of potential consequence, as discussed in Section 2, is a valuable approach, especially when monitoring data or new exposure scenarios are being considered with limited record of actual exposure or media residue. However, the assumption described in Section 2, lines 368-375, that the highest end of an exposure path begins with industrial releases should be chronicled/defended somehow because it drives the entire sentinel assessment paradigm on which these analyses rest. The industrial releases may indeed yield high end exposure pathways, but there may be other sentinel progenitor sources for phthalates which are also generating high end exposure pathways…potentially also sentinel. And, given there are no monitoring or residue data to declare which "sentinel" is the biggest, all potentially high-end pathways may be legitimate to include in this assessment process.
- The EPA assessment of phthalate exposure and subsequent risk does not include the world of distribution of products from the production through the wholesaler, retailer (or on-line distributor) to the consumer. That pathway involves wrapping individual products and whole plats of product, movement, stacking, and storage in massive warehouses. Workers in these

facilities are in constant proximity to phthalate-rich products, wrapping materials, insulation materials, packing materials, and the dust in the buildings, shelves and on interior structural components of the buildings. Just as in residences, the exposures could be significant, and to these workers, one can assume long daily exposure periods over 5-6 days per week. Hence, unlike the industrial fugitive release into outdoor spaces, here we have the potential of exposure to phthalate rich dust for chronic exposure scenarios. This could be a sentinel exposure pathway for many thousands of workers—perhaps in addition to the pathway proposed by EPA. In Table 1.1 of Section 2, p 11, "Distribution in Commerce" is listed but is apparently not discussed in the assessment.

- If EPA assumes the massive distribution centers do not accrue dust from the products, packaging or other phthalate items entering or part of the buildings, there must be some kind of purging of those particles. Indeed, these buildings are vented into the ambient air of the community, potentially creating a constant supply of fugitive phthalates—not unlike the scenario of industrial emission which was considered by EPA. The potential for fugitive chemical emissions from distribution warehouses may be a significant issue for communities located in the near proximity of such distribution hubs. These locations would include areas that are economically and logistically advantageous to the industry. (Sutapa, I. and Wullur, M., 2020). Sophisticated logistical modeling calculates the optimum placement of such warehouses considering logistical, financial, and other factors. Such locations become hubs with many, rarely one, massive distribution centers (Rodrigue, J-P, 2024). Nearby communities could be considered Fenceline communities given this new reality of pollution potential throughout the country.

- Workers in areas with phthalate dust may transport those particles to their homes. Track-home residue may not be sentinel but could also be significant to the contamination of home spaces and the multigenerational people living there.

Section 2.2 and other sections state "General population exposures occur when DIDP is released into the environment and the environmental media is then a pathway for exposure." The Committee agrees, but questions why EPA contemplates only one initiator of the sentinel exposures? What is the evidence or body of evidence that only an industrial release scenario is always the progenitor of a sentinel exposure? If this is to be the only progenitor scenario considered by EPA…as a practice of science if not a policy, then the evidence for it should be at least cited in the document, especially if other initiating scenarios are not to be considered.

Regarding potential exposure from DIDP in water, the Committee challenged the assumption that when phthalates (including DIDP) entered the water, they would likely not be available for exposure opportunities to humans, other organisms, food chain, etc. The Committee agreed that the phthalates are unlikely to exist primarily in free form in the water and are very likely to sorb onto particles or other surfaces in the water. That could result in settlement of the particulate with adhered phthalate to the bottom or lower part of the water column. However, the Committee was not convinced that scenario removed the phthalates from exposure opportunities for the following reasons.

- Water bodies are not all clear with particulates predominantly and permanently in bottom sediment. Surface waters, even those frequently clear throughout the water column, are sometimes murky as their bottom sediment is disturbed by turbulence or new particulates are

flushed into the area. That condition provides opportunities for exposure, especially where untreated surface water provides drinking and bathing water and use in food preparation. Those conditions frequently exist in Tribal and other subsistence communities. Those surface waters also provide foods and materials for those communities.

- EPA estimated concentrations to be about 27,000 mg/kg. The Committee considered that high contaminant concentrations, even if adhering to particulates, need to be explored in detail.
- Flooding scenarios can mobilize media containing the phthalate, placing the sediment and adhered phthalates into a new environment with potential for widespread exposure, especially to recovery workers cleaning up the disaster and families returning to flooded residences and businesses, schools, etc. Sentinel exposure scenarios could be hypothesized to test the assumption of risk for these ever-more-frequent situations. Such a hypothetical paradigm could serve as a template for similar sentinel assessments for other chemicals and could serve as a marker for future residue testing in flood waters and post-event debris.

Regarding the calculation of potential exposure from water-born sources, the Committee noted omission or under-representation of potential exposures.

- The Committee applauded consideration of fish consumption by subsistence fishers and tribal communities for calculations in the sentinel exposure scenario (Sections 7.2 and 7.3 on Pages 41 and 42). Since DIDP has a high K_{OW} and high K_{OA}, it is anticipated that fish consumption, more so than terrestrial food sources, makes the highest contribution to the total chemical intake because such chemicals may be more "bioaccumulative" in aquatic animals than in terrestrial animals.
- Although EPA's report recognized Tribal scenarios, it limited the "sentinel" exposure scenario to fish consumption. This is discussed with references by Dr. Diane Barton, National Tribal Toxics Council in the public comments. The daily fish consumption estimate, as well as frequency of consumption seems to have been under-estimated by EPA. Moreover, the food contribution from the local surface waters would likely be broader than just fish. Subsistence diets affected by those waters would include shellfish, birds and other animals that live in or are sustained by those waters. Plants from the waters or water's edge are harvested for food and for reeds used in arts. If the exposure assessment for this PESS community is meant to be "sentinel", these daily and repetitive exposures are important to include, especially since alternatives to those sources or water bodies are unlikely for those PESS communities. Estimates of residue could be made for these food sources, extrapolating from the ecological assessments using representative aquatic and land animals noted in the EPA report. An upper-bound estimate of possible residue could be used to represent the sentinel exposure sources for Tribal and subsistence communities.
- Another PESS scenario could exist for the rural, low-income, subsistence communities of the coast of the Gulf of Mexico. Diets there frequently include water-dwelling species such as alligator, duck, fish, shrimp.
- The Committee noted similar concerns for communities in the Pacific Northwest, New England coastal and Chesapeake Bay areas where dietary intake of waterborne fish, shrimp, bivalves, and

other creatures are frequent and higher than represented by EPA's fish intake, especially as it is to represent sentinel exposure for these populations.

The Committee also noted the absence of sentinel exposure calculations for exposures from soil that may have been dredged from waterways or other areas contaminated with phthalates. Construction workers, gardeners, landscapers and other professions may experience daily exposures under such conditions.

Recommendations

The Committee offers the following recommendations:

- Expand the initial (progenitor) source of contamination beyond the industrial emissions scenario to include warehouse dust and consider the exposure scenarios consequential to exposures inside the distribution centers and the emissions into the community from continuous emissions via exhaust from multiple buildings in distribution hubs.
- Consider Tribal exposure scenarios and consumption values presented by the National Tribal Toxics Council as submitted by Dr. Diane Barton.
- Expand the exposure scenarios and calculations of those scenario estimates to include the conditions from sediment disturbance, dislocation and turbulence. Consider other exposure scenarios and subsistence foods, calculating the exposure from representative residue estimates using tissue loading calculations from species studied in the ecological evaluations.

Charge Question 1.b.ii

Please include a consideration of the strengths and uncertainties associated with methods related to calculating surface water concentrations for DIDP.

Specific Comments

The Committee identified the following main issues that are related to the methods, approaches, and data used in the EPA's assessment in the "Draft Environmental Media and General Population Exposure for diisodecyl phthalate" document.

1. Overestimation of DIDP concentrations in water and sediment

The Committee expressed concerns over the possible substantial overestimation of DIDP concentrations in water and sediment and the use of overestimated DIDP concentrations in subsequent human population exposure analysis. This uncertainty could be easily remedied by having monitoring data from manufacturers or users.

As described in Tables 4 and 5 and related texts on Pages 26 and 27, using the Variable Volume Water Model with the Point Source Calculator tool, the EPA predicted DIDP concentrations to range from 1.47 to 10,200 µg/L if no wastewater treatment techniques were applied (Table 4-4). The concentration is 547 µg/L even if it is assumed that 94% of DIDP is removed during wastewater treatment (Table 4-5). These predicted concentrations far exceed the water solubility of DIDP (0.17 µg/L), by up to 60,000 times. It should also be noted that in the absence of monitoring data from industrial effluent, exposure assessments must necessarily be conservative (protective).

It is not surprising to see concentrations higher than the water solubility in environmental monitoring. This is because the monitored concentration represents the total concentration in water, not only the freely dissolved fraction in the aqueous phase, and slightly water-soluble chemicals like DIDP may be absorbed strongly by suspended particles. For example, Tran *et al*., 2014 reported measured concentrations in surface water from municipal (not industrial) effluents before wastewater treatment, with a high centile of 62.8 µg/L and an average of 23.4 ± 19.7 µg/L. These numbers are greater than 100 times greater than water solubility and include a fraction sorbed to suspended particles within the water.

However, it is unlikely for the total concentration to be 60,000 times higher than the water solubility under normal levels of Total Suspended Solids (TSS), unless there are phthalate droplets present in water. One of the Committee members performed a quick calculation. Given that DIDP has a water solubility of 0.17 µg/L and a K_{OC} of 105.09 L/kg as reported by the EPA, if using the default value of 0.37 for the fraction of organic carbon in sewage sludge (taken from the European Union System for the Evaluation of Substances model), one can calculate the concentration in effluent sewage sludge to be 7.74×10^3 µg/kg when solids come into contact with a saturated DIDP aqueous phase. In addition, assuming (1) all TSS in wastewater treatment influent and effluent are small sewage sludge particles, (2) TSS levels are 3000 mg/L in influent and 10 mg/L in effluent, respectively, and (3) DIDP is saturated in the aqueous phase (i.e., aqueous concentration is 0.17 µg/L), the total concentration can be calculated as 23.4 µg/L in influent and 0.25 µg/L in effluent, respectively. These numbers match the measured concentrations of 23.4 ± 19.7 µg/L and 0.26 ± 0.22 µg/L in influent and effluent reported by Tran *et al*., 2014. These TSS levels are at the higher end of what is typically observed in wastewater treatment. If the total concentration needs to be 10,200 µg/L as calculated by the EPA, then the TSS level would need to be 1,300,000 mg/L (1.3 kg/L). Considering the typical density of dry sewage sludge is 1.5 kg/L, this TSS level is close to impossible. Therefore, such a huge difference between the calculated total concentration and water solubility cannot be rationalized by the difference between the total and freely dissolved concentrations without having free DIDP suspended in solution.

This implies that DIDP concentrations in water, and consequently in sediment, may be overestimated in this assessment. As described in Section 4.1 (Lines 575-576), the modeling was based on "generic modeled waterbody parameters," representing a rectangular cuboid with a small volume of 200 m^3 (width of 5 m, length of 40 m, and depth of 1 m). The EPA assumed that all DIDP released from an industrial site flow into within such a small rectangular cuboid, which is orders of magnitude smaller than natural water bodies (e.g., rivers and lakes) and even the sedimentation or aeration tanks in typical wastewater treatment plants. It is unclear what the EPA intended this small rectangular cuboid to represent. If this size represents characteristics of known receiving basins for effluents, please specify that. Additionally, if the EPA intended to represent confined wastewater depositories, DIDP would form films or droplets of undissolved, pure phase separated from the aqueous phase in reality, rather than a concentration exceeding the water solubility by orders of magnitude. In this case, the EPA needs to determine whether this calculated total concentration is ecotoxicologically relevant because the DIDP films or droplets (or DIDP sorbed to TSS) may have variable bioavailable to aquatic organisms and humans. If the EPA intended to represent natural water bodies, DIDP would be diluted and not confined within this small area. In either case, the assumed emission rates or the scale of the receiving environment should be revisited. As mentioned before, without monitoring data conservative estimates are needed in exposure assessments.

2. The use of environmental monitoring data

The Committee expressed concerns over the way that the EPA counted or discounted environmental monitoring data.

First, in L677-678 on Page 28, the sentence reads, "Eight studies within the pool of reasonably available information reported DIDP concentrations within surface water. No US studies were identified." The Committee expressed the concern that no US water monitoring data were used in this assessment and no industrial effluent monitoring data from any jurisdiction were included. The EPA cited a lack of available US data. However, manufacturer requests for reviews cannot be scientifically justified without sufficient evidence documenting chemical release from manufacturing facilities and municipal effluents that can allow a robust exposure assessment. It should also be noted that a lack of studies does not indicate of lack of exposure. Measurement of DIDP in industrial effluent is required to inform a defensible risk assessment.

Second, in Lines 722 –724 on Page 29, the sentence reads, "Sediment associated with urban stormwater runoff collected within an underground sedimentation facility in Göteborg, Sweden, represents the highest concentration of DIDP within sediment at 60,000 µg/kg (Björklund *et al*., 2009). The nature of the sedimentation facility is to isolate and retain sediments from stormwater runoff within a treatment facility and not representative of sediments associated with surface waters." This means the EPA differentiated between wastewater depositories and natural water bodies and considered only the latter as the relevant target for exposure and impact assessments, given the reported high removal efficiency of DIDP in wastewater treatment processes. The Committee stated that discounting the 60,000 ug/kg (60 mg/kg) of DIDP in stormwater sediments is troubling. In this assessment, the EPA omitted most monitoring data retrieved from treatment facilities, which is an unjustified practice. The Committee notes that, as reported by the EPA, as of January 2023, there are around 700 communities in the United States that experience combined sewer overflows. Most of these communities are located in the Northeast Great Lakes in the Pacific Northwest, and this issue impacts around 40 million people who rely on local waters for drinking water sources. Even if DIDP and DINP can be efficiently removed via wastewater processes, it is problematic to assume adequate wastewater treatment across the country. The untreated municipal wastewater treatment data from Europe (Tran *et al*., 2014) could be used to estimate concentrations released in such cases.

Recommendations

- The EPA should revisit the modeling of DIDP concentrations in water and sediment by reconsidering the rates of environmental releases or the scale of the receiving environment used in the modeling while maintaining conservatism in the assessment.
- The EPA should obtain the US environmental monitoring data from manufacturers, for both wastewater depositories and natural water bodies, and revisit the appropriateness of assuming a >90% removal efficiency in wastewater treatment processes across the US

Additional Comments

This charge question requests comments on the calculation of surface water concentrations and the resulting exposure of the general human population. Although impacts on ecological receptors were not asked as part of the charge, the Committee believes it is important to address these ecological impacts,

and that is done at the end of the response to the DIDP charges. Presently, most of the EPA's predicted DIDP concentrations, if confirmed after revisiting the calculation as suggested above, exceed the toxicity thresholds for aquatic species. Additionally, the DIDP concentrations collected from environmental biomonitoring data, especially the highest concentration of DIDP in sediment at 60,000 µg/kg, resulting from municipal runoff are quite high. These concentrations should be compared to toxicity thresholds for ecological receptors to assess potential ecosystem impacts, rather than focusing solely on human exposure. For more comments on this issue, please see the consideration of Risk Assessment topics that is situated between the end of the DIDP charge question responses and the beginning of the DINP response.

Editorial Comments

- Table 5-3 on Page 33 provides estimated acute doses (ADRs) for different age groups. In the footnote, it states "Table 1-1 provides the crosswalk of OES to COUs" to indicate how different scenarios were made. The sentence in Lines 849-850 reads, "Using the acute dose based on the highest modeled 95th percentile, the MOEs are greater than the benchmark of 30."

  The Committee suggests (1) providing more explanation of the MOEs greater than the benchmark of 30 (Table 5-3), and (2) providing further references for the assumptions made for the ADRs for different age groups to link the data to the information (beyond Table 1-1).

- Line 1015 on Page 39: The sentence reads, "However, DIDP is not expected to be bioavailable for uptake by aquatic organisms due to its strong sorption to organic matter and hydrophobicity".

  The Committee believes that the statement that DIDP is not expected to be taken up by aquatic organisms is directly contradicted by monitoring data presented in the "Draft Environmental Exposure Assessment". The Committee suggests that all of these types of language need significant harmonization across the assemblage of reports in this docket.

- Table 7-1 on Page 40:

  The Committee believes the values in the "surface water concentration" column all need citations. The monitored surface water data in Table 7.1 are means from a single study (Tran *et al*. 2015). The single study can be noted in the caption. The mean must be changed to a high centile and perhaps from a system with higher aqueous concentrations. Higher centile values from this study would produce a value of 87 µg/L.

- Regarding numbers in Table 11-2 on Page 66, the Committee notes that the 30Q5 concentration of 100 µg/L differs from the 547 µg/L concentration reported for lubricants and functional fluids in Table 5.1 and other tables in that section. The Committee suggests either clarifying this discrepancy or correcting the misalignment.

Charge Question 1.b.iii

In light of comments on charge questions 1.b.i and 1.b.ii, please comment on the weight of scientific evidence and its conclusions for the general population exposure assessment (Section 11.3 of Draft Environmental Media and General Population Exposure). Please include in these comments a discussion of the clarity and transparency of the data used, and EPA's interpretation of the exposure results.

Comments

In its concluding statements concerning exposure of the General Population to DIDP, the Agency expressed "robust" confidence in the modeled exposure levels yielding no exposure pathways of concern (L1831-1833). This confidence was supported by a comparison of modeled exposure levels for each exposure scenario to calculated exposure levels based on NHANES biomonitoring data, which represents aggregate exposure from all sources, indicating that calculated exposure levels based on NHANES data were below the modeled exposure levels, suggesting that the modeled levels overestimated the actual exposure (L1836). The reviewers support the Agency's conclusion regarding the confidence of the estimated exposures and that there were no exposure pathways of concern.

Uncertainties

As stated in Section 10.2.2, "reverse dosimetry" has its limitations and uncertainties, namely:

1. a urinary excretion factor for DIDP or its metabolites has not been determined, although the excretion factor for MCOP, a metabolite of DINP is likely to be a reasonable substitute as EPA proposed, and
2. NHANES samples are from a limited population.

Strengths

As noted by EPA on page 57 in Section 10.2, the NHANES dataset is considered a national, statistically representative sample of the US civilian population and the data represent an aggregate exposure from all pathways and should, therefore, be comprehensive. Also, EPA cited that other regulatory agencies view the exposure levels calculated from NHANES data to be realistic.

Regarding the clarity and transparency of the data used to reach these conclusions, the following comments should be considered.

In Section 8.1, there is a discussion of input values used in the AERMOD to estimate airborne concentration; however, it is not clear what is meant by "higher end meteorology" (L1186)?

In Table 8.1 (L1211), the data listed would all be highly dependent on particle size, and physical state (i.e., vapor or aerosol). A brief description of those parameters and their selection should be included in this section. Or provide a reference to the document where this information can be found.

In Table 8.2 (L 1251), what is the likelihood of a release being less than 100 m from a fenceline community? Data are needed related to locations of emission sources and surrounding communities.

There is a need for close examination of distances at which PESS communities may experience phthalate exposures.

In Appendix C, Section C1.1, L2104-2107, what does the parenthetical mean in the statement… "it was determined that meteorological conditions from Sioux Falls, South Dakota led to central-tendency modeled concentrations and particle deposition, and those from Lake Charles, Louisiana led to higher-end modeled concentrations (though more central-tendency results for particle deposition), relative to the other regional stations." If this means Lake Charles provided central tendency particulate values is that appropriate for this use?

Editorial comments

L734 "days-on" should be "days."

Recommendations

The Committee supports the Agency's use of NHANES data to provide exposures for the General Population.

Charge Question 1.b.iv

For the remaining phthalates (i.e., DEHP, DBP, DIBP, BBP, DCHP, DINP), EPA anticipates potentially needing to refine the exposure assessment for the environment and general population. Please suggest exposure data sources, models, and related methods for estimating concentrations in environmental media paying special attention to those media most relevant to phthalates, e.g. water, sediment, and soil. In your consideration, please keep in mind that methods, data, and approaches should be reasonably available and can be conducted in a timely fashion that allows EPA to meet statutory timelines for TSCA risk evaluations.

Discussion

Many of the comments about the approaches for exposure assessment and risk assessment offered in previous Charge Question responses are pertinent to this discussion. In particular, The Committee noted significant omissions in the COUs and environmental exposure scenarios considered by EPA. Complex consumer items, such as vehicles, contain many individual phthalates in separate components of the car, creating a unique environment for exposure different from those modeled by the EPA analysis. The vehicle scenario can be thought of as an "environment" and requires a true aggregate exposure assessment for the repetitive exposures to different ages and potentially vulnerable people. The Committee urged EPA to consider those comments when reflecting on the approaches to the other phthalates and certainly when considering a cumulative assessment from the environmental exposures.

Below is a specific, important example of issues expected to reappear for EPA as they utilize their current models with the choice of parameters for incorporation into the algorithms for the environmental media. Such issues with methods and application of data can magnify when multiple chemicals are considered in cumulative exposures for cumulative risk assessments.

The Committee noted a major issue regarding EPA's use of different models to target different environmental media, such as the Variable Volume Water Model (VVWM) for surface water and

AERMOD for air and soil deposition. This may be acceptable, or even ideal, for chemicals that primarily reside in a single medium, such as PFAS in water and volatile organic compounds in air. However, it may not appropriately consider the multimedia behavior of DIDP, chemicals with a high K_{OW} and high K_{OA}. Therefore, there may be inconsistent considerations when assessing different environmental media. For example, when calculating chemical concentrations in water, the EPA considered the deposition of chemicals from the air, which is a process that is not directly considered by the VVWM. The EPA relied on atmospheric deposition rates derived from AERMOD. However, it should be noted that the two models use different environmental settings and spatial scales. AERMOD considers various distances from the source, from 10 meters to 10000 meters, in a large area. However, the VVWM considers placing only a small water body (a swimming pool size, width of 5 m, length of 40 m, and depth of 1 m) in a place adjacent to the source. In this case, we can imagine that the calculated water contamination is unrealistically higher than the calculated soil contamination. Therefore, it is clear that separate considerations in water and soil contamination lead to inconsistencies.

Accordingly, the US EPA may consider using multimedia mass balance models for semi-volatile organic chemicals like phthalates. The Committee acknowledged that single-medium models are advantageous because they focus on a single medium at a time, which allows them to use sophisticated representations of individual media and detailed characterizations of individual physical, chemical, or biological processes. Since multimedia mass balance models need to accommodate multiple environmental media, they use relatively coarse spatial resolution and simplified algorithms for processes within each medium. But their advantage is that they can integrate multiple environmental media simultaneously and consider the interactions between them. There are many multimedia mass balance models available, ranging from those with very simple configurations like the “unit world” Level III model built into the EPI Suite, to more advanced models like the “Risk Assessment IDentification And Ranking (RAIDAR)” model (Arnot *et al*. 2008) or the “PROduction-To-EXposure (PROTEX)” model (Li *et al*., 2021), or the “UNEP-SETAC toxicity (USEtox)” model. They contain both aquatic and terrestrial environmental media, and support considering multiple exposure pathways simultaneously. This may be especially important when considering multiple phthalates in a cumulative assessment or comparing different phthalates in different polymeric formulations or over different conditions.

Regarding the environmental exposure assessment and environmental release assessment, as discussed in Charge Question 1.a.v, there must be consideration of how the various phthalates become available to organisms. For example, an Exposure Assessment would include information on the movement of a phthalate such as DIDP to enter various dust compartments for modeling. Models must consider whether volatilization to air is a route for chemical migration from products, articles, and industrial sources. Although Charge Question 1.a.v. emphasizes exposure assessment for consumer and indoor dust exposure, whereas this charge question emphasizes the environment and general population, there are similar issues including potency, exposure scenarios, sources, movement in the environment, and availability to living organisms.

In addition, it is important to consider aggregate exposures that include assessment of individual chemicals and their bioactivity as well as environmental effects and exposure to multiple chemicals. Some of these environmentally available chemicals may bioaccumulate and in the case of phthalates, they appear at least for some forms to have minimal bioaccumulation and therefore potentially less effects though biomagnification. The exposure/risk scenarios will need to be modeled, using information

available for each of these chemicals individually as well as evaluation of potential exposure to multiple environmental chemicals simultaneously and over time.

According to the Charge Questions, five other phthalates are to be reviewed, including butyl benzyl phthalate (BBP), dibutyl phthalate (DBP), dicyclohexyl phthalate (DCHP), diethylhexyl phthalate (DEHP), diisobutyl phthalate (DIBP). These remaining phthalates will be reviewed using methods that are similar for each individual phthalate. However, the Committee noted that there are potential differences in hazard values and consequently individual risk profiles. As such, each of these additional phthalates must be considered on an individual basis for their characteristics. If several of these phthalates exhibit similar characteristics, and information on sources indicate that they are expected to be collocated, then exposures will be most likely to be concurrent and reflective of mixtures in the environment. It may be appropriate to combine the predicted concentrations for exposure assessment.

The predicted adverse outcome from exposures must be based on exposure data from the literature, if possible. If these data are not available, then develop models based on the chemical characteristics and predicted concentrations in the environment.

There appear to be many uncertainties that complicate environmental exposure assessment including availability of data on the relative concentrations of the remaining phthalates in water, sediment, and soil, and if deposition from air is a significant source. The relevant media span a wide array, including soil, air, and surface water. Testing concentrations in these media should provide information about environmental contamination by phthalates. However, distance from the source of pollution as well as mode of transfer in the environment remain critical variables that will affect the outcomes of assessments and accuracy of models.

Recommendations

- For multiple environmental media considerations, models based on principles of mass balance should be considered and a potentially better approach.
- The Committee recommended use of models that consider multiple sources of exposure (and multiple products and environments) for a given exposure event so a true aggregation of the exposure to populations could be estimated.
- Recommendations noted in previous Charge Question discussions are pertinent to the approaches for all phthalates.
- The Committee recommended that all future phthalate assessments receive review by the SACC, and urged EPA to present a proposal for the approach to cumulative assessment with competent models to the SACC for review as it proceeds to undertake a cumulative risk assessment for all phthalates.
- Prioritize the remaining phthalates (DEHP, DBP, DIBP, BBP, DCHP, DINP) beyond DIDP and DINP as to the following criteria: likely concentrations in soil, land, and air, potential sources for point pollution and chemical releases, volatility and other chemical characteristics, and potential for adverse effects on wildlife, both aquatic and terrestrial. This is an acknowledgement that the analytical and modeling methods will be similar in approach to those already used for the DIDP

and DINP. The Committee assumed these additional evaluations will be added to DINP into a cumulative risk assessment which the Committee recommends be reviewed by SACC.

- Incorporate reviews with studies demonstrating a strong adverse effect of DEHP and other phthalates on reproductive function, especially with developmental exposure (Lyche, J.L., 2017). Lee *et al*, 2023 reviewed the evidence of prenatal exposure to phthalates. Additional references for this topic are provided below.
- The sources of DEHP exposure include those beyond the scope of this review, including pharmaceuticals, beauty and heath care products. This complicates the assessment of exposure and potential adverse effects. These additional sources should be acknowledged and where exposure routes and PESS conditions exist that are not covered in assessments of other regulatory agencies, they could be included by EPA's assessments.

Charge Question 1.c

As described in Section 5 of the Draft Environmental Exposure Assessment for DIDP, EPA conducted a screening trophic transfer analysis to estimate dietary exposure resulting from modeled surface water releases and air deposition to soil, including use of monitoring and biomonitoring data. The resulting dietary exposure estimates were compared to the hazard threshold for semi-aquatic and terrestrial mammals. EPA anticipates that the exposure methodologies demonstrated in the Draft Risk Evaluation for DIDP will be applicable to DINP exposure scenarios.

Charge Question 1.c.i

Please comment on the methods and data used for estimating dietary exposures for ecologically relevant species and comparison of the exposure estimates to the hazard threshold for terrestrial mammals.

Specific Comments

The Committee identified the following main issues that are related to the methods, approaches, and data used in EPA's assessment in the "Draft Environmental Exposure Assessment for Diisodecyl Phthalate" document.

1. Overestimation of DIDP concentrations in sediment and ecological exposures.

The Committee expressed concerns over the lack of data that lead to a need to model concentrations that possibly substantially overestimate DIDP concentrations in sediment and the use of overestimated DIDP concentrations in subsequent ecological exposure assessment.

Section 3.2 shows that the calculation of exposure of aquatic species (such as chironomid) was based on "conservative modeling approaches that produces high concentrations of DIDP in sediment", which can be "16,560 mg/kg bw (body weight) for the COUs and OES with the highest surface water release and resulting sediment concentration."

Recalling the possible substantial overestimation of DIDP concentrations in water (60,000 times higher than the water solubility), the Committee believes that the DIDP concentrations in sediment and DIDP concentrations in aquatic species are overestimated as well. For example, DIDP concentrations were

estimated to be 16,560 mg/kg in sediment, meaning that 1.6% of the sediment mass consists of DIDP, which may not be environmentally realistic. Although, one Committee member noted that measured concentrations of DIDP in stormwater sediments were measured at much higher concentrations, the Committee appreciates the EPA presenting two sets of calculations for chironomid DIDP concentrations in Table 3-1: one based on the modeled sediment concentration and the other on the measured sediment concentration reported in the literature. However, it is unfortunate that only the chironomid DIDP concentrations based on the modeled sediment concentration were used to calculate fish exposure, as shown in Table 5-2.

In fact, the Committee notes that the EPA may already be aware of the possible overestimation. Tables 5-4 and 5-5 show much lower concentrations from samples taken in Taiwan, Sweden, and Canada. However, the EPA did not explain whether these differences reflect an overestimation or are due to variations in sampling design and/or analytical methods. Section 6 discusses confidence in the modeled concentrations potentially being overestimates. However, the lack of publications from the US involving sampling and measurement of DIDP reflects the limited availability of research and the criteria used to evaluate its quality.

The Committee also notes (1) the absence of environmental monitoring data sampled from industrial effluents in any location, much less in the US, and (2) inadequate information on DIDP releases along with industrial effluents. The lack of such data prevents the evaluation of predicted DIDP concentrations to assess whether they are overestimated. This limitation could be addressed by providing empirical DIDP release data.

2. Difference between exposure rate (dose) and concentration; Table 5-2 on Page 17.

The Committee points out a lack of transparency in the calculation of dietary exposure for American Mink. Table 5-2 indicates that this calculation builds on DIDP concentration (in mg/kg) in fish. It states that “fish concentration is calculated from DIDP-contaminated sediment ingestion and DIDP-contaminated prey ingestion values presented in Table 5-4.” However, Table 5-4 only presents the calculated fish dietary exposure rate (in mg/kg/d). It should be noted that a concentration differs from an exposure rate (i.e., a dose), and the two quantities are linked by dosimetric relationships. However, the EPA did not specify whether the fish exposure rate was converted to fish concentration, and if so, what specific dosimetric relationship was used for this conversion.

3. Potential toxicological effects at the predicted exposure level.

The EPA estimated a mammal Toxicity Reference Value (TRV) of 128 mg/kg/d based on empirical toxicity data for rats. Section 7, especially Tables 7-1 and 7-2, shows comparisons between dietary exposure estimates and this mammal TRV. When calculating based on predicted DIDP concentrations in water, the EPA determined a mink dietary exposure rate of 92.4 mg/kg/day. When calculating based on predicted DIDP air deposition to soil, the EPA determined a mink dietary exposure rate of 0.0019 mg/kg/day and a shrew dietary exposure rate of 0.03 mg/kg/day. Based on these numbers, the EPA concluded that “exposure concentrations are below the TRV”.

The Committee encourages the EPA to consider the uncertainty in deriving the TRV, before concluding that “exposure concentrations are below the TRV.” The Committee notes that many factors, such as the use of human health models to represent terrestrial mammals, lab-to-field differences, and inter-species

variability, may collectively contribute to the uncertainty in deriving the TRV. However, these factors may not necessarily be reflected in the TRV derived here. Notably, the value of 92 mg/kg/day falls within the range of the NOAELs and LOAELs from the studies used to derive the TRV (see Figure 6-1 of "Draft Environmental Hazard Assessment for Diisodecyl Phthalate"). This exposure estimate also surpasses non-cancer PODs (before the application of uncertainty factors) selected from the same pool of rodent studies for the human health assessment. While acknowledging the differences in conventions between human health and ecological assessments, the EPA may still wish to consider whether this overlap indicates the potential for reproductive and developmental effects relevant to terrestrial mammals from the high-end estimates for dietary exposure.

4. The use of "representative species"; Section 5.

EPA selected short-tailed shrew, blacktail redhorse, and American mink as "representative species", or the sentinels, for trophic transfer assessment.

The Committee believes that the report can benefit from clarification of and justification for the selection of these "representative species". Specifically, modeling the dietary exposure scenario should contain some information about potential related adverse outcomes and information from those selected representative species, such as relative sensitivity to contaminants and potential exposure to other stressors in the environment that might affect the adverse effects associated with dietary exposure.

The Committee emphasizes the importance of including other species, for example, bird eggs, especially those near water surfaces. This is because birds consume terrestrial and aquatic animals that are considered in the current assessment, and bird eggs may accumulate higher concentrations of phthalates. Valuable information is available from domestic species, including studies conducted in poultry on the effects of phthalate exposure, which showed effects on testicular function, oxidative stress, histopathology (Abdul-Ghani *et al*., 2012; Alam and Kurohmaru, 2021; Bello *et al*., 2014; Wang *et al*. 2019, 2020; Zakariah *et al*., 2022). Although these studies are not on the specific phthalates reviewed here, there is important information on the mechanisms and modes of action that accompany exposures. While we may never have comprehensive databases for these animals, the partial information collected from the literature and model predictions could still provide representative values.

Recommendations

- The EPA should revisit the modeling of DIDP concentrations in water and sediment by reconsidering the rates of environmental releases or the scale of the receiving environment used in the modeling. The EPA should also require the industry to provide more empirical release data and mandate this to be a requirement before any further expedited reviews are conducted.

- The EPA should revisit the calculation of dietary exposure for American Mink through consumption of fish.

- The EPA should be cautious in concluding "exposure concentrations are below the TRV".

- The EPA may consider justifying the use of the short-tailed shrew, blacktail redhorse, and American mink as "representative species" in the trophic transfer assessment. For example, the EPA may need to specify (1) any biological data from these sentinel/representative species that

demonstrate their sensitivity to DIDP, and (2) the measurement endpoints that would be selected to observe effects. Although not directly relevant to dietary exposure, the selection of representative species should be further rationalized in terms of their predictive response to varied levels of exposure.

Editorial Comments

- Line 318 on Page 14: The sentence reads, "DIDP is expected to have a low potential for bioaccumulation and biomagnification in both aquatic and terrestrial organisms."

  The Committee requests clarification on whether this sentence implies that this is a short-term issue with limited potential impacts.

- Lines 351-352 on Page 14: The sentence reads, "Because surface water sources for wildlife water ingestion are typically ephemeral, the trophic transfer analysis for terrestrial organisms assumed DIDP exposure concentration for wildlife water intake are equal to soil concentrations for each corresponding exposure scenario."

  The Committee requests clarification on whether this sentence indicates that DIDP exposures via ingestion of water are assumed to be equal to DIDP exposures via soil ingestion. If this is the case, then the EPA may consider (i) rephrasing the sentence and (ii) detailing how the soil concentration is used for equations, such as Equation 5-1, that require a water concentration as input, given that they have completely different units (mg/kg dry weight versus mg/L).

- Lines 435-441 on Page 17: The Committee suggests editing this text because it is redundant with text in the preceding section.

- Line 448 on Page 18: The Committee suggests changing "contaminate level" to "contaminant concentration."

- Lines 477-478 on Page 19: The sentence reads, "As a conservative assumption, 100 percent of the American mink's diet is predicted to come from fish". The Committee requests clarification on whether this sentence means no sediment in the diet or that organism X comprises 100% of the non-sediment diet.

- Table 5-3 on Page 19: Table 5-3 states that "estimated DIDP concentration in representative soil invertebrate, earthworm, assumed equal to aggregated highest and lowest calculated soil via air deposition to soil". The Committee suggests (1) rephrasing and expanding the sentence to detail how this was done and (2) clarifying whether there were any data from measured concentrations in earthworms.

Charge Question 1.c.ii

For the remaining phthalates, EPA anticipates potentially needing to refine the environmental exposure assessment. Please suggest exposure data sources, models, and related methods for estimating dietary exposures via environmental media paying special attention to those media most relevant to phthalates, e.g. water, sediment, and soil. In your consideration, please keep in mind that methods, data, and approaches should be reasonably available and can be conducted in a timely fashion that allows EPA to meet statutory timelines for TSCA risk evaluations.

Specific Comments

1. The Committee highlights the importance of considering the co-occurrence of multiple phthalates (DEHP, DBP, DIBP, BBP, DCHP, and DINP) and/or their primary metabolites as "mixtures" in the environment for cumulative exposure assessment. The Committee suggests combining multiple phthalates and/or their primary metabolites, if they (1) follow a similar mechanism of action or adverse outcome pathway (e.g., anti-androgenic), and/or (2) share similar environmental release characteristics and sources. The EPA is encouraged to evaluate how often the phthalates of interest (e.g., DEHP, DBP, DIBP, BBP, DCHP, and DINP) and/or their primary metabolites are detected together in organisms or environmental media to inform the future cumulative exposure assessment.

2. The Committee recommends that since multiple phthalates need to be assessed using the same analytical and modeling methods already applied to DIDP and DINP, it is important for the EPA to rank and prioritize these phthalates in their assessment. Criteria for the prioritization include (i) likely concentrations in soil, land, and air, (ii) potential sources for point pollution and chemical releases, (iii) volatility and other chemical properties, and (iv) potential for adverse effects on wildlife, both aquatic and terrestrial. It is also important to consider cumulative exposures by combining concentrations of multiple phthalates based on toxicity or potency equivalence with a consideration of their modes of toxic actions.

3. The Committee also provides additional resources of data for the EPA to strengthen the analysis.

The Committee recommends the EPA consider collecting data from the Washington Department of Ecology, Environmental Information Management (EIM) System database. Several studies on phthalates have been conducted throughout Puget Sound and Washington state, with measurements in sediment and surface water. All these data are publicly available in the EIM database, along with links to related publications, Quality Assurance Project Plans, and/or technical reports.

EIM database is available at: https://apps.ecology.wa.gov/eim/search/default.aspx

The Committee also recommends the EPA read the following publication to collect environmental monitoring data on marine and freshwater organisms that were not captured in the current review.

Savoca, D., Barreca, S., Lo Coco, R., Punginelli, D., Orecchio, S., Maccotta, A. Environmental Aspect Concerning Phthalates Contamination: Analytical Approaches and Assessment of Biomonitoring in the Aquatic Environment. *Environments* **2023**, *10*, 99

Recommendations

- The EPA should (1) consider the co-occurrence of multiple phthalates and/or their primary metabolites as "mixtures" in the environment, and (2) prioritize certain phthalates based on their environmental occurrence, release, chemical properties, and/or toxicity.

- The EPA should consider other sources of data (as described in the test above) that have not been included in the DIDP assessment.

Charge Question 1.d

In light of comments on charge question 1.c.i, please comment on the weight of scientific evidence and its conclusions for the environmental exposure assessment (Sections 6 and 7 of Draft Environmental Exposure Assessment). Please include in these comments a discussion of the clarity and transparency of the data used, hazard values, and EPA's interpretation of the results.

Specific Comments

- While the use of data from articles rated at least "medium" or "high" quality is appropriate, the lack of data available for several levels of trophic transfer warrants reconsideration of cells noted in Table 6-1 as "moderate" confidence.

- The overall confidence level for the modeled concentrations as being representative of actual releases is characterized as "slight" in several places, whereas many of the associated component data sources are characterized as "moderate".

- For trophic transfer, the lack of metabolic transformation may explain more of the discrepancy between modeled and observed concentrations than currently noted.

- The assumptions for proportion of diet, and the concentrations available to the predators are reasonable and based when available on empirical data. The choice of sentinel/representative species is appropriate associated with their feeding profiles and location.

Recommendations

- In light of the disconnect between the modeled calculations and measured concentrations, plus relatively few US measurements available, the EPA should add greater detail to its discussion.

- The EPA should reconsider confidence level assignments in Table 6-1 for transfer levels lacking available data.

- The EPA should address uncertainty from lack of metabolic transformation by using emerging methods for probabilistic estimation of metabolism.

- To support clarity and transparency, the EPA should include more detailed justification for the selection of the TRV.

Charge Question 1.e

As described in Section 3 of the Draft Environment Release and Occupational Exposure Assessment for DIDP, production volumes for Manufacturing and Import/Repackaging OES were determined using Chemical Data Repository (CDR) information. The production volumes for the other OES came from CDR and/or percent production volume (PV) (percentage of manufactured DIDP used for a particular OES) reported in the European Union (EU) Risk Assessment on DIDP since the use rate of DIDP is similar in USA and EU. EPA anticipates that the exposure methodologies demonstrated in the Draft Risk Evaluation for DIDP will be applicable to DINP exposure scenarios.

Charge Question 1.e.i

For environmental release assessments, please comment on the strengths and uncertainties of using EU PV % to estimate production volumes for DIDP.

Overall, the Committee felt comfortable with the proposed estimated production volume and percent which EPA cited in section 3.8.2 of the Draft Environmental Release and Occupational Exposure Assessment. A Committee member commented that US law prohibits sharing information within and between industry groups about production volumes or market shares, but that information is provided to the American Chemistry Council (ACC) panel coordinators so that they can determine company dues to each panel. The European Union (EU) has no such restrictions. Since the ACC, comprised of the manufacturers of DIDP, indicated that the use rate of DIDP in the EU is similar to the use rate in the US (ACC, 2020a) the respondents felt it appropriate to use the 2003 DIDP Risk Assessment published by the EU (ECB, 2003) to estimate production volume for the various sectors. The EU and US market are likely to be comparable. A respondent mentioned that the only other option would be to obtain data on global production, but those will not reflect the US market accurately.

One Committee member found it appropriate to split the production of 'non-polymer uses' equally between paints/coatings, adhesives/sealants, and inks since industry has not given a more specific breakdown.

One Committee member noted that production volumes for several sectors were reported as a range, some of which were extremely large.

Recommendations

- EPA should request that industry representatives review the estimated production volume breakdowns to ensure that the potential releases are estimated correctly.

- It is preferred to estimate a narrower range for these sectors with wide ranges of production volumes or provide context as to why the ranges are so large [examples: paints and coatings was 169,485- 1,679,970 kg/year (Draft Environmental Release and Occupational Exposure Assessment for Diisodecyl Phthalate (DIDP), page 64, lines 2037-2038), polyvinyl Chloride (PVC) plastics compounding 43,859,857-434,749,009 kg/year (Draft Environmental Release and Occupational Exposure Assessment for Diisodecyl Phthalate (DIDP), P 82 lines 2520-2521)].

Charge Question 1.e.ii

For the remaining phthalates (i.e., DEHP, DBP, DIBP, BBP, DCHP, DINP), EPA anticipates potentially needing to refine the environmental release assessment. Please suggest additional data sources, models, and related methods for determining production volumes that are reasonably available and can be conducted in a timely fashion that allows EPA to meet statutory timelines for TSCA risk evaluations. For environmental release assessments, please comment on the strengths and uncertainties of using EU PV % to estimate production volumes for DIDP.

Recommendations

- EPA should explore the feasibility of compiling information from purchase records or manufacturing that can serve as inputs in conjunction with TRI data, which is already in use. In particular, the modeling to predict indirect surface water deposition and land deposition can be strengthened, particularly in regions of highest production. A respondent mentioned that waste stream identification and monitoring is critical, and using estimates from sewage outfalls, but the Committee did not have specific recommendations for EPA as to where to access these data.

- One Committee member indicated it is preferable to rely on industry data, or primary exposure data collected by a qualified hygiene professional, as opposed to modeling data. This was informed by comparing modeling data to actual monitoring data from Exxon (*Draft Environmental Release and Occupational Exposure 8 Assessment for Diisodecyl Phthalate (DIDP*) page 50 lines 1700-1704). The use of industry supplied data can be confirmed and used to determine production volumes, therefore the use of the CDR appears to be appropriate. Another Committee member indicated that using modeling data was an appropriate way to estimate higher end exposures which is protective to more workers and in particular more vulnerable workers. The Committee reminded EPA that they should not look at EU production values for the phthalates that are restricted in the EU as they would not reflect US production.

- As Exxon indicated a half-year production schedule (Draft Environmental Release and Occupational Exposure Assessment for Diisodecyl Phthalate (DIDP) page 46, lines 1609-1611), the EPA should obtain the full year production schedule for Exxon and for other manufacturers and formulators to inform estimates.
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- EPA states that "Import and repackaging facilities operate 24 hours/day, 7 days/week (*i.e.*, multiple shifts). However, EPA capped the total number of operating days, so as not to exceed estimated site throughputs" (Draft Environmental Release and Occupational Exposure Assessment for Diisodecyl Phthalate (DIDP), page 52, lines 1764-1766). EPA "did not identify chemical- or site-specific information on site throughputs; site throughput information was estimated through Monte Carlo Modeling, with a 50th to 95th percentile range of 46-55 kg/site-day" (Draft Environmental Release and Occupational Exposure Assessment for Diisodecyl Phthalate (DIDP), P 52 lines 1768-1770). One Committee member indicated estimating on an estimation creates more uncertainty which may also create a higher estimated occupational

exposure potential; but other members appreciated EPA modeling on the higher percentiles to represent the worst-case occupational exposure, which would be more protective of workers.

Charge Question 2- Ecological Hazard

Charge Question 2.a

As described in Section 4 of the Draft Environmental Hazard Assessment for DIDP, EPA had limited empirical toxicity data available for terrestrial mammals and therefore relied on data from controlled laboratory animal studies using human health animal models to derive a toxicity reference value (TRV) to evaluate risk from chronic dietary exposure to DIDP. Please comment on the strengths and uncertainties of the methodology and data used to derive a toxicity reference value (TRV) for DIDP.

The Committee noted that the EPA Draft Environmental Hazard Assessment considered aquatic invertebrates, fish, and algae for toxicity assessment; however, none was observed with sediment or pore water exposure (acute or chronic). No hazard data were available for wildlife (birds or mammals). Instead, laboratory data collected in rats was used to derive hazard values for terrestrial mammals, resulting in a toxicity reference value (TRV) of 128 mg/kg-bw/day due to an absence of toxicity data for DIDP on soil invertebrates. In addition, DINP data from one earthworm hazard study was used for read-across for DIDP. In total, 11 studies were used for toxicity quantitative assessment in fish, with two studies using DIDP concentrations higher than solubility, raising the question of true exposure if the compound is not fully available to the fish.

Given that the log Kow for DIDP exceeds the model domain, the Committee agreed with the EPA's choice not to use predictive toxicity data from ECOSAR. The Committee also observed that TRV derivation process did not include a means of accounting for uncertainty as would be used to derive a Concentration of Concern (using assessment factors, uncertainty factors, confidence intervals, etc.) for comparable aquatic assessments. This seems prudent for a screening type analysis with limited experimental data.

Strengths

The strength of the approach was that experimental rat model studies of DIDP are a good estimation of effects of DIDP on wildlife mammals. The strength of the data is that they come from medium quality studies in rats, and that there were similar values for NOAEL and LOAEL for reduced body weight that were generated from two different studies (Cho *et al*., 2008 and Hushka *et al*., 2001). A potential uncertainty is that wildlife mammalian populations might be more or less sensitive to exposure, and it is not predicable due to genetic diversity within and between species. Unfortunately, there are no data available for DIDP or DINP to gain information and insights useful for models.

EPA identified two reproduction studies, three growth studies, and two survival studies, all in rat models, containing relevant data for DIDP hazard assessment in terrestrial mammals. The rat model is established, which lends confidence to this approach and there is reason to believe that it is an adequate model that responds to phthalates similarly to other terrestrial mammals. For example, the National Toxicology Program exposed two different rodent species (rats and mice) to di(2-ethylhexyl)phthalate (DEHP) and concluded that DEHP caused hepatocellular carcinoma in both species (NTP TR-601; NTP-TR-

217). These species support the use of inbred rodent models that should provide more consistency in response; albeit that these models may not capture all the variability in wildlife. Additionally, the spectrum of effects was similar across the identified studies, increasing confidence that these are reproducible toxic effects of DIDP.

EPA did not include data from any other phthalates in this section, consistent with EPA's determination that DIDP does not follow the same toxicity mode of action (i.e., inhibition of fetal testicular testosterone production)/adverse outcome pathway as the lower molecular weight phthalates. The EPA appropriately has focused on data from other phthalates that are deemed high priority in the other charge questions other than those for DIDP.

Weaknesses

Although the approach used in section 6 of the Draft Environmental Hazard Assessment for DIDP is reasonable, the underlying data are insufficient to draw these conclusions. There are relatively few studies on this chemical, and the reported NOAEL/LOAEL values diverge significantly, sometimes by more than 1-log unit. Although there is significant qualitative similarity, this is evidence of potentially high quantitative variability in inter-individual response.

Additional studies that are available but not deemed high or medium could be reevaluated for utility of the information, and potentially including useful data. These data could be reevaluated for the consistency in the draft report. At terrestrial concentrations, it is likely that the dose to the animals will be in a region that is below the doses tested in the older (Exxon (1996a and 1996b) and Hushka (2001)) studies. Low dose extrapolation may miss markers of endocrine disruption. EPA should discuss the resultant implication to populations of terrestrial mammals.

The overall conclusion that DIDP has low hazard potential for aquatic species does not agree with the data reviewed. The predominant end point in Table 3-1 is mortality with little information on sublethal effects. Acute and chronic studies on fish appear to be highly flawed, with fish hazard data based on an acute study with high control mortality and a chronic study with no dose response and limited to developmental and reproductive measurement end points.

Recommendations

- Rodent models for human health evaluations being transferable to a wildlife TRV is adequately rationalized. Additional data are available for phthalate exposure effects which should be included in the assessment factors and formulation of the TRV. Please add information on potential adverse effects that would occur in wildlife and the utility for applications and potential models that will be critical in assessing hazard and risk.

- There are no data available or requested on the toxicity of DIDP for terrestrial plants or avians. Given that DIDP poses a potential hazard to mammals, the Committee suggests that the EPA consider read-across data as they did for earthworms or request testing to complete the rest of the terrestrial assessment to provide coverage for plants and avians.

- The assessors should consider quantifying inter- and intra-study variability and uncertainty in the assessment (e.g., calculating a measure of std error or 95% CIs around the geometric mean of

NOAELs and using the lower 95% CI to derive to TRV), applying an AF, or adding to their descriptions of the unaccounted uncertainties.

- The EPA should consider using New Approach Methodologies (NAMs) data for phthalates that is publicly available from EPA's ToxCast program (see also the EPA's Endocrine Disruptor Screening Program, https://www.epa.gov/endocrine-disruption). Considering mechanistic effects and data from multiple levels of biological organization (comparing mechanistic and apical) could be justified for the phthalates. Methods used to derive Activity Concentrations and Cut off (ACC) from ToxCast data and exposure activity ratio (EARs) and subsequent comparisons to the primary apical endpoints to provide an additional line of evidence could be considered (e.g., applications for screening/use in Weight of Evidence (for more information, see Corsi *et al*., 2019, Schaupp *et al*., 2023, James *et al*., 2023).

- Given EPA's choice to use laboratory rodents from human health studies to derive the TRV and the lack of toxicity data available for ecologically relevant species, the derivation of the TRV does not include a means of accounting for the added uncertainty of using only laboratory rodents used as human health models (which could be less or more sensitive than ecologically relevant species). The EPA should consider a means for accounting for the added uncertainty of using only laboratory rodents (used as human health models) when deriving the TRV for terrestrial wildlife species.

- EPA should explain why the acute and chronic studies on fish studies are highlighted and deemed acceptable. Similarly, the aquatic invertebrate, benthic invertebrate, amphibian, and algae hazard studies were not rated as high or medium confidence. The EPA should consider if some of the lower rated hazard studies of aquatic invertebrates, benthic invertebrates, amphibians, and algae might be useful for estimating hazard. One Committee member suggested weighting the results from these papers based on their quality. Another Committee member suggested the EPA could look at the lower quality studies to determine whether the results were consistent with the high/medium quality studies. If there is consistency, this information would increase the confidence in the outcomes of models and TRV calculations.

- The TRV estimated for terrestrial mammals must consider potential sensitivity of the rat strain (Norway rat, SC rat—Waterman *et al*., 1999) for toxicity testing and the range of end points must include non-lethal endocrine disruption as short- and long-term potential effects as in the Waterman *et al*., 1999, Hushka *et al*., 2001; Exxon Biomedical, 2000, 1998 studies. However, basing the TRV on these rodent studies still must consider transferability and relevance to wildlife at the concentrations that will be potentially encountered.

- Additional terrestrial wildlife, including birds should be considered in the wildlife hazard and risk evaluations. Discuss relevant field measurements for wildlife, including mammals, birds, and other species and how the conclusions were reached using weight of scientific evidence to determines little or no hazards to wildlife. As mentioned in #5 above, these data are critical in order to develop a reliable TRV.

- There are insufficient robust datasets despite high confidence in some of the aquatic assessment as shown in Table 5-1. The EPA should identify any reported measurements of environmental

concentrations and which species (urban, rural, ecosystem type) that are likely to be most exposed.

- EPA should include information regarding the cut-off date for the literature identification for the Environmental Health Hazard Assessment. This information was included in the DIDP Human Health Hazard Assessment as well as a description of sources used to identify the environmental health studies.

- Environmental Hazard Assessment (Section 3.1): Provide clarification and detail for the following issue. There are no exposure concentrations to which TRVs are compared. Reviewing the supporting documents provides confusion. The Aquatic Fate section of the Draft Environmental Fate and Transport Assessment for Diisodecyl Phthalate contains less than 20 lines of text with no tables or figures depicting available or modeled data. The fate assessment acknowledges that measured concentrations in waters are above solubility limits and are likely associated with droplets in the water but provides no further information. Aqueous concentrations are only found in the Environmental Media and General Population Exposures document.

Additional comments and minor/editorial comments

- Lines 93-94: Please change wording from "narcotic mode of toxic action" to "narcosis mode of action" presuming that EPA means narcosis (non-specific toxicity that is reversible (https://pubs.acs.org/doi/10.1021/acs.est.0c06551)) mode of action.

- Line 322, Table 3.2, Foot note b: The study by Rhodes *et al*., (1995) was not specific about the influence of this phenomenon on DIDP or DINP toxicity within their study of 14 phthalate esters, stating specifically: "Physical entrapment of daphnids was often seen in the highest one or two concentrations and was, in some cases, related to a visible surface film." Furthermore, this surface tension effect results from phthalate preference to reside at the surface of the water layer. In fact, an allied paper by Adams *et al*., (1995) addressing acute toxicity states specifically: "This phenomenon appeared to be caused by a microlayer of test chemical on the surface of the water." Although there was no observable film in the chronic study by Rhodes *et al*. (1995), daphnia were observed at the surface. Please clarify that DIDP and DINP caused mortality and discuss the possible general narcosis may have impaired the mobility of daphnia. DIDP may also have disrupted the daphnia exoskeleton.

- Lines 795-798: This section needs to EXPLICITLY state that there is a lack of measured DIDP in samples from the USA and that many exposure estimates are based on a single study or studies of a single location outside the USA.

- There were a number of comments pertaining to the earthworm studies as listed below.

    - Line 326 Table 4-1, last row, Study quality (last cell): Study quality information is missing from earthworm study. EPA rated it as high quality on page 129 of "Data Quality Evaluation Information for Environmental Hazard for Diisodecyl Phthalate (DIDP)" (US EPA, 2024a)

    - Line 326 Table 4-1, last row, ExxonMobil 2010, mortality: The effect: No difference in mortality between earthworms in the control soil and those exposed to 1,000 mg

DINP/kg-dw (dry weight) soil. In Table 4-1, there is none for the NOAEL and 1,000 mg/kg-dw for the LOAEL. If the focus is on mortality, the NOAEL should be 1,000 mg DINP/kg-dw soil according to the listed effect.

  - Line 432-433, EPA states that the ExxonMobil (2010) study found a statistically significant increase between the number of juveniles found in 1,000 mg DINP/kg dw soil compared to controls. Please clarify if the significantly higher number of juveniles of the 1000 mg DINP/kg-dw soil relative to controls indicates changes in the population age distribution in the earthworm population, in the absence of changes in mortality. Should the change in population age distribution be noted in Table 4-1 if this is what is used for the LOAEL?

- Lines 217-219: in Draft Environmental Hazard Assessment for DIDP Technical Support Document for the Draft Risk Evaluation. Please comment on whether mechanistic endpoints were also evaluated for DINP. If there are data available for gene expression and protein synthesis for DINP, please expand the discussion of the Aquatic Organisms summary section to consider this additional information.

- Lines 269-274: Studies also noted significant decreased body weight and survival (F344 rat) in both males and females. Please comment on whether this is a palatability or treatment issue. Females also experienced reduced number of offspring; is this effect due to reduced food consumption, potentially associated with palatability.

- Line 326, Table 4-1, Hellwig *et al*.1997: Hellwig *et al*. 1997 is listed in the six studies that were given overall quality determination of high or medium, but it is not included in Table 4-1 (Terrestrial Organisms Environmental Hazard Studies used for DIDP). Provide justification/discussion for not including Hellwig *et al*. 1997 in Table 4-1. Hellwig *et al*. 1997 is also cited in Appendix B.

- Line 326, Table 4-1 and accompanying text: The NOAELs/LOAELs in Table 4-1 are not always discussed in the text of Section 4 (Terrestrial Species Hazard). For example, under growth and development for Hushka *et al*. 2001, Table 4-1 states a NOAEL of 178 mg/kg-day and a LOAEL of 356 mg/kg-day for increased age at preputial separation in F2 males at 0.4% (356 mg/kg-day). However, this effect is not included in the text. Include discussion of all effects in Table 4-1 in the text, or some text to explain why it is not done.

- Lines 420-422, Figure 6-1: Suggest making Figure 6-1 (Terrestrial Mammal TR Flow Chart) and Figure 6-2 (Mammalian TRV Derivation for DIDP) easier to read. Specifically, identify to what the reference numbers are referring as it would be helpful to be able to quickly relate those back to the studies in Table 4-1.

- Lines 426-433: Add specific justification for why a Soil Invertebrate Threshold was not calculated.

- Line 451: Delete the word “of” in the sentence: Empirical toxicity data for rats were used to estimate a chronic toxicity reference value (TRV) for terrestrial mammals at 128 of mg/kg-bw/day.

- Line 715, Table_Apx A-3: Suggest defining dw (dry weight) used in concentration of Exxon Mobil 2010 and in Table_Apx A-3.

- Line 1071 DIDP RE –please elaborate as to why release data were not obtainable.

Charge Question 2.b

Fate and transport modeling analyses indicate that when DIDP is released to the environment it is expected to partition primarily to soils and sediments, therefore, these media are of high priority for environmental exposure analyses. As described in Section 4 of the Draft Environmental Hazard Assessment for DIDP, no hazard data were identified for DIDP for soil invertebrates. DINP was selected as an analog for read across of soil invertebrate hazard data as described in Appendix A of the Draft Environmental Hazard Assessment for DIDP. Please comment on the appropriateness of the methods used to identify DINP as an analog for DIDP.

Specific Comments:

- The selection of DINP as a suitable analog for DIDP was based on a sound approach. The use of NAMs for comparison of structural and chemical characteristics identified 57 analogs. The further screening of analog candidates to those with physical properties of log K_{OW} and log K_{OC} that were within one log unit relative to DIDP refined the list of potential analogs to 6 candidates of which two were DINP (one-third of the possible choices). Finally, DINP was selected as the appropriate analogue for DIDP, largely based on the already available data for DINP from previous literature identification, data extraction and risk-of-bias assessment from toxicity studies.

- The octanol-water partition coefficient (Kow) of both DIDP and DINP are outside the domain of applicability for ECOSAR, which could cast doubt on reliability of predictions for these substances. The EPA addressed this potential concern by not supplementing empirical hazard data with unreliable predictions.

- The methods of the ExxonMobil (2010) study do not report measured DIDP concentrations, so the purity of the test chemical or the heterogeneity of it within the soil are unknown. However, it was noted by one member that a Certificate of Analysis typically provides structural identify and purity information for the batch tested, and that for short-term studies, a Certificate of Analysis has been accepted by regulatory agencies as complying with the GLP requirements for "identity, purity, strength, and composition" [1].

- There was discussion of why other read-across data from DINP or other analogues were not considered for other species in the environmental assessment that lacked empirical data (e.g. avians). The Committee discussed the lack of data in wild birds, which would be essential to do an accurate risk assessment. In lieu of the availability of these measurements in wild birds, there are numerous laboratory studies that would provide information on the response of birds to DIDP, DINP and other phthalates that may occur in the environment [2-15].

- The paragraph beginning on LL710 does not include the observed effects in aquatic tests.

Recommendations

- The EPA should correct bioaccumulation potential estimates where uptake in sediment data were dissimilar.

- The EPA should evaluate the use of sediment bioaccumulation data to estimate the relative difference in K_{ow}s. Sediment bioaccumulation data can be used to estimate the relative difference in K_{ow}s. This would provide more certainty in the assessment, as the worst case/best case scenarios for accumulation if the high/low and low/high K_{ow}s combinations of DIDP and DINP could be used for comparisons. That would bound the uptake scenarios, with DIDP and DINP K_{ow}s of 10.36 and 8.8 in one instance and 8.8 and 9.7 in another.
- The EPA should list ranges for water solubilities and Kow in Table Appendix A-2.
- The EPA should add text regarding observed effects in aquatic tests on Line 710.
- In the Draft Environmental Hazard Assessment for DIDP Technical Support Document for the Draft Risk Evaluation (Line 317), the EPA should consider adjusting the confidence assignment to "slight" for the statement, "EPA has…robust confidence that DIDP poses no hazards to soil invertebrates…", given the support of only one study from an analogue chemical.

Editorial Comments:

- Lines 399-340, Draft Environmental Hazard Assessment for DIDP Technical Support Document for the Draft Risk Evaluation – Please double-check that all determinations of confidence are the same confidence of terrestrial invertebrate assessment. Table 5.1 also indicates "moderate confidence;" However, line 317 states "robust confidence in soil invertebrates."
- Line 678, and elsewhere, "vs" should be replaced with "versus".
- Line 716, the range for DINP toxicity to worms should not be reported to 4 significant figures. It should read ">390".

Charge Question 3- Human Health Hazard

Charge Question 3.a

As described in Section 6.1.4 of the Draft Human Health Hazard Assessment for DIDP, EPA has preliminarily concluded that the HED of 9.0 mg/kg (NOAEL of 38 mg/kg-day) from the two-generation study of reproduction of Sprague Dawley (SD) rats based on reduced F2 offspring survival on PND1 and PND4 is appropriate for calculation of non-cancer risk from acute, intermediate and chronic durations. Please comment on the strengths and uncertainties of EPA's preliminary conclusion.

The Committee noted that the no observed adverse effect level (NOAEL) of 38 mg/kg-day was estimated from a two-generation rat study and converted to a human equivalent dose (HED) of 9 mg/kg-day, based on literature through 2023. Some information is available about the mechanism/mode of action for DIDP. The biotransformation pathway for DIDP is important for formation of potential bioactive metabolites available for excretion; a radioactive tracer study indicated that most clearance occurs over 2-3 days following oral exposure (Table 2-2 Draft Human Health Hazard Assessment for DIDP).

There is evidence of reproductive effects of DIDP. According to Page 24, Lines 813-815, DIDP does not appear to have anti-androgenic effects similar to DEHP. Wistar rats administered DIDP orally during pregnancy had pups with increased skeletal abnormalities; however, CD-1 mice dosed with higher

concentrations of DIDP (lines 837-842) showed no adverse effects on pups or viability. Conversely, Sprague Dawley (SD) rats in 1- and 2-generation tests showed developmental abnormalities and reduced viability with decreased pup body weight, as well as effects on female body weight.

Both mammalian model and *in vitro* studies did not reveal activities for estrogen or androgen responses. Rather the mechanism of action appears to be PPARα activation. It is noted that thyroid and corticosterone were not examined, thereby providing no information about the thyroid or adrenal endocrine systems. The two generation tests conducted do not include hormone measurements; only survival, sperm parameters and other 'downstream' indicators that are relatively insensitive measures of hormone-mediated outcomes. However, the lack of effects on fertility does strengthen the assertion that the primary target window for effects is during the developmental period for reproductive as well as possibly other systems (kidney, liver, etc.) toxicities (see Appendix C-1). There was one study of DIDP (Hushka *et al*., 2001) that suggested effects on the dam's ability to maintain pregnancy, which appeared to be a separate issue from the significant loss of body weight observed and was not factored into the pregnancy maintenance results. Interestingly, cross-fostering postnatally with control dams did not improve survival, again supporting evidence for adverse developmental effects. There is limited evidence besides a previous study by the same author supporting decreased F2 survival on postnatal day (PND)1 and PND4. While there are other studies suggesting developmental toxicity, this two-generation study did not include some relevant measures to characterize these potential effects.

Strengths noted by the Committee

The strength of the EPA's preliminary conclusion to use a human equivalent dose (HED) of 9.0 mg/kg (NOAEL of 38 mg/kg-day) is that it is based on the results of a two-generation study in Sprague-Dawley rats (ExxonMobil, 2000) comprised of two studies (Study A and Study B). In study A, the lowest dose was the LOAEL and in Study B, the lowest dose of 38 mg/kg-day was the NOAEL. Furthermore, there were additional studies principally of liver endpoints that had a similar NOAEL value that translated into a comparable HED. The main uncertainties were identified by the EPA: the mechanism by which DIDP inhibits survival is not clear. Finally, the EPA's preliminary conclusion is consistent with the hazard characterization of several other regulatory and authoritative bodies risk assessments around the world (EFSA, 2019; EC/HC, 2015; NICNAS, 2015; ECHA, 2013b; US CPSC, 2010; EFSA, 2005; ECB, 2003; NTP-CERHR, 2003).

Treatment-related developmental toxicity is associated with DIDP exposure and the HED based on the NOAEL for reduced F2 offspring survival is the most appropriate and lowest HED. The slightly lower POD/HED from the Cho *et al*. studies (Cho *et al*., 2008, 2010, 2011) had too many uncertainties to be used; the POD identified from these two studies is based on a LOAEL for increased incidence of spongiosis hepatitis and microgranuloma. In addition, EPA stated that BMD modeling showed that the HED of 9.0 mg/kg is more sensitive than the HED from the Cho *et al*. studies (see lines 2097-2106). There is compelling evidence of developmental effects of DIDP in animal models, which is supported by developmental effects revealed from the limited epidemiologic studies.

Weaknesses and uncertainties

In the absence of inhalation and dermal DIDP data, additional text in Section 6.1.4 (Weight of Evidence Conclusion: POD for Acute, Intermediate, and Chronic Durations) is needed to clearly describe the major uncertainties/issues with using the oral HED for DIDP to extrapolate to the inhalation and dermal routes.

Using a NOAEL as the basis for the POD has associated uncertainties, including the fact that the NOAEL is a function of study design. By extension, measures of indicators, such as hormone levels at PND1 and PND4 are not as complete in Hushka *et al*. (2001) as they would be if the study was done today.

EPA did not conduct benchmark dose (BMD) modeling on Hushka *et al*. (2001) or any of the other candidate PODs, except for Cho *et al*. (2008; 2010) as per EPA's own guidance. There is less certainty about the most sensitive endpoint without comparing the full BMD-based analyses.

The Committee suggested that EPA reconsider its decision to apply the POD/HED for developmental effects following acute exposure as the POD/HED for intermediate and chronic durations of exposure. There is agreement across most, if not all, other regulatory bodies internationally, that the liver is the most sensitive target tissue when assessing DIDP's long(er)-term effects and deriving hazard values for long(er)-term/chronic exposures. Thus, the agency should consider studies with intermediate and subchronic exposure durations that evaluate liver effects for selecting the POD/HED for risk characterization.

For example, no NOAEL for liver effects was identified, and its LOAEL was significantly lower than the NOAEL for reproductive development effects that was identified in the 2-generation reproduction study (LOAEL of 22 mg/kg/day versus NOAEL of 33 mg/kg/day). The rat study would likely have yielded a NOAEL even lower if a lower dose had been tested. However, the agency expressed some uncertainty about this study and dismissed it as a candidate. Furthermore, the EPA points out, "there is consensus across existing assessments of DIDP by US CPSC (2014), ECHA (2013), EFSA (2019), Health Canada (ECCC/HC, 2020), OECD (2019), and NICNAS (2015) that the study (Hazelton Laboratories, 1985b) supports a NOAEL of 15 mg/kg-day, "based on increased liver weight and histopathological findings (swelling and vacuolation of hepatocytes)." Several of those other regulatory authorities have used this study in the derivation for their long-term/chronic health value. EPA seems to have dismissed this study for use in the derivation of hazard values because in its view "this study is limited by its small sample size and lack of statistical analysis."

The EPA should review what statistical analyses were employed by these other agencies to analyze the Hazleton Laboratories (1985b) data to identify a NOAEL. A Committee member pointed out that the statistical power for the study in dogs is low and the study in rodents provides the important insights.

As EPA's Office of Pesticide Programs (OPP) states "Even for the small percentage where there are indications that a 1-year dog toxicity study would potentially provide a lower LOAEL than a 13-week study for purposes of RfD derivation, differences between LOAELs and NOAELs between the two dog studies were small (4-fold or less). It is unclear to what extent these small differences in LOAELs are meaningful from a practical standpoint relative to the 100-fold default uncertainty factor commonly used in calculating the RfD. In no case did these small differences have a regulatory impact on pesticide risk assessments" (in good measure that is because the NOAELs/LOAELs identified in the chronic rat study for that chemical were the drivers for derivation of the RfD) (US EPA Office of Pesticide Programs 2006. Length of Dog Toxicity Study(ies) that is Appropriate). As a result of their large retrospective analysis cited above, OPP eliminated the routine requirement of the 1-year dog study while retaining the 13-week dog study.

EFSA (2022) states " For the approval of plant protection products, the scientific rationale of using the dog as 'second' species in the regulatory process has been debated since (a) long time and culminated

with the elimination of the one-year dog study (OECD TG 452; OECD, 2018a) from the data requirements in the EU, the US, Brazil, Canada, Australia and, recently, Japan, leaving the 90-day study (OECD TG 409; OECD, 1998) as the only study available in the dataset for the hazard assessment in a non-rodent species" (Panzerea et. al., 2022) https://pubmed.ncbi.nlm.nih.gov/36188063/).

Recommendations

- The studies chosen for setting the HED at 9.0 mg/kg are appropriate and the two-generation study of the SD rats is most rigorous for demonstrating developmental effects. Points raised in other sections regarding loss of body weight for dams and pups should be mentioned here as additional outcomes, albeit separate from the frank toxicity effects (liver and lethality).
- EPA is considering the 2-generational study as acute exposure; however, it is unclear if EPA considers indirect exposure of the F1 generation based on the following statement "EPA considered reduced F2 offspring survival to be potentially relevant for both acute and chronic exposures (page 55, lines 2003-2004)." Although not direct exposure to developing fetuses, the developmental toxicity endpoints were not observed in the F1 generation, indicating that indirect exposure to F1 animals did influence the F2 animals. That effect should be acknowledged and utilized in the assessment.
- The conclusion of no endocrine disruption is incomplete without consideration of thyroid and adrenal axes tests. The EPA should include any available data on hormones associated with the thyroid and adrenal axes. It should be noted that immunohistochemical and histological analyses of the thyroid gland correlate with changes in thyroid hormones (Akane *et al*., 2024). Also see Table 3 in charge question 2d for an excellent example of Adverse Outcomes to visualize the suite of impacted physiological systems.
- While the basis for extrapolation of oral exposure to dermal or inhalation routes of exposure are detailed in Appendix D, the Committee recommends additional information be added to help to clarify the rationale. Specifically, the Committee would like to know how much exposure would be predicted, whether dermal or inhalation routes of exposure pose significant hazard, and, if so, how far from the source is a hazard.
- EPA should reconsider its decision to apply the POD/HED for developmental effects following acute exposure as the POD/HED for intermediate and chronic durations of exposure. Most, if not all international regulatory bodies agree that the liver is the most sensitive target tissue when assessing DIDP's long(er)-term effects and deriving hazard values for long(er)-term/chronic exposures. Thus, EPA should consider studies with intermediate and subchronic exposure durations that evaluate liver effects for selecting the POD/HED for risk characterization.

Additional and editorial comments

- Please review the naming of the exposure time frames outlined throughout the documents as they are inconsistent.
    - For example, starting on page 32 in the *Draft Human Health Hazard Assessment for DIDP,* EPA uses the term short-term (>1 to 30 days), subchronic *(>30 to 90 Days)*, and chronic *(>90 Days)*.

- But then the term acute and intermediate are used starting on page 49. Please clarify if short-term and acute are the same exposure time frame. Also, please clarify if sub-chronic and intermediate are considered the same.
- It is unclear if EPA designated the liver toxicity studies as intermediate exposure scenarios (Table 6-2, Page 54), not designating the studies intermediate exposure. This is confusing, especially considering that they would fit in the definition of short term (>1 to 30 days). The longest exposure indicated in the Table 6-2 is 28 which should be considered "short term."

- Line 292 - Please double-check which citations should be included. The text indicates the first two-generation study is Exxon 1998 and the associated table (Table ES-1) indicates that it is Hushka 2001.
- Line 501 - Adjust to, "...to set a cutoff date".
- Line 253 - Consider using abbreviation MIDP since it is previously defined.
- Line 1529 - Correct spelling of "Australia's".
- Line 1537 - Revise text to "310 participants" (plural versus singular).
- Line 1559 – Remove "s" from "theirs" to read "..their sons".
- Line 1586 - Change "give" to "given".
- Line 1847 - Add "is" after "This descriptor".
- Line 1872 - Should this read "two chronic dietary studies" (Cho *et al*. 2010 and Cho *et al*. 2008)?
- Line 2156 - This phrase appears to be is missing a noun. Please review.
- Lines 2771-2775 - Please clarify the point of this sentence - Are you stating that the EPA considers the study to support a developmental toxicity NOAEL of 40 mg/kg-day? If so, then consider removing the "and" before the phrase, …EPA considers the study to support a developmental NOAEL of 40 mg/kg-day…".
- Table Apx C-9, page 97, Chronic exposure >90 days - Please correct the citations for the first two rows of chronic exposure studies. They are currently displaying as Greek letters. Should this be Cho *et al*?

Charge Question 3.b

As described in Section 5.3 of the Draft Human Health Hazard Assessment for DIDP, EPA has preliminarily concluded there is Suggestive Evidence of Carcinogenic Potential of DIDP in rodents. EPA's preliminary conclusion is based on evidence of mononuclear cell leukemia (MNCL) in male and female F344 rats and hepatocellular adenomas in male CB6F1-rasH2 transgenic mice. EPA has further preliminarily concluded that MNCL observed in F344 rats and hepatocellular adenomas observed only in male CB6F1-rasH2 transgenic mice are not appropriate for conducting dose-response assessment for human health risk assessment. Please comment on the strengths and

uncertainties of EPA's preliminary cancer classification and rationale for not carrying forward rodent cancers into dose response assessment.

Carcinogenicity conclusions for DIDP

Health Canada (HC) has done extensive work to determine the cancer risk of DIDP and concluded that the descriptor "Suggestive Evidence for Carcinogenic Potential" is appropriate for DIDP. Most the Committee members disagreed and supported "Not Likely" as the conclusion, one Committee member suggested that the analysis performed supports this claim. Studies showed only two types of tumors including Mononuclear Cell Leukemia (MNCL), which has high background incidence in the strain studied (F344 rats), and hepatic adenomas. The tumors were not observed in all groups and at all doses. The mode of action suggests PPARα activation. Taken together, the evidence for carcinogenic risk is towards the lower end. The analysis is detailed, and conclusions are supported by evidence. Based on the available information, the Agency's decision not to conduct dose response assessment is justified.

Mononuclear Cell Leukemia

DIDP exposures in a 2-year rat study (Cho 2008, 2010) produced an increase in MNCL. The increase was seen in both males and females. This is likely a strain-specific effect, given the historically high spontaneous rates of occurrence in F344 rats (Thomas *et al*., 2007). Given this, there appears to be a consensus that increases in MNCL rates of occurrence in Fisher 344 rats is not a useful predictor of human carcinogenic potential. This view is supported by Maronpot *et al*. (2016), Caldwell (1999) and King-Herbert and Thayer (2006).

The etiology of the most similar human large granular lymphocyte (LGL) leukemia, aggressive natural killer cell leukemia (ANKCL), to F344 rat MNCL is related to infection with Epstein–Barr virus and is not associated with drug or chemical exposure. Though the specific mode of action for the F344 rat MNCL is not known, it is not associated with a viral etiology. There is a qualitative difference in how human ANKCL leukemia and F344 rat MNCL are initiated; therefore, despite some commonalities between the pathologies of these tumors, MNCL is not a model for human LGL leukemia. In addition, there is no evidence for a genotoxic mechanism of action for MNCL induction; rather it is due to a yet unknown secondary mechanism. These data indicate there is not a concern for prediction of a site-concordant or non-concordant human relevant tumor type (Maronpot *et al*., 2016).

While the Maronpot *et al*. (2016) and Caldwell (1999) papers are cited in Section 5.3 of the DIDP Draft Human Health Hazard Assessment, no mention is made of King-Herbert and Thayer (2006) (King-Herbert and Thayer, 2006. Including a publication on an NTP Workshop that recommended not using the F344 rat: Animal Models for the NTP Rodent Cancer Bioassay: Stocks and Strains—Should We Switch? Toxicol. Pathol. Oct 34 (6):802–805) https://journals.sagepub.com/doi/10.1080/01926230600935938).

Reference Recommendation

The Committee recommended the inclusion of King-Herbert and Thayer (2006) to the Reference section along with a summary of it in Section 5.3 of the document.

This paper describes a 2005 National Toxicology Program (NTP) workshop, the objectives of which were to determine whether the models then used in the standard 2-species, 2-strain NTP bioassay (the F344/N rat and B6C3F1/N mouse) remained appropriate to identify substances that may pose a

carcinogenic hazard for humans. Workshop participants advised the NTP to discontinue use of the F344/N strain. Mononuclear Cell Leukemia (also called Fisher Rat Leukemia because it is so common) was a major reason that the F344 rat was no longer the primary rat species used by the NTP as it was a confounder in the bioassay interpretation. In 2006, the NTP decided to switch to a different rat stock due largely to high background control incidences of Leydig cell tumors (LCTs) and MNCLs (Maronpot *et al*., 2016). The NTP replaced the Fisher strain with the Harlan Sprague Dawley (HSD) strain.

Based upon the discussion above, the observation of an increased incidence of MNCL in a chronic bioassay employing the Fisher 344 rat should not be considered a factor in the determination of the cancer classification for DIDP.

Most Committee members agreed that given the material presented in a retrospective review, MNCL and Leydig Cell Tumors, among other tumor responses in F344 rat carcinogenicity studies lack relevance in predicting human carcinogenicity (Maronpot *et al*., 2016).

Regarding EPA's comments on historical control data (HCD) Recommendation

The Committee recommended that more recent information describing the use of HCD (historical control data references) should also be considered (Keenan *et al*., 2009; Kluxen *et al*., 2021).

The rasH2 mouse model

The DIDP document describes the increase in "hepatocellular adenomas in male CB6F1-rasH2 transgenic mice at the highest dose tested, 1500 mg/kg-day, well above the typical limit dose of 1000 mg/kg/day. Hepatocellular adenomas were not found in female transgenic mice nor in wild-type male or female mice." It is important to note the proposed use for the rasH2 mouse in drug development (Bogdanffy *et al*., 2020). In a pharma-based interpretation adenomas would not be considered a positive cancer call. Whereas in the more precautionary approach for environmental risk assessment, an adenoma is considered of potential concern. Thus, Tg mouse models were not designed to address human cancer risk in an EPA setting but rather to identify potential malignant responses quickly for an FDA setting. These mouse models were designed to be susceptibility models, so they are more likely to result in a tumor response but are no more sensitive than the wild type mouse models. In other words, studies in Tg mouse models will not demonstrate tumors at lower doses, but they will arise earlier in the exposure timeline.

rasH2 dose selection recommendation

It is recognized by the Committee that the dose selection for the rasH2 model was based on toxicity effects where the high dose of 1% reduced body weight, followed the guidance for dose selection in animal carcinogenicity studies (US FDA, 2008).

The Committee recommended the inclusion of a discussion comparing the exposure ratio of rodent to human plasma area under the curve (AUC) of parent compound. The pharmacokinetic endpoints (AUC ratio) for dose selection of low toxicity pharmaceuticals are of interest in light of the recent publication by Hisada *et al*., (2022) where they conclude "exceeding a high dose level of 50-fold AUC in rasH2-Tg mouse carcinogenicity studies does not appear to be of value." Several references are provided regarding the use of TK in dose selection (OPPTS 870.4300 (US EPA (2019); OECD TGs 443, 453 (OECD (2018b;

OECD (2018c); Tan *et al*., 2020; Tan *et al*., 2021; Lowe *et al*., 2021; Hoer *et al*., 2022; US FDA, 2008; Hisada *et al*., 2022).

As the document describes, DIDP is considered to be a peroxisome proliferator that can activate PPARα. Health Canada and ECHA have hypothesized that the liver tumors in the male rasH2 mice occur through a PPARα MOA (as described in Corton *et al*., 2018). However, a complete analysis of the MOA for liver tumors consistent with US EPA (2005) and International Programme on Chemical Safety (2007) guidance has not been completed. It is recommended and assumed that this analysis is under way and will be completed and included in a revised final Human Health Hazard Assessment and Risk Evaluation. Depending upon the outcome of the analysis, the agency may have to consider a different descriptor of carcinogenicity for DIDP, if the analysis supports the hypothesis that DIDP is a PPARα activator and intermediate key events, and modulating factors are confirmed or suggested by the data. Several Committee members suggested using a biological read-across approach for informing the mode of action in addition to the chemical read-across approach. If data are consistent with this mode of action, then the appropriate choice would be "Not Likely to be Carcinogenic to Humans," since neither tumor type observed is considered predictive of human carcinogenic potential.

One commenter suggested that the carcinogenic potential of DIDP in humans remains unclear and is still an uncertainty (EC/HC 2015). Committee members noted there was sufficient information regarding DIDP as a PPARα agonist and that the agency should consider a determination of "Not likely to be Carcinogenic to humans" based on the fact that neither MNCL in F344 rat nor adenomas in rasH2 mouse are relevant for human concern. Also, adverse outcomes occurred in the rodent studies at high doses above the limit dose, and if tumors do occur through a PPARα MOA, they are not relevant for human cancer risk.

Based on the US EPA cancer guidelines "Not likely" is appropriate when "convincing and extensive experimental evidence showing that the only carcinogenic effects observed in animals are not relevant to humans," and "convincing evidence that carcinogenic effects are not likely below a defined dose range. " Both are true in this case.

Cancer Descriptor Recommendation

The Committee recommended further analysis of the MOA for liver tumors to be consistent with US EPA (2005) and International Programme on Chemical Safety (2007) guidance to determine if "Not likely to be Carcinogenic to humans" is a more appropriate descriptor. A majority of Committee members agree with this recommendation.

RISK21 Recommendation

The Committee recommended the use of the RISK21 (www.risk21.org) framework approach to enhance communication of conclusions in a sample plot embedded file. This publicly available tool was developed through a Health and Environmental Sciences Institute (HESI) collaboration of which multiple government scientists were instrumental contributors, including staff from the US EPA. The Risk21 tool should be considered to improve communication to senior leaders within the agency as well as the public. The OECD, Health Canada, and the Chinese Food Safety Authority endorse this framework tool. The Chinese Food Safety Authority routinely uses RISK21 as their primary decision support tool.

RISK21 sample plot has a couple of examples for DIDP. These are for illustrative purposes only and used HED for the y-axis and overall exposure data from the various tables.

General comments

Peroxisomes

Peroxisomes are found in all eucaryotic cells. They contain oxidative enzymes, such as *catalase* and *urate oxidase*, at such high concentrations that in some cells the peroxisomes stand out in electron micrographs because of the presence of a crystalloid core.

Thus, with any compound that is a Peroxisome proliferator-activated receptor alpha (PPARα) agonist peroxisomes can increase in any cell/tissue increasing oxidative stress as a byproduct and possibly organ weight with enough expansion of peroxisome numbers (Albert et al., 2002; Vasko, 2016).

A number of references can be found at:
https://www.sciencedirect.com/topics/neuroscience/peroxisome

Health Canada (HC) states "However, the relevance of the hepatotoxic effects of phthalates observed in rodents is difficult to establish due to the species-specific differences in the peroxisomal proliferation response (rodents being significantly more sensitive than humans to PPARα-mediated induction of peroxisome proliferation)" (EC/HC 2015).

Essential Comments from the Committee Regarding Exposure and Risk Assessments for Ecological and Human Health

Summary/Discussion

Environmental Hazard/Risk: There are numerous concerns regarding the current assessment of hazard and consequently risk from DIDP and DINP in the environment. Particularly of concern is the lack of data, not only from the USA, but also from industrial releases. There is also a lack of sentinel species toxicity data that would provide information for models and for more accurate hazard and risk assessments. The Committee notes that the American Chemical Society (ACS) has taken a position regarding the need for and essential aspects of Risk Assessment (ACS 2023). That position states that "Government and industry play critical roles in risk assessment and regulation. Toxicological and epidemiological data and safety information must be accessible to regulators to assure safe use and maintain public trust." And "ACS supports government agencies adopting a tiered approach to risk assessment that encourages the use of NAMs, analog data, and data derived from traditional *in vivo* testing when validated animal alternatives are unavailable. Agencies should model transparency in baseline assumptions, reasoning, minimum data set requirements and data utilized when assessing risk. Likewise, industry needs to provide information for technical purposes…"

Monitoring data from non-industrialized areas with municipal wastewater treatment plants indicate that measured concentrations of contaminants frequently exceed those found to cause toxicity in laboratory studies (Table 1). Therefore, the EPA cannot disregard these laboratory findings and must include them in their assessments. Although perspectives on the Committee may vary regarding the extent of these risks, dismissing the data is inappropriate given that measured environmental concentrations surpass those used in aquatic testing.

Specific items within Table 5.4 (L855) should be corrected. The Scenario for High from monitoring with wastewater does not represent a high value, it represents a mean. These data do not represent industrial effluent. They represent municipal effluent. Thus, the current assessment completely omits industrial effluents. Wen et al. found a median concentration of 0.43 µg/L with a maximum of 0.88 µg/L (Wen, Huang et al. 2018), but these were not industrial effluents. Data reportage within these two studies provides insufficient information to determine centiles of exposure from variance and sample numbers. The European study (Tran-Lam, Quan et al. 2024), the 90th centile water concentration from municipal WWT effluent can be estimated as mean + 2 x Standard Deviation, or (0.43+2x0.22) = 0.87 µg/L. The WWT input values from the same study are 23.4+/-19.7 µg/L, which produces an upper 90th centile of 62.8 µg/L. It is unclear why these values are omitted from the environmental assessment. Doing so would produce HQs above 1 (Table 1). Also, the toxicity value reported in the hazard assessment (0.06 mg/L) is a low observed effect concentration (LOEC) not a no observed effect concentration (NOEC). The NOECs for these tests were 0.03 mg/L, which provides a geometric mean or Maximum Acceptable Toxicant Concentration (MATC) of 0.042 mg/L. Note that in the same study by Tran, DINP concentrations were 0.56+/- 0.61 µg/L, clearly indicating a gamma or logarithmic distribution. Thus, estimating the upper centiles will be difficult without knowing samples numbers contributing to these statistics. Two standard deviations above the mean would be 1.78 µg/L. There are uncertainties in how phthalates sorbed to suspended sediments would behave in toxicity tests. Such sorption lowers dissolved concentrations, but ingestion of suspended particulates by filter feeders would increase exposure via ingestion.

The agreement of the maximum from Wen's watershed study and upper centile from Tran's municipal wastewater study suggests that the Wen study does not represent the high level of contamination that the Draft RE portrays for industrialized water bodies. EPA has estimated DIDP concentrations from Functional Fluid processing, and those concentrations far exceeded effect concentrations seen for Daphnia, regardless of whether WWT was considered or not. The EPA should elaborate on why a high centile value for discharge without WWT from the European study and the estimates from functional fluid effluents were not used in ecological assessments.

Also, it is possible to use the MATC for daphnia and compare it with observed effects for DIDP to derive a ratio that could predict toxicity in sensitive species like trout (Table 2). This approach might reveal similar sensitivities in chronic conditions, although such data for trout do not currently exist. Data from Rhodes et al, 1995 demonstrate reasonable alignment of phthalate adverse effects on daphnia and rainbow trout. The MATC determined for dimethyl phthalate (DMP) and DIDP can be calculated as the geometric mean of the LOEC and NOEC for an exposure of a given organism to a toxicant.

These data allow estimation of MATC values for effects on rainbow trout of 0.046 mg/L (Table 2), much as EPA did for earthworms in this same DIDP assessment. This MATC value would translate into HQs that are only 10% larger than those in Table 1, without inclusion of any type of uncertainty factor. Please note that Rhodes et al. (1995) recorded up to 10% mortality in various fish treatment groups, but the exact numbers in different treatments are not available in the publication. There is also uncertainty that uptake of higher molecular weight phthalates by fish may be less than by aquatic invertebrates.

Table 1: Hazard quotients using modeled releases estimates and actual high concentrations from monitoring of municipal wastewater as provided in the Draft Risk Evaluation for Diisodecylphthalte (DIDP).

Scenario	DIDP conc in water (µg/L)	MATC[a] (µg/L)	Hazard Quotient[b]
Lubricants and Functional Fluids (no wastewater treatment)	9100	20	455
	9100	42	217
Lubricants and Functional Fluids (with wastewater treatment)	547	20	27
	547	42	13
High from Municipal Monitoring Before WWT	62.8	20	3.1
	62.8	42	1.5
High from Municipal Monitoring after WWT	0.87	20	0.043
	0.87	42	0.021
Wen Monitoring	0.88	20	0.044
	0.88	42	0.021

a- Maximum Acceptable Toxicant Concentration computed from Adams et al 1995 and Rhodes et al. 1995.
b- Bold values exceed HQ of 1

Table 2: Estimation of Diisodecylphthalate (DIDP) Chronic Toxicity (mg/L) to Rainbow Trout.

Species	Dimethyl phthalate (DMP)		DMP Chronic MATC	DIDP Chronic MATC	Ratio
	NOEC	LOEC			
Daphnia	9.6	23	14.9	0.042[a]	355[b]
Rainbow Trout	11	24	16.2	*0.046*[c]	

a- Mean of Measured LOEC and NOEC
b- Calculated as (DMP MATC)/(DIDP MATC)
c- Calculated value: (DMP MATC)/Ratio

The statement that DIDP is not expected to be taken up by aquatic organisms (L1015) is directly contradicted by monitoring data presented in the Draft Environmental Exposure Assessment. In fact, EPA uses an empirical Biota Sediment Accumulation Factor (Brown *et al*. 1996) to compute uptake into chironomids. Perhaps DIDP does not bioaccumulate, but it is taken-up. All of these types of language need significant harmonization across the assemblage of reports in this docket.

All values in the surface water column (L1024) need citations. The monitored surface water data represent means from a single study (Tran, Teil *et al*. 2015). The single study can be noted in the caption. The mean in this table must be changed to a high centile value and perhaps from a system with higher aqueous concentrations. Higher centile values from this study would produce a value of 0.87 mg/L (Table 1).

In toxicity assays for low water-solubility chemicals like DIDP, the insoluble component on the water's surface lowers concentrations beneath, leading to a physical smothering effect on organisms. Considering the partitioning behavior of the chemical, it is incumbent upon the EPA to justify the exclusion of these data. Studies by Adams *et al*. (1995) noted that the daphnia became entrapped in DIDP and floated to the surface, suggesting they encountered DIDP as microdroplets in the water column rather than being trapped in a surface film. Additionally, the concentration exceeds water solubility, leading to a film of undissolved material where daphnia is trapped and immobilized does not represent the chemical's inherent aquatic toxicity but rather a mechanical problem causing mortality.

In invertebrates and other non-mammalian vertebrates, similar modes of action could potentially be applied universally, suggesting that measurements could determine this. Also, it remains unclear whether these organisms are suffocating due to the surface film, becoming entrapped in the film, or experiencing a direct effect from dissolved phthalate exposure.

Data from wildlife and representative sentinel species are critical. It is important to include other species, for example, bird eggs, especially those for birds that may forage near water surfaces could provide data on environmental levels, transfer to eggs, and exposure. This is because birds consume terrestrial and aquatic animals that are considered in the current assessment, and bird eggs may accumulate higher phthalate concentrations. While we may never have comprehensive databases for these animals, the partial information collected from the literature and model predictions could still provide representative values. Additionally, there have been studies on domestic species that could provide insights to assess potential risks to wildlife (see references). References are provided that show the availability of phthalates globally to wildlife (see Fragão *et al*., 2021; Grace *et al*., 2022) through microplastics that release these compounds as they break down.

The discussion in the public session revealed the request from the EPA to hear the breadth of perspectives that Committee members had regarding the current handling of ecological effects in the Draft RE.

Weight of Evidence

EPA asked the Committee to focus on comments that identify potential underestimates of risk.

Addressing contributions of products to environmental chemical mass does not seem quantitatively possible, but at the minimum use and wear of plastic products should be identified as a potentially large and diverse non-point source that is not included and therefore brings substantial uncertainty to the

environmental or general population exposure modeling. The Committee stated that it is important to find opportunities to clarify potential occupational exposure to DIDP during application of products containing DIDP. Accordingly, there is a connection between the use of the rodent lab studies and the need to query any NAM data. It is possible that at terrestrial concentrations, the dose to the animals will be in a region that is below the doses tested in the older (Exxon and Hushka) studies. Low dose extrapolation may miss markers of endocrine disruption. It may be appropriate for EPA to discuss the resultant uncertainty/implication to populations of terrestrial mammals.

There are specific comments related to the draft report addressing chemical fate as follows:

Section 3.1: Biodegradation

A more thorough explanation of half-life is needed. Half-life does not indicate a time to decrease toxicity by 50%. To what extent has transformation of DIDP to mono-isodecyl phthalate been assessed in the context of the toxicological relevance of half-lives and the influence of half-life on availability of toxic transformation products.

LL538-540: There are no data to support the lack of DIDP in landfill leachate and this is a simple thing to evaluate with monitoring at sites known to receive DIDP or similar phthalates. Moreover, the fact that DIDP concentrations reported in the DIDP assessment in water are found to exceed predicted solubilities, there is no reason to assume that models for this type of behavior are protective of environmental or human receptors.

L674: 30Q5 concentration estimates of 9,110 and 547 ug/L should be compared to effect concentrations for fish and aquatic invertebrate toxicity. Both of these values exceed acute mortality effects for multiple fish species listed in Table 3.1 of Draft Environmental Hazard Assessment. Harmonization of information and predicted concentrations across these documents is essential. All of this could be resolved or at least mitigated with monitoring data at facilities using or releasing significant amounts or DIDP.

LL 677-688: Aquatic data that EPA consider reasonably available include European wastewater treatment plants (WWTP) discharge with 0.26 ± 0.22 ug/L (Tran, Teil *et al*. 2015) and a Chinese study reporting maximum and median values of 0.88 ug/L and 0.43 ug/L. A high centile DIDP concentration from the European study or the median value from the Chinese study would exceed both chronic and acute toxicity thresholds contained in Table 3.1 of the Draft Hazard Assessment. Thus, the current Draft Hazard Assessment does not make a convincing case that there is no hazard or risk to aquatic invertebrates. A toxicity test with a larger invertebrate would clearly solve this problem, and DIDP producers or users could have easily provide such information within the timeframe of the work that EPA has done to complete this assessment.

Discounting the 60,000 ug/kg (60 mg/kg) of DIDP in stormwater sediments in troubling. The distribution of concentrations in this study could be used to compare with acute sediment toxicity data. This same study contains values for DIDP and DINP in storm water discharge, which could be used in comparing to acute toxicity values for ecological receptors. The Committee has noted in responses to previous Charge Questions the high percentage of DIDP that would be expected to be in suspended sediments versus water. That same logic would suggest that the 60,000 mg/kg is not an unreasonable concentration to be in a contaminated sediment or one that contains overflow from a wastewater treatment or facility or industrial effluent, which would be more likely during a storm event.

Human Exposure:

These comments primarily address the potential for human exposure in response to Section 3 of the Draft Environmental Release and Occupational Exposure Assessment for Diisodecyl Phthalate (DIDP), the EPA repeatedly indicates potential exposure to DIDP from "vapors" (e.g., L1631, 1785, 1929, 1959) even during transfer operations from drums. That assumption is inconsistent with the characterization by EPA that DIDP is not volatile (L 96-97 “When released to air, will not likely exist in gaseous phase, but will show strong affinity for adsorption to particulate matter”). In lines 604-605 of the Draft Environmental Release and Occupational Exposure Assessment for Diisodecyl Phthalate (DIDP), EPA suggests that workers are likely to be exposed to DIDP "present in PVC materials". These potential sources of spread of DIDP to the environment could contribute a presumably low level to broader environmental hazard from DIDP, especially given airborne sources of DIDP adsorbed to particulate matter.

Recommendations

- Insufficient data are provided in this document for exposure assessments in environmental media. This information gap must be addressed, especially with a manufacturer requested review that moves a requested chemical ahead of other priority chemicals in the EPA review process. It is unacceptable to have no air or water monitoring data within the USA and no measures of releases from 1,1- dichloroethane (DCA) manufacturers to support exposure assessment.
- EPA should clearly articulate that lack of studies does not indicate of lack of exposure.
- At a Minimum, EPA must compute and report the hazard values for aquatic receptors that are included in the current assessment using toxicity data and measured concentration data from treated and untreated municipal wastewater as well as estimated concentrations from Industrial effluents.

DINP Hazard Assessment

Charge Question 1- Ecological Hazard

Charge Question 1.a

As described in Section 4 of the Draft Environmental Hazard Assessment for DINP, EPA had limited empirical toxicity data available for terrestrial mammals and therefore relied on data from controlled laboratory animal studies using human health animal models to derive a toxicity reference value (TRV) to evaluate risk from chronic dietary exposure to DINP. Please comment on the strengths and weaknesses of the methodology and data used to derive a toxicity reference value (TRV) for DINP.

The EPA considered high or medium quality data from 32 publications. These studies included acute and chronic exposures via water, soil, sediment, and food in both aquatic and terrestrial habitats. From the available data, the chronic toxicity reference value (TRV) for DINP of 139 mg/kg-bw/d was derived. This TRV was based on exposure effects for a generalized terrestrial mammal and from one earthworm study.

The EPA concluded that there were no effects on organism survival and fitness. However, in the Executive Summary, EPA states: "Few adverse effects on survival, growth, development, or reproduction were observed in acute and chronic exposure duration tests at concentrations up to and exceeding the DINP solubility and saturation limits." This statement appears contradictory to a conclusion of no effects on survival or fitness.

Strengths

Predicting wildlife toxicity using test results from an experimental model mammal toxicity testing to support human health is a reasonable alternative if data are unavailable for species of wildlife. Accordingly, it appears appropriate to use the available mammalian studies to develop a TRV for terrestrial vertebrates. EPA followed the Guidelines in the Wildlife Toxicity Reference Values (US EPA, 2007). Each step in the process was detailed and met criteria before proceeding to the next step and arriving at the resulting reference value was explained (*Draft Environmental Hazard Assessment for Diisononyl Phthalate (DINP)*, Pages 23-24, Lines 485-517).

Other strengths in the approach used by EPA to derive a TRV are the data in the studies utilized. These studies measured survival, offspring body weight data from *in utero* DINP rodent studies, and body weight/growth data from adult animals to define TRVs for terrestrial mammals. A significant quantity of data describing body weight was available from seven reproduction (*in utero*/postnatal studies, eight studies of the growth (adult) body weight, and three survival studies. The reproduction studies range in exposure duration and test organism age, to include *in utero*, early postnatal, and one two-generation study. Table 4-1 in the Draft Environmental Hazard Assessment for Diisononyl Phthalate (DINP) is much clearer than the similar table in the DIDP Environmental Hazard Assessment and could be added to the DIDP Environmental Hazard Assessment to update the complementary DIDP information similar to DINP. This would provide the reader with a comparative overview of the available information. Overall, EPA considered 12 high and medium quality rodent studies in the derivation of the TRV that considered a span of apical endpoints (such as reproduction, development, or survival) which are highly relevant to terrestrial mammals.

Weaknesses

Although there was a documented increase in the number of juveniles in the earthworm study, it is unclear if these data were considered with models of effects on the population (ExxonMobil, 2010). Lines 423-425 page 19 of Draft Environmental Hazard Assessment states "The soil concentrations were analyzed by gas chromatography with flame ionization detection and ranged from 925.2 to 1052 mg/kg on Day 0 and from 651.4 to 795.8 mg/kg on Day 28 and from 389.6 to 477.1 mg/kg on Day 56." These data are not available in the actual reports, and the Committee could not locate these data, which are essential to the understanding of the earthworm study quality.

No studies of terrestrial plants were available to assess potential hazards from DINP exposure (*Draft Environmental Hazard Assessment for Diisononyl Phthalate (DINP),* P 19, Line 430). This would indicate that soils and sediments should be of high priority for environmental exposure analyses. The *Draft Fate Assessment for Diisononyl Phthalate (DINP)* indicates DINP affinity for sorption to soil and its organic constituents having a log K_{OC} = 5.5–5.7 and log Kd of 2.55–3.27 (Li *et al*., 2017b; Li *et al*., 2017a; US EPA, 2012) and an estimated log K_{OW} of 10.21 (US 402 EPA, 2017a). Given that these properties indicate the likelihood of strong sorption to organic carbon present in soil, DINP is expected to have low mobility in

soil environments (P 17 Lines 401- 404 of Draft Fate Assessment for Diisononyl Phthalate (DINP) Technical Support Document for the Draft Risk Evaluation).

Similarly, EPA should not assume that there is no toxicity because no testing was performed. In the *Draft Environmental Hazard Assessment for Diisononyl Phthalate (DINP),* EPA states "… no studies on exposure to wild mammals, birds, or plants were available to assess DINP hazard, indicating that no hazard has been observed in these groups under realistic exposure conditions." (P 19 lines 434-435). That statement is misleading. The lack of testing indicates a need for testing to fill the data gap.

It is unclear how EPA defines a "definitive hazard" and why inhibition of fetal testosterone production in rats is not a definitive hazard. There are lower effect doses for inhibition of fetal testosterone than for body weight/growth. The TRV derived here is a higher dose than the human reference dose based on inhibition of fetal testosterone and suggests that this endpoint may be applicable to terrestrial mammals in general.

The report should clarify why the confidence in the terrestrial mammal hazard is only "moderate." The confidence rating is included in Table 5-1, with a footnote defining 'moderate'. Although the report does not specify which value was used to set the TRV, it appears to be the NOAEL for body weight in the two-generation study (Exxon Biomedical 1996b). However, five of the studies considered had lower NOAEL values. No exclusion criteria are listed, so it is unclear why the lowest NOAEL was not selected. The value of 139 mg/kg/d does not match one of the tested doses listed in the table for the Exxon study (0, 143, 288, 560 mg/kg/day; see Howdeshell *et al*., 2007, 2008). The EPA's Guidance Eco-Soil Screening Levels Standard Operating Procedure (US (EPA 2007) provides additional information on the method used. It also appears that some explanation is provided on page 23 Lines 509-511, Draft Environmental Hazard Assessment for DINP: "*Step 4: When the geometric mean of the NOAEL for reproduction and growth is higher than the lowest bounded LOAEL for reproduction, growth, or mortality, then the TRV is equal to the highest bounded NOAEL below the lowest bounded LOAEL*." Please clarify.

There is significant variability in the LOAEL and NOAEL values from the 12 high and medium rated rodent studies used to derive the TRV. This variability is not accounted for with the current derivations process.

Recommendations

- Discuss the distribution of DINP in the environment, likely exposure related to distance from the point source and ½ life of DINP in the environment.
- EPA should clarify their conclusion of no hazard for wild mammals, birds, and plants, given that there were no studies available.
- EPA should discuss the relevance and transferability of laboratory studies on rat or mouse on a TRV for wildlife—small mammals for deriving TRV for DINP. Will these studies provide transferable information about other terrestrial wildlife, such as birds and reptiles? If so, this should be explained.
- Discussion is needed to clearly relate the effects of environmental conditions on the half-life of DINP and the likely scenario for exposures and spread—i.e. air, water, sediment.

- Many of the studies demonstrated general as well as reproductive effects, including lower maternal and offspring/postnatal body weights. Describe how this might translate into hazard and risk assessments for terrestrial wildlife, including mammals and birds.
- The EPA should include justification for the statement that earthworms are the most sensitive terrestrial species, given there are no plant studies. Further, the study on earthworms demonstrated no effects on mortality in adults; however, there was an effect on number of juveniles. Discuss what this means for the population over short- and long-term bringing into focus potential effects on the food web.
- The EPA should consider either a) calculating 95% CIs around the geometric mean of the NOAELs and using the lower 95% CI as the TRV, b) using generic assessment factors as would be done to derive COCs for aquatic hazard assessments, or c) adding a description of the uncertainty that is not addressed in the TRV derivation process (rodent models versus ecological models, lab to field, etc.). Simply adding the description could lead to a TRV that is not protective or fully representative of terrestrial mammals. If there are concerns that species are not representative a UF of 3 could be used as a protective measure.
- As for DIDP, the human health non-cancer hazard assessment used the same original pool of studies from rodent models to derive points of departure. Acknowledging the differences in convention for hazard assessments for the two fields, the Committee recommends EPA further harmonize the TRV and PODs. The EPA should add a comparison describing why the TRV is higher than comparable PODs (all also derived from rodents), and further describe why the PODs themselves (before the UFs are applied to account for rodent to human differences) could not be used for environmental hazard assessment. The Committee also recommends EPA consider using similar Benchmark Dose Modeling approaches as were used in the human health non-cancer assessment to derive a more robust TRV.
- Generate plant toxicity data to determine that plants are not the most sensitive terrestrial species since no toxicity studies on avian or terrestrial plant species were identified.
- Other considerations in future TRVs should include adjustments for species inbreeding, selective breeding for specific sensitivity, and non-representativeness of wild strains are the primary argument against using animals that are normally used to model human effects. Regardless using them is better than having no data at all.
- The EPA should consider requiring toxicity tests with species or in vitro tests that are more representative of wildlife for evaluation of ecological risk in future assessments. That would fill the current data gap. In addition, references are provided below for pertinent literature available from domestic birds to gain insight into the comparability of estimated TRV for wild birds.

Additional and editorial comments

- Draft Environmental Hazard Assessment for Diisononyl Phthalate (DINP) document P 23: Add “Step 3” in Line 506.

- L506 (Step 3) Nine reproduction NOAEL results and 12 growth NOAEL results were reported from these studies. Because this condition was met, EPA proceeded to Step 4, L508.

- Page 7, line 153: For terrestrial species, EPA estimates hazard by calculating a TRV, in the case of terrestrial mammals and birds, or by assigning the hazard value as the hazard threshold in the case of terrestrial plants and soil invertebrates. Is this appropriate?

- Page 7 of 38, lines 183-189: Clarify the statement where it says 12 mice and rat studies were used to derive a TRV. Then, it states an additional 12 studies of dietary DINP dietary exposures to lab rodents were used to derive a TRV.

- Page 16 of 38, line 377: A reproductive or reproduction subheading is missing from the text. Line 363 states reproductive and Table 4-1 refers to effects as reproduction.

- Page 17 of 38, line 413: Part of sentence is missing: "Using these studies and guidance from Eco-SSLs (US EPA, 2007)"

- Page 19 of 38, lines 421-427: The Exxon Mobil 2010 earthworm study was included in Table 4-1 in the DIDP Environmental Health Assessment. Recommend that it should be included in the similar table in the DINP Environmental Health Assessment.

- Page 24 of 38, lines 515-517: This states the highest bounded NOAEL…was 139 mg/kg-bw/day DINP from Waterman *et al*. 2000 a concentration corresponding to a reduction in second generation male rat body weight after 19 weeks of dietary exposure.

    - Waterman *et al*. 2000 is not in Table 4-1 (Terrestrial Mammal Hazard Studies of DINP Used for TRV Derivation). Should it be cited as Exxon Biomedical 1996b? If it should be cited as Exxon Biomedical 1996b, Table 4-1 lists the study diet concentrations of 0, 143, 288, and 560 mg/kg-day (and not 139 mg/kg-day or the LOAEL of 274 mg/kg-day).

    - Should Waterman *et al*. 2000 be included in Table 4-1?

- Lines 139 – 140. "Like most phthalates, DINP would be expected to cause adverse effects on aquatic organisms through a non-specific, narcotic mode of toxic action (Parkerton and Konkel, 2000)". DINP could also be expected to cause adverse effects through specific modes of action (as described in the cumulative assessment and DINP non-cancer human health assessment). EPA may wish to acknowledge in the introduction the specific MOA as well: anti-androgenic effects resulting in impaired male reproductive systems and reduced fitness in vertebrates. This would apply to aquatic and terrestrial vertebrates as much as humans and rodent model systems.

- Line 264 – 266 "Finally, the relatively short duration (21-day) of feeding exposure to adult fish may be inadequate for detecting apical effects that are most likely to translate to effects on fish populations." The Committee agreed and noted that this is well stated.

- Line 433 EPA could consider reducing the confidence (currently "robust confidence") in the assessment for soil dwelling organisms as there was only one study available.

- Line 435 “No studies on DINP exposure to wild mammals, birds, or plants were available to assess DINP hazard, indicating that no hazard has been observed in these groups under realistic exposure.” Suggestion to change this language as it is misleading. The finding that no studies have been conducted or found for the assessment does not mean there is no hazard (toxicity). That would remain to be tested, should the studies be conducted.
- There is one minor weakness with respect to the writing/formatting of the report. The reproduction studies are separately identified by the term “reproduction” in Table 4-1 but are not referred to using the same language under the Mammals heading. They also do not have a subheading or paragraph title, while the following sections are titled with the subheadings, “Growth” and “Survival.” Growth is ambiguous in this context, particularly because as applied, it does not include the development/reproduction studies.

The Committee expressed difficulty finding the basis of the TRV - NOAEL listed of 139 mg/kg-day as the reference cited (Waterman *et al*. 2000) is not in Table 4-1. It appears the reference cited should be Exxon Biomedical 1996b, but check the dietary concentrations listed for NOAEL/LOAEL and in the study details.

Charge Question 2 – Human Health Hazard

Charge Question 2.a

In Sections 4.1.1 and 4.1.2 of the Draft Non-Cancer Human Health Hazard Assessment for DINP, EPA has preliminarily selected the HED of 12 mg/kg-day (BMDL5 of 49 mg/kg-day) based on decreased fetal testicular testosterone production for assessing risks from acute and intermediate duration exposure to DINP. EPA is using benchmark dose (BMD) estimates calculated by the National Academies of Sciences, Engineering, and Medicine (NASEM, 2017). Please comment on the strengths and uncertainties in the selected acute/intermediate HED, including its appropriateness for these durations.

Specific Comments

In the Draft Hazard Assessment for DINP, EPA derived points of departure (POD) and corresponding human equivalent doses (HED) for DINP from benchmark dose (BMD) analysis conducted by the National Academies of Science, Engineering, and Medicine (NASEM) in 2017. Committee members agreed with the scientific justification to use developmental toxicity studies, specifically fetal testicular testosterone production data, to determine HED for both acute and intermediate duration POD, and also enumerated a number of sources of uncertainty.

Strengths

Strengths of the approach include the use of DINP developmental toxicity studies to derive the acute POD and HED. The endpoint used in the Draft Hazard Assessment is inhibition of testosterone production in the fetal rat testis, which is a rapid response, sensitive to reduction by a single-dose phthalate exposure, consistent with an acute mode of action (Thompson *et al*., 2005). It is appropriate to use data from developmental toxicity studies when deriving toxicity values for acute exposure, in accordance with EPA policy as described on Page 70 of the Draft Hazard Assessment. Two recent publications from Earl Gray and colleagues (Gray, 2023, Gray *et al*., 2024) support the conclusion that reduction of fetal

testosterone production by DINP can cause male reproductive tract malformations, the apical outcome associated with this mode of action, and that DINP exerts dose-additive anti-androgenic action when combined with another anti-androgenic phthalate, which in the case of the 2024 publication was dibutyl phthalate (DBP).

The Committee agreed that the selection of the same POD for short- and intermediate-term toxicity is reasonable, given that fetal testicular testosterone production was the most sensitive endpoint over any duration in the studies that were included in the NASEM BMD analysis. Although the duration of exposure in days in the developmental studies is shorter than what might typically be considered "intermediate" duration, it could be argued that the time period modeled by these exposures (Gestation Day, GD 6 to parturition in rats) is equivalent to an intermediate exposure duration in comparison to human gestation time. In other words, for developmental endpoints, the duration of exposure in the animal should be scaled to the timing of development, rather than an arbitrary duration of exposure such as 30 days. The Committee agreed that the intermediate duration POD was appropriately selected for DINP.

Uncertainties

The Agency applied the ¾ body weight conversion as a default assumption to substitute for the 3X toxicokinetic component of the $UF_{A.}$ This could over- or under- estimate actual species differences. The Committee largely agreed that the interspecies uncertainty factor of 3 is consistent with known toxicokinetic similarity between rats and humans for phthalates, while accounting for uncertainties about toxicodynamic similarity. However, the Committee requests that EPA provide more written detail to justify the selected uncertainty factors. Notably, there is uncertainty about the toxicodynamic similarity across species, based on phthalate experiments conducted in human fetal tissue xenograft or culture models. Those experiments indicated that at least under certain circumstances, human fetal testis tissue is less sensitive to the antiandrogenic effects of phthalates than the rat fetal testis (Heger *et al*., 2012, Mitchell *et al*., 2012, Habert *et al*., 2014, Spade *et al*., 2014). This introduces uncertainty with respect to the sensitivity of the human fetal testis to phthalate-induced testosterone reduction, although phthalates cause germ cell toxicity in all species that have been tested (Li & Spade, 2021). This source of uncertainty was addressed by EPA in section 3.1.4.1 (p 77-79) of the Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act (EPA-HQ-OPPT-2023) in February 2023. However, the Committee requests that EPA clarify the rationale for selection of the interspecies UF_A of 3, which may account for: toxicokinetic similarity between species, allometric scaling to determine HED, and/or knowledge of toxicodynamic differences between species. Specifically, the text note in Table 4-2 should be included in the text of the report on page 72 of 184, line 2446. Adequate justification is not provided in the text of this report for the selection of the uncertainty factors for DINP, as was provided in the assessment for DIDP.

The Committee also identified as a concern that EPA relied on the 2017 NASEM BMD analysis rather than conducting a new BMD analysis. Adopting the NASEM analysis means that some decisions made by NASEM introduced uncertainty, including:

1. It is unclear whether EPA attempted to replicate the BMD modeling, and whether the results were confirmed. This was not discussed.

2. No justification was provided for the use of BMDL values instead of BMD for determining HED.

3. The rationale for the use of only the BMDL5 and BMDL40 values that correspond to a benchmark response (BMR) of either 5% or 40% was unclear. The 2012 EPA Benchmark Dose Guidance document (US EPA. 2012. Benchmark Dose Technical Guidance. US Environmental Protection Agency, Washington, DC. EPA/100/R-12/001 June 2012) states: "For quantal data, an extra risk of 10% is the BMR for standard reporting (to serve as a basis for comparisons across chemicals and endpoints), and often for hazard ranking, since the 10% response is near the limit of sensitivity in most cancer bioassays and in some noncancer bioassays as well." Further, BMD5 is considered biologically relevant for nested data, which may be available for developmental endpoints such as reproductive tract malformations. The Guidance also says "For continuous data, the preferred approach is to define a BMR based on the level of change in the endpoint at which the effect is considered to become biologically significant (as determined by expert judgment or relevant guidance documents)." The EPA should augment the limited discussion t as to why the BMDL5 was chosen over the BMDL40, despite a biological reasoning being provided for why the initial NASEM meta-regression conducted the analysis with a benchmark response (BMR) of 40% in the legend of Table 4-1 (but not in the text).

4. The BMD Guidance document also recommends that if values other than BMD10 are used in the hazard assessment, the BMD10 numbers for the selected endpoint should be given in the document for comparison purposes.

The Committee was also concerned about the inclusion or exclusion of data in the NASEM BMD analysis, because those inclusion and exclusion decisions are reproduced here by default. It is unclear if EPA conducted a literature search that identified any relevant DINP studies other than acute developmental studies, and there is a lack of clarity about the justification of exclusion of studies. Specifically:

1. In the 2017 NASEM analysis, four DINP studies were identified (Adammson *et al*., 2009, Boberg *et al*., 2011, Hannas *et al*., 2011b, and L. Li *et al*., 2015) [Table 3-19, Studies of DINP and Fetal Testosterone in Rats]. However, NASEM used only two studies (Boberg *et al*., 2011, Hannas *et al*., 2011b) [Figure C6-15, Meta-analyses of studies of DINP and fetal testosterone in rats]. EPA states that they have high confidence in the NASEM meta-analysis because it considers data from multiple studies. However, it appears that the BMD modeling and meta-regression analysis was conducted using only two studies. As a minor comment, there is a discrepancy in the written report about which two studies were included in the NASEM analysis.

2. EPA also mentions one acceptable study (Clewell *et al*., 2013) that was not included in the NASEM 2017 study [noted on page 175 of Appendix C, Protocol for Systematic Review of Phthalates].

3. Although exclusion of single-dose studies is reasonable if each study is being considered in isolation to identify NOAEL or LOAEL values, it seems that the data points contained in single dose studies could strengthen modeling estimates if a new meta-analysis was performed.

4. Discussants noted that the two recent publications from Earl Gray and colleagues (Gray 2023, Gray *et al*., 2024) would also strengthen the analysis and should be included if EPA decides to conduct a new analysis.

5. Several Committee members expressed concern regarding the lack of human epidemiological studies used in the DINP dose-response assessment, although there are epidemiology studies showing that exposure to DINP is related to reduced testosterone (Henrotin *et al*., 2020, Woodward *et al*., 2020). Not including available epidemiological data in the analysis introduces uncertainty about the dose-response analysis.

Finally, there was disagreement among members of the Committee about the assessment of DINP risk as a single chemical, without considering co-occurring phthalates. This concern was raised by several Committee members. As the report states, reduction of fetal testicular testosterone production in the rat model following developmental exposure to phthalates is similar across phthalates, with differing potency but similar mode of action DINP (Furr *et al*., 2014, Conley *et al*., 2021, Gray *et al*., 2021). Because phthalates co-occur and inhibition of androgen production is a mode of action relevant for many other phthalates as well, several discussants stated that deriving an HED for a single chemical is inconsistent with recommendations of the SACC's review of the "Draft Proposed Principles of Cumulative Risk Assessment (CRA) under the Toxic Substances Control Act and a Draft Proposed Approach for CRA of High-Priority Phthalates and a Manufacturer-Requested Phthalate (EPA-HQ-OPPT-2023). With respect to DINP specifically, the recent paper by Gray *et al*. (2024) supports the argument that DINP and DBP have dose-additive effects on testosterone-driven endpoints, which would justify including DINP in planned CRA. Given efforts within EPA to conduct cumulative risk assessments for multiple phthalates, those discussants are concerned that reaching a conclusion on a HED without the cumulative assessments would be incomplete. Hence, the *lack of consideration of mixtures and/or interactions leads to potential underestimation of risk*.

However, other members of the Committee argued that the current approach is consistent with EPA's approach to CRA, which consists of three steps: first, to derive individual chemical HEDs/PODs; second, to develop relative potency factors; and third, to perform the cumulative assessment using the relative potency factors. This approach is based on the view that it is not possible to complete a cumulative risk assessment (CRA) without already having PODs/HEDs for the individual chemicals. On this basis, it would be premature to consider cumulative assessment at this point in the review process for the phthalates. EPA has issued Scope documents for each of the seven phthalates under review. Public comments on those Scope documents urged the agency to conduct cumulative risk assessment(s) on the group, as it has committed to do. However, individual risk evaluations for DEHP, BBP, DBP, DIBP, DCHP, DINP and DIDP, which will characterize risk from their respective conditions of use (COUs) *must* be done first so that chemical-specific Relative Potency Factors (RPF) can be derived and each chemical's proportional contribution to a cumulative assessment can be determined in order for the agency to identify the appropriate risk management measures that may need to be taken to assure that the group, as a whole, does not pose an unreasonable risk. Mixing cumulative factors into the derivation of a POD/HED will make these actions difficult, if not impossible, and inappropriately skewed. The agency should supplement their published guidance with published approaches that would help with problem formulation, evaluate common exposure and effects groupings, and addition of modifying factors that could impact the final cumulative human risk (Solomon *et al*., 2016, http://dx.doi.org/10.1080/10408444.2016.1211617; Moretto *et al*., 2016; http://dx.doi.org/10.1080/10408444.2016.1211618).

Recommendations

- The Committee recommended that EPA consider conducting a new BMD modeling analysis, comparing multiple endpoints including variables for which nested data is available, and that EPA should clearly state its rationale for selection of the BMR and the use of BMD or BMDL to generate a POD, as both choices could lead to over- or under-estimation of risk. A new analysis should consider new experimental studies and epidemiological data applicable to DINP dose-response assessment.

Rather than using the ¾ body weight scaling and default 3-fold UF_A, EPA should consider refining this value by making use of the recently developed DINP PBPK model (Campbell *et al*., 2020). The DINP model is an adaptation of the existing models for DEHP and DBP, using both pregnant rat and human time-course plasma and urine data. This could/should be done in accordance with EPA's guidance on Data-derived Extrapolation Factors (DDEF) (US EPA, 2014)

Charge Question 2.b

In Section 4.1.3 of the Draft Non-Cancer Human Health Hazard Assessment for DINP, EPA has preliminarily selected the HED of 3.5 mg/kg-day (NOAEL of 15 mg/kg-day) based on a spectrum of liver effects, including incidence of spongiosis hepatis, increased liver weight, and serum chemistry for assessing risks from chronic duration exposure to DINP. This NOAEL has been selected by other regulatory agencies (e.g., US CPSC, Health Canada, EFSA, ECHA) to characterize non-cancer risks associated with exposure to DINP. Please comment on the strengths and uncertainties in the selected chronic HED, including its appropriateness for this duration.

Summary of EPA approach

EPA determined the chronic duration non-cancer POD based on a NOAEL of 15 mg/kg-day, with the critical effect of liver toxicity (i.e., increased relative liver weight, increased serum chemistry (AST, ALT, ALP), histopathologic findings (e.g., focal necrosis, spongiosis hepatis)) in F344 rats following two years of dietary exposure to DINP (Lington *et al*., 1997; Bio/dynamics, 1986). (US EPA, (2024b), p.184: 4481-4502)

No data were available for the dermal or inhalation routes that were suitable for deriving route-specific PODs. Therefore, EPA used the acute/intermediate and chronic oral PODs to evaluate risks from dermal exposure to DINP. For the inhalation route, EPA extrapolated the oral HED to an inhalation human equivalent concentration (HEC) using a human body weight and breathing rate relevant to a continuous exposure of an individual at rest (US EPA, 1994).

Adverse non-cancer effects on the liver were primarily observed in rats and mice of both sexes, although there was also evidence of hepatotoxicity from one study in beagles. Two studies in non-human primates with dose ranges comparable to those in the rodent and beagle studies did not provide evidence of non-cancer or pre-neoplastic effects on the liver following 14- (Pugh *et al*., 2000) and 90-day oral exposures to DINP (Hall *et al*., 1999). (US EPA (2024b), p.43, Lines 1155-1159)

EPA states "In general, short term (9 of the 12 studies) and subchronic duration studies (9 of 9) consistently reported increases in absolute and/or relative liver weight, sometimes in parallel with exposure-related histopathological effects on the liver (e.g., hepatocellular hypertrophy) or coinciding with increases in liver enzymes (e.g., ALT, AST, ALP), suggesting impaired liver function. These effects

were generally dose-dependent, observed in both sexes, and in multiple species, including rats, mice, and beagle dogs. (US EPA (2024b), p.43: lines 1164-1168)

EPA states that no human epidemiologic studies evaluating hepatic effects were identified in its review of existing assessments (primarily Health Canada (2018a). (US EPA (2024b), page 120 lines 3590-3591)

Strengths

The strengths of the selected chronic exposure HED of 3.5 mg/kg-day of DINP (NOAEL of 15 mg/kg-day) are that:

1. there were several adverse liver outcomes in a high quality two-year dietary study,
2. many additional chronic exposure studies observed similar adverse liver effects (although they had higher NOAELs), and
3. several authoritative and regulatory agencies, in the US and around the world, selected same point of departure of 15 mg/kg-day (NOAEL) based on liver outcomes in experimental rodent models.

EPA reviewed twelve studies to determine the chronic POD and determine an HED for a spectrum of liver effects.

Furthermore, the acute exposure HED of 12 mg/kg-day of DINP based on the NOAEL for decreases in fetal testicular testosterone production occurred at slightly higher doses than the HED for adverse liver effects, and it reinforced the ability of DINP to induce adverse health outcomes in mammals (i.e., the experimental rat model). The chronic exposure duration is an appropriate exposure to consider because it demonstrated consistency with the acute exposure duration HED (12 mg/kg-day) for decreased fetal testicular testosterone production.

Uncertainties

EPA considered new studies published since Health Canada's assessment (Health Canada, 2018a) (i.e., studies published from 2018 to 2019); however, no studies were identified that fall within this date range and evaluated liver injury for DINP and/or its metabolites. (US EPA (2024b), page 120 lines 3593-3595)

The use of liver endpoints for this purpose is also substantiated using sufficient data. Of note, the study in beagles also showed some liver toxicity but has a slightly higher NOAEL. The Agency did not use several studies in dog and rats due to either limited samples size or lack of GLP while performing the studies, which seems appropriate. The lack of human relevance of spongiosis hepatis is a concern but concomitant change in liver injury markers somewhat reduces the uncertainty.

EPA chose the Lington *et al.*(1997) developmental toxicity NOAEL as the POD because it was more sensitive (i.e., lower) than all other candidate NOAELs and LOAELs (Table 4-5), but neglects to determine Benchmark Doses for all the candidate studies - allowing the identification of endpoints and doses. This is particularly important for developmental effects for which inference about potential MOA cannot be gleaned from 2 generation GLP studies conducted before understanding of endocrine disruption and potential effects on developing systems. Rodent studies that form the basis for the selected NOAEL-based POD are: 1) insensitive compared with more recent in vivo studies or the use of NAMs where endocrine systems are targets and 2) lack concordance with the epidemiologic studies regarding endpoints (including PPARα-mediated induction of human relevant pathways). Health Canada stated

"However, the relevance of the hepatotoxic effects of phthalates observed in rodents is difficult to establish due to the species-specific differences in the peroxisomal proliferation response (rodents being significantly more sensitive than humans to PPARα-mediated induction of peroxisome proliferation)" (EC/HC 2015, Page 72).

EPA did not give an explanation as to why the toxicokinetics would be similar by oral, inhalation and dermal routes and if this extrapolation is appropriate. EPA states that differences in absorption will be accounted for in dermal exposure estimates in the draft risk evaluation for DINP. However, specifics are not provided.

Several recent human epidemiology studies of DINP non-cancer effects, including developmental effects were excluded from the dose-response assessment. These studies were excluded because of uncertainty about exposure. However, the studies focused on measurement of urinary biomarkers of phthalates, including metabolites of DINP. While there are technical issues when using urinary biomarkers for determination of exposure, this is a common approach and the gold standard for phthalates to understand the association between the chemicals and outcomes relevant in people. EPA individually assessed the merits of 53 epidemiology studies of DINP, published from 2018 to 2021, applying a pre-specified set of study quality domains and metrics that closely mirrors the approach used by EPA's IRIS program, which has been favorably reviewed by the NASEM. EPA's overall quality determination was "Medium" or "High" for 46 of these epidemiology studies. Each study was individually assessed for its exposure measurement methods (Domain 2) and treatment of potential confounding (Domain 4).

EPA has not released the systematic review protocol used for DINP and so the SACC is unable to review this approach or its findings.

Based on the two high quality data sets from GLP contract laboratories (Lington *et al.*, 1997/Biodynamics, 1986 and Covance Labs, 1998 shown below) where F344 rats show the same effect (increased organ weights and histopathological findings) the higher NOAEL could be used as a POD, such that the NOAEL from Covance-Labs can be considered as the highest NOAEL which falls below the lowest LOAEL from the Lington *et al.*, 1997/Biodynamics, 1986 studies).

Brief Study Description	TSCA Data Quality[f]	NOAEL/ LOAEL (mg/kg-day)	Critical Effect
Male and female F344 rats (110/sex/dose) fed diets containing 0, 300, 3,000, 6,000 ppm DINP (CASRN 68515-48-0) for two years (equivalent to 15, 152, 307 mg/kg-day for males; 18, 184, 375 mg/kg-day for females) (GLP-compliant, non-guideline study) (Lington et al., 1997; Bio/dynamics, 1986)	High	15/ 152	↑ in absolute and relative liver and kidney weight with increase in histopathological changes (*e.g.*, spongiosis hepatis) and other signs of hepatotoxicity
Male and female F344 rats (70-85/sex/dose) administered 0, 500, 1500, 6000, 12,000 ppm in the diet for 104 weeks (equivalent to 29, 88, 358, 733 mg/kg-day in males; 36, 108, 4422, 885 mg/kg-day in females) (GLP-compliant, adhered to 40 CFR Part 798 (§ 798.330)) (Covance Labs, 1998c)	High	88/ 358	↑ Liver and kidney weight, biochemical changes (↑ serum ALT, AST), and histopathological findings

Recommendations:

Overall, the available data support the Agency's selection of NOAEL and HED. The fact that several other regulatory studies have similar chronic POD is reassuring to some Committee members.

- Committee members agree that EPA should consider the fetal testicular testosterone production is the most sensitive effects based on the evidence from the animal studies. However, EPA should use all available dose range studies from which BMD-based POD should be developed, compared with each other to select the lowest BMD-based POD as the basis for the derivation for the HED.
- EPA should provide an explanation as to why the toxicokinetics would be similar by oral, inhalation and dermal routes and if this extrapolation is appropriate.
- EPA should provide documentation of approach used for route-to-route extrapolation in the absence of dermal and inhalation data.
- EPA should release the systematic review protocol for DINP.
- EPA has disqualified epidemiology studies in a manner inconsistent with its own pre-specified procedures. EPA's own overall quality determinations indicate that these studies are suitable for use. EPA should include these studies in its identification of studies potentially suitable for informing a POD. Alternatively, EPA should justify why these studies are not relevant.
- EPA should apply benchmark dose modeling to derive chronic non-cancer points of departure and select the one that is most sensitive (lowest).
- Including a flow chart similar to that used for the TRV in the DINP ecological hazard assessment would be useful for the Hazard Assessment for Human Health.

Editorial Comments

- Line 729 - Clarify what DINP delivery route is being compared to orally administered DINP. Presumably it is dermally applied DINP.
- Line 789 - Please clarify what "0" refers to at the end of this sentence. It appears that there is a missing citation.
- Lines 1053-1054 - This sentence does not appear to be complete: "The DINP treatment group showed a decreased birth rate, a non-significant increase in liver masses in males at 10 months (9.1 percent control versus 33 percent treated)." Please clarify.
- Lines 1614, 1616, and 1617 - The descriptor for the set 2 images is written differently in each of these three sentences (e.g., set 2 images, set 2 image, set 2). Please ensure that the descriptors are consistent if they are referring to the same images.
- Line 1884-1885 - Consider changing "…overweights as well as obese" to "…overweight as well as obese women…".
- Line 1898 - Section on Cardiotoxicity Effects, Laboratory Animals – Parts of this section did not fully identify and describe the literature. For example, lines 1923-1928 begin, "Two additional studies are available that provide data on changes in triglycerides and cholesterol following short-term duration exposure…"but the paragraph only identifies and describes one study. Also,

lines 1930-1934 begin “Four studies were identified that provide data on the effect of DINP on heart rate…” yet only 3 studies are cited. The EPA should include these studies or state that reviews are limited the low and medium risk-of-bias studies.

- Line 1993 – Please clarify that the Soomro 2018 study was assessing an association between incidence of eczema and urinary phthalate metabolites, not specifically DINP metabolites. Please clarify that only one DINP metabolite (MCOP) was included in this study (e.g., text currently reads DINP metabolites (line 1993) and DINP metabolite (line 1994).
- Line 2093 - noun missing from sentence. should it be "it diminished"?
- Lines 2124 - Change "symptom" to "symptoms".
- Table 4-2 Row for Furr 2014 - consider lowercase f for fetal testis testosterone production.
- Line 2745 - Check grammar of the phrase, "Differences in absorption will accounted for...". Should it be "...will be accounted for"?

Charge Question 2.c

In the Draft Cancer Human Health Hazard Assessment for DINP, EPA considered MNCL (Section 3.2.2), kidney tumors (Section 3.2.3), and liver tumors (Section 3.2.1). EPA has preliminarily determined α2u-globulin MOA for kidney tumors, and that there is too much scientific uncertainty associated with the incidences of MNCL observed in F344 rats to use quantitatively to estimate human risk from exposure to DINP. Therefore, EPA focused its MOA analysis and dose-response analysis on liver tumors. Please comment on the strengths and uncertainties of EPA’s decision to focus its cancer assessment on liver tumors.

The Agency’s decision to focus on liver tumors rather than other types of tumors for cancer risk evaluation is justified, as it was the only tumor type observed to be significantly increased in both rats and mice following chronic exposure in the diet. However, some Committee members noted that there is uncertainty in relying upon this endpoint to extrapolate to the human. The Agency provides evidence from multiple studies to support that these liver tumors in rodents could occur through a PPARα mode of action. This suggests a mode of action in the rodent that has been evaluated in multiple assessments, beginning with Klaunig *et al*. (2003), and the most recent being Corton *et al*. (2018), which is cited by the Agency. While this mode of action for liver tumors in rodents is biologically plausible, it has been determined in multiple assessments by multiple authoritative bodies cited by the Agency (e.g., NICNAS 2012; USCPSC 2010; ECHA 2013; Health Canada 2015) to lack human relevance. In these evaluations for DINP referred to by the Agency, no quantitative evaluation of these liver tumors was conducted to assess the potential for carcinogenicity in the human.

The Agency’s decision not to consider MNCL to drive quantitative risk assessment of cancer hazard is well supported by data. The Agency has provided substantial evidence that the kidney tumors produced by DINP are due to a 2u-globulin MOA and correctly classified them as not relevant to humans.

Specific comments

- The comment that Health Canada was unable to identify any epidemiological studies is made without proper context and does not seem like a good start of this section. It would be better to start with EPA studies.

- Page 10, line 267, 'non-statistically significant" should be changed to "statistically non-significant". Same applied to page 19, line 482.
- Page 20, line 509, tubular regeneration should be replaced 'tubular repair'. This is because regeneration implies change in organ size while repair shows structural repair without change in size. Livers show true regeneration while kidneys show repair.
- It is recommended that the data in Table 3-3 be treated the same as in Tables 3-1 and 3-2, combining the neoplastic findings and comparing across dose groups (Thus compare males 4, 7, 12, 9 and females 1, 1, 10, 9).
- It is appropriate to combine various hepatocellular neoplasms as they are a continuum from atypical hyperplasia through adenoma to carcinoma. The studies referenced are old and the term neoplastic nodule is no longer used. (See Wolf and Mann, TAAP 202 302 2005, https://doi.org/10.1016/j.taap.2004.06.022)
- Page 16 line 394 regarding control data - evaluation of control data see Keenan *et al*. Tox Path https://doi.org/10.1177/0192623309336154
- Page 22 line 55-563, interstitial cell tumors, these are common tumors and one of the reasons that the F344 rat was no longer the primary rat species used by the NTP as it was a confounder in the bioassay interpretation. (https://www.tandfonline.com/doi/full/10.1080/10408444.2016.1174669)
- Table 3-10, Pancreatic Islet cell tumors can be combined and evaluated (i.e. 7, 0, 0, 12 and 1, 0, 0, 1)
- The inactivity of DINP in the ToxCast for nuclear receptors (i.e., CAR, AhR, PPARα, PPARγ) and other pregnane X receptor (PXR) assays including 953 TOX21_PXR_Agonist, TOX21_PXR_viability are in contrast to positive responses found in other *in vitro* studies (section 4.6, pg 33). Therefore, a comparison of the doses and experimental conditions used from other *in vitro* studies is warranted (Laurenzana, *et al*., 2016, https://doi.org/10.1021/acs.chemrestox.6b00186).
- Males are more sensitive to KE1 in PPAR MOA in rats. However, the species differences which are known, should be included in Table 4-2 & 4-5-3, pages 31-32 since there are species differences in tumor dose-responses.
- Line 333 Table 3-5. I, column headings are inconsistent with the other tables, M/F are not abbreviated, and they are in the other tables.
- While referencing is generally good, no mention is made of the National Toxicology Program's (NTP) replacement of the Fischer 344/N rat with the Harlan Sprague Dawley (HSD) strain following a 2005 NTP workshop, as described in King-Herbert and Thayer (2006) (King-Herbert and Thayer. 2006. NTP Workshop: Animal Models for the NTP Rodent Cancer Bioassay: Stocks and Strains—Should We Switch? Toxicologic Pathol. Oct 34 (6):802–805, https://journals.sagepub.com/doi/10.1080/01926230600935938). This citation should be added

to the reference section along with a brief summary of it in the relevant section of the document.

Charge Question 2.d

In the Draft Cancer Human Health Hazard Assessment for DINP, EPA preliminarily concluded that the weight of scientific evidence supports a peroxisome proliferator activated receptor alpha (PPARα) MOA for liver tumors in rats and mice (Section 4.1). Please comment on the strengths and uncertainties of EPA's preliminary conclusion. In your response, please include discussion of the strengths and uncertainties of available data supporting key events in the PPARα MOA and the scientific rationale for a threshold approach for cancer dose-response.

General comments

Section 4 is well-written, clear and straight-forward in a manner consistent with the principles articulated in the WHO IPCS Mode of Action/Human Relevance Framework (MOA/HRF) (IPCS, 2007) and EPA's Guidelines for Carcinogen Risk Assessment (US EPA, 2005). It is very well done and represents an exceptional example of how this type of analysis should be conducted..

Nonetheless, it could be strengthened by referencing and including analysis of key studies in the extensive database on examining the ability of many PPARα agonists to produce liver tumors in rodents and other species in a specific, predictable way, rather than depending only upon DINP-specific information. The extensive literature on this mode of action (MOA) pursuant to other chemicals that bind to, and activate PPARα, including other closely related phthalates, would be very useful in filling some of the gaps for those key events for which there are less or no DINP-specific data.

On that latter point, one of the public commenters provided several references, claiming that they could provide information which would fill in those data gaps. Hopefully, that will be the case, and the agency can resolve any remaining uncertainties they may have about whether DINP produces the liver tumors by this MOA.

In any case, the existing extensive body of literature, collectively, describes and integrates the postulated key events into well-characterized downstream consequences of binding to the PPARα receptor resulting in liver tumors in rodents. Corton, *et al*. (2018) does a particularly nice job of summarizing the then-current knowledge about this MOA, including figures which incorporate confirmation of the key events and modulating factors involved, the order in which they occur supported by data on chemicals representing more than one class of chemicals. Included below is the figure from that publication which visually presents the Occurrence of Key Events (KE)in the PPARα Mode of Action (MOA) in rats, as an example.

One will notice that, collectively, the entire MOA pathway is filled in. If the table were updated to the present, more chemicals would be added (e.g., some additional phthalates and PFAS as well as permethrin (Kondo *et al*, 2019)).

The Corton *et al*. (2018) figure includes data for some phthalates other than DINP. As the remaining five phthalate risk evaluations are drafted, additional phthalate chemicals may be added to this figure. Other phthalates, not currently on the TSCA high priority list but on the TSCA Inventory, may also meet the

criteria for inclusion if an MOA analysis was conducted for those observed to induce rodent liver tumors. At a minimum, EPA should screen the literature for information on all those on the TSCA Inventory.

To address lingering uncertainties that the agency may have now about DINP acting via the PPARα pathway, it is incumbent upon the agency to exercise its historical practices of employing the tools used in the new chemicals program such as (Q)SAR and read-across to fill in the DINP Key Event (KE) gaps currently devoid of adequate empirical data. This is a scientifically credible approach since all of the KEs are based on the initial molecular initiating event (MIE) of PPARα binding to the ligand. Figure 1 shows there are relevant data related to KE2 for two other phthalates (DEHP and DBP). Additional candidates for read-across include the other examples in the figure, the other five TSCA priority phthalates for which risk evaluations are being drafted currently, and others on the TSCA Inventory including some additional ones that are listed in NAS (2008) and NASEM (2017). Even though these phthalates were evaluated in those two National Academies reports with a focus on their effects on male reproduction, these chemicals have other adverse effects which may include the liver tumors.

Applying read-across information from other PPARα agonists is especially relevant to KE4 (clonal expansion) as well. KE4 is obligatory in the pathogenesis of liver tumorigenesis in rodents, no matter the MOA. The population model as described in Wolf *et al*. (2019) illustrates how this occurs from the initial burst of mitogenesis to a new larger population of hepatocytes resulting in a greater population at risk of developing a neoplastic response.

Chemical	KE1: PPARα Activation	KE2: Alteration of Cell Growth Pathways		KE3: Perturbation of Cell Growth and Survival			KE4: Clonal Expansion	Apical Endpoint: Liver Tumors
				Acute Cell Prolif.	Chronic Cell Prolif.	Apoptosis		
WY-14,643	↑[1]	↑[7,9,53,54]	NC[8]	↑[2]	↑[4]	↓[3]	↑[5]	↑[6]
DEHP	↑[10]	↑[14]	NC[15]	↑[11]	↑[52] NC[13]	↓[12]		↑[14]
Clofibrate	↑[16]	↑[20,55,56]	NC[21]	↑[17]	↑[18]			↑[19]
Nafenopin	↑[22]	↑[27,57]	NC[28,29]	↑[6]	↑[24] NC[6]	↓[23]	↑[25]	↑[26]
Ciprofibrate	↑[22]	↑[34,35,58]		↑[30]	↑[31]		↑[32]	↑[33]
Methyl Clofenapate		↑[39]	NC[40]	↑[36]	↑[38]	↓[37]		↑[39]
Gemfibrozil (CI-718)	↑[22]	↑[42,43,55]		↑[57]			NC[41]	↑[41] NC[41]
Di-n-butyl phthalate	NC[10]	↑[43,44,59]						
Trichloroacetate	↑[50]							NC[45]
Perfluorooctanoate	↑[51]	↑[48]	NC[49]	↑[46]				↑[47]

Figure 1. Occurrence of Key Events (KE) in the PPARα Mode of Action (MOA) in rats (from Corton *et al*., 2018)

Regarding the strengths and weaknesses related to the agency's preliminary conclusion that DINP induces liver tumors via the PPARα MOA, there is little doubt that this MOA is the operative one based upon the DINP-specific data and those for many of the related and other chemicals as summarized in Corton *et al*. (2018). This conclusion will only be strengthened further when the agency more carefully reviews the Corton *et al*. (2018) paper and performs the read-across exercise. As for the potential uncertainties articulated by EPA in the DINP cancer hazard assessment, more should be resolved after doing the aforementioned work and reviewing the papers submitted by the public commenter.

EPA states on Page 29 lines 817-820, "Overall, there is some evidence to support dose-response concordance for KE1, KE3, and the adverse outcome: hepatocellular adenomas and/or carcinomas. However, no (DINP-specific) data are available for KE2 or KE4, or apoptosis (part of KE3) in rat hepatocytes, which prevents a complete analysis of dose-response concordance across all KEs in the postulated MOA." Most of the Committee members thought this was an unsupportable statement, in the first instance because it is not necessary to illustrate all Key Events in a well-established MOA as long as the Molecular-initiating-event (MIE; in this case, PPARα activation) and some of the KEs are qualitatively and quantitatively addressed, which they are in this case. Using data from compounds that have the same biological effects also support this mode of action conclusion for the reasons presented above. Some modest additional work on the agency's part, as recommended, will hopefully resolve this concern to their satisfaction.

On Page 32 lines 888-890, the Agency states "In contrast, other studies have demonstrated that PPARα activation (KE1) and cellular proliferation (KE3) occur at lower doses in male mice compared to females (Kaufmann *et al*. 2002). This apparent inconsistency cannot be explained." This inconsistency is identified by EPA as an area of uncertainty. Some Committee members thought this was not a valid area of uncertainty in this context. This apparent disparity does not impact the characterization of the MOA, any dose-response characterization or determination of the appropriate descriptor for prediction of human carcinogenic potential. In the latter case, gender discrepancy might matter only if one sex experienced a statistically significant increase in the incidence of a specific tumor type and the other did not, depending upon what other data are available to aid in determining human carcinogenic potential.

The scientific rationale that the PPARα activation MOA is a threshold phenomenon is supported by the available science. Section 2 of the cancer hazard assessment summarizes a series of 20 studies that evaluated genotoxicity potential in a variety of systems. All of the studies were carried out in *in vitro* systems, except for the *in vivo* micronucleus studies in mice. The only positive result was observed in one of the nine available *in vitro* transformation assays in Balb/c-3T3 A31 mouse cells in the absence of metabolic activation (Microbiological Associates, 1982c). The agency concluded that the weight of scientific evidence indicates that DINP is not likely to be genotoxic or mutagenic, a conclusion with which the Committee agrees. This conclusion, coupled with the observation that other nuclear receptor-mediated MOAs (e.g., CAR, PXR, AhR, PPARγ) are generally observed to be threshold phenomena, supports the conclusion that the MOA for PPARα activation is also.

Recommendations

- Section 4 would benefit from a more substantial discussion of species differences, structurally and functionally, in the behavior of the PPARα nuclear receptor itself. Activation of it in rodents may lead to liver tumors via the described MOA. Activation in humans does not, based on

available epidemiology studies that explored the relationship between exposure to PPARα agonists and cancer outcomes (e.g. Bonavas *et al*., 2012).

- While ligand-receptor binding kinetics are well documented for some chemicals, including some phthalates, the Committee recommends that EPA provide a more robust discussion in Section 4 of the work that describes 1) species-specific differences in potency and efficacy of activation of PPARα and 2) how and why mice respond differently if the mice express mouse PPARα versus human PPARα (and/or versus null mice). Studies by Felge *et al*. (2010) show that in mice expressing human PPARα the background levels of hepatocarcinogenesis are higher than in mice expressing mouse PPARα. Additionally, a high affinity PPARα ligand does not induce carcinogenesis in mice expressing human PPARα. The results demonstrate species differences and that mouse PPARα is required to induce carcinogenesis in response to PPARα ligand exposure.

Observations on study results seen in PPARα-null mice reveal that there is redundancy in physiology such that when one nuclear receptor (NR) is knocked out another may take up some of the role such that enzymes still get induced. However, enzyme induction is an associated event as an indicator of NR agonism and not a KE in the MOA to tumor response. Thus, some Committee members do not agree that chemically induced treatment effects in PPARα-null mice indicate other mechanistic considerations for the tumor response. One can see from the extensive work performed in the US EPA ToxCast program that many NRs are promiscuous and can interact with numerous ligands. However, for an intact organism with a full complement of genes, there tends to be a single NR that is primary over the others with a given agonist and MOA. However, other reviewers felt that there may be other mechanisms, but did not suggest any avenues to explore.

Recommendation: Given that using human-relevant rodent models continues to raise questions about how the evidence is used to conclude and justify an MOA and its human relevance, Section 4 should be expanded to include a more robust discussion of the topics raised in Point 1 and Point 2 above, incorporating studies on other chemicals to provide enhanced perspective on the DINP studies.

Section 3.2 would benefit from the inclusion of additional human epidemiology studies which examine the relationship between exposure to *any* PPARα agonist and cancer (e.g., Bonavas *et al*. (2012) and Tan *et al*. (2021)).

Alternative Opinions/ Clarifying Comments

While most of the Committee members agreed with the agency's conclusion that the weight of scientific evidence supports the PPARα activation MOA for liver tumors in rats and mice, a few felt there was inadequate consideration given to epidemiologic evidence. One multi-study meta-analysis is described in some detail in the panel's comments above and Recommendation 2 makes the point that inclusion and evaluation of additional epidemiology studies which examine the relationship between exposure to *any* PPARα agonist and cancer would strengthen the analysis.

Also, as one Committee member noted, many of the existing epidemiology studies focus on MiNP as a biomarker of DINP exposure. It would be helpful if the cancer hazard document included clear statements as to whether it has been shown if it is the parent or (a) metabolite(s) or both that is/are the active principal(s) in this MOA. At the present time, DINP toxicokinetics are addressed only in the non-

cancer hazard assessment document. In this case, it is appropriate to note and present the relevant toxicokinetics information as an early step in an MOA/adverse outcome pathway analysis, usually before the identification of the MIE, in this case, PPARα activation.

One Committee member suggested that EPA review Smith *et al*. (2016) to evaluate their approach to how key characteristics of carcinogens could be used in organizing data to describe a mode/mechanism of action and use this information to support the argument, in this case, that the PPARα MOA supports quantification using a threshold approach. Figure 2 from Cohen *et al*., (2019) below shows where EPA did incorporate consideration of the KCs in their assessment. However, it would have been more transparent and useful if the document were to include such a figure which lays out visually where relevant elements of the carcinogenic response via the PPARα MOA would fit as was done, for instance, in Corton, *et al*. (2018). The Committee recommends that EPA include such a visual in the document. See Figure 2 below.

The key characteristics (KC) that Smith *et al*. (2016) present in their paper are not always transferable to serve as Key Events in the determination of a mode of action and cannot be plugged in, unexamined, as a substitute for them. Simply because an agent happens to check off a KC box does not mean the agent will cause the adverse endpoint of concern that is being examined. One needs to have adequate dose response data which evaluate known element(s) of a KC. If the study(ies) yield results showing a directional change, either upwards or downwards , then incorporation of that information into an MOA analysis must be done in accordance with specific Bradford-Hill criteria, among which is fitting into the right place at the right time in the pathway (MOA) that is known to lead to the adverse effect of concern, in this case for DINP, liver tumors. If the data do not meet the Bradford-Hill criteria, their value is questionable. If the results are negative, in other words, showing no directional changes, that would indicate that that KC is not a factor in the MOA being examined.

One Committee member provided an example of the complexities and challenges Inherent in conducting a MOA/human relevance analysis, stating "In section 4.1.5, EPA discusses the relationship between DINP and oxidative stress *in vivo* in animal models and in *in vitro* models, but neglects the epidemiologic evidence on DINP and oxidative stress *in vivo,* (van'T Erve *et al*., 2019). The authors found that a statistically-significant relationship existed between DINP and key oxidative stress biomarkers – including 8-isoprostanes, which are known to activate PPARs, affecting different pathways ultimately leading to different dose-response curves." Thus, they are affecting (a) different pathway(s) leading to different dose-response curve(s) and (a) different potential adverse outcome(s).

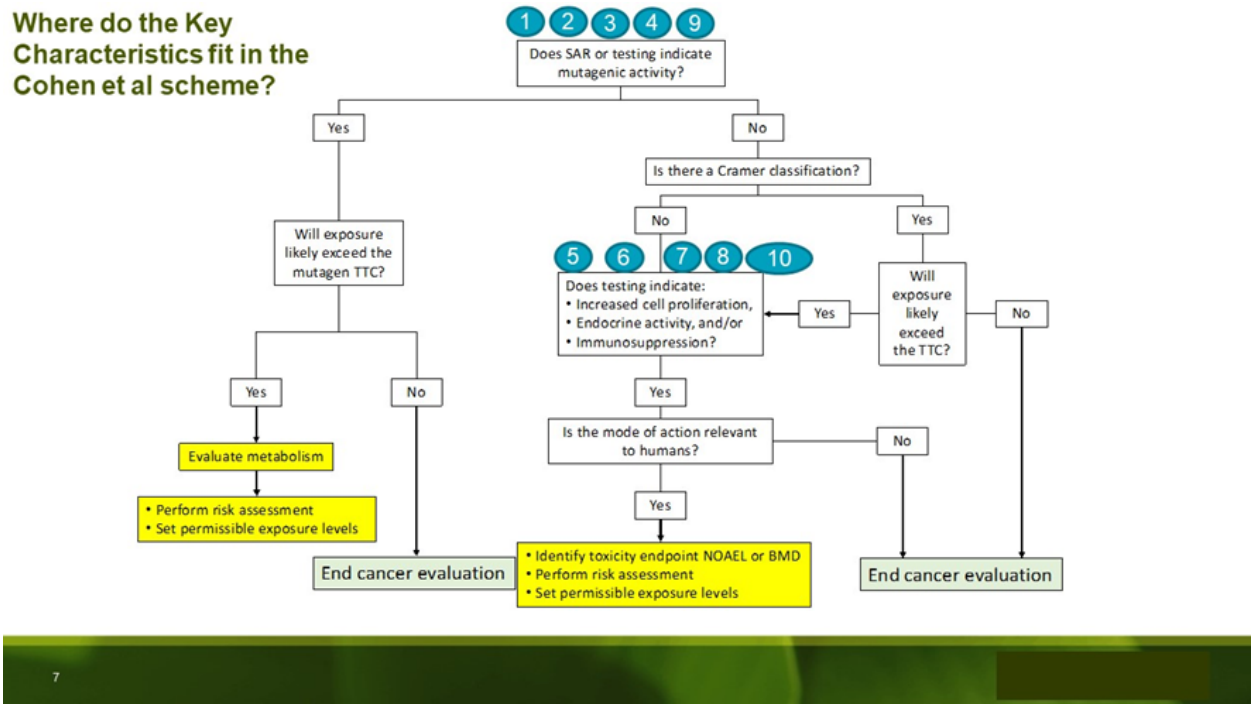

Figure 2. Overview of suggested carcinogenic assessment process (Cohen *et al*., 2019)

Harrison and Doe (2021) have recently published a paper that may shed some light on the current dilemma. They attempt to provide some perspective on where the KCs of cancer could fit in the risk assessment paradigm along with other well-established understandings of carcinogenicity.

The KCs that Smith *et al*. (2016) ascribe to a carcinogenic response are not unique only to that adverse outcome, as became apparent when some of the Smith *et al*. authors and others applied the approach to other endpoints of concern. There is significant overlap, as summarized in Table 3 below, with relevant reference citations. One would expect to see this overlapping pattern repeated as additional endpoints of concern are subjected to a similar analysis.

One can use the KCs to help with literature searches as well as to organize data to inform MOA analyses. However, as noted above, it is important to have dose-response data for the KCs to incorporate them into an explanation of their biological relevance to a carcinogenic outcome. How that might be done for DINP and the PPARα MOA is presented in Figure 2 above, adapted from Cohen *et al*. (2019). The figure shows very clearly how one can determine if, and where, a KC fits in (shown in the figure in the teal circles). The decision matrix supports a determination whether or not the agent produces the predicted adverse effect in a manner consistent with a known MOA and whether the outcome is relevant to human health. This is followed by a determination whether or not to derive a POD/HED in the form of a NOAEL/LOAEL or a BMD. If so, then one proceeds with an exposure and risk assessment which will assist in determining, along with non-risk factors, whether risk mitigation measures are warranted. Note: The decision matrix is equally useful in the assessment of non-cancer endpoints of toxicity (e.g., Seed *et al*. 2005; WHO IPCS, 2007).

Summary of Recommendations

- Section 4 would benefit from a more substantial discussion of species differences, structurally and functionally, in the behavior of the PPARα nuclear receptor itself.
- The Agency should provide a more robust discussion in Section 4 of the work that describes 1) species- specific differences in potency and efficacy of activation of PPARα and 2) how and why mice respond differently if the mice express mouse PPARα versus human PPARα (and/or versus null mice).
- Section 3.2 would benefit from the inclusion of additional human epidemiology studies which examine the relationship between exposure to any PPARα agonist and cancer.

Charge Question 2.e

As described in Section 4.8 of the Draft Cancer Human Health Hazard Assessment for DINP, EPA has preliminarily concluded that DINP is Not Likely to be Carcinogenic to Humans at doses below levels that do not result in PPARα activation and that the non-cancer chronic POD based on liver toxicity is appropriate. Please comment on the strengths and uncertainties of this preliminary conclusion.

General comments

EPA's 2005 Guidelines for Carcinogen Risk Assessment include a discussion of the weight-of-evidence (WOE) narrative to be included in all agency cancer hazard assessments. A WOE narrative is a short summary of the detailed analysis conducted for the agent under evaluation "that explains the agent's human carcinogenic potential and the conditions that characterize its expression." The guidelines go on to state "The weight of the evidence should be presented as a narrative laying out the complexity of information that is essential to understanding the hazard and its dependence on the quality, quantity, and type(s) of data available, as well as the circumstances of exposure or the traits of an exposed population that may be required for expression of cancer."

A WOE narrative also includes the selection of a descriptor that summarizes the EPA's conclusions about the agent's human carcinogenic potential. In the March 2024 *Draft Cancer Human Health Hazard Assessment for Diisononyl Phthalate (DINP),* the relevant text is found in Section 4.8 Weight of Scientific Evidence: Cancer Classification and Section 4.9 Human Relevancy.

EPA's preliminary determination is that the descriptor should be "*Not Likely to be Carcinogenic to Humans* at doses below levels that do not result in PPARα activation (KE1)." The majority of the committee agreed with the portion of the EPA's preliminary determination that the descriptor should be "*Not Likely to be Carcinogenic to Humans*," but disagreed with the inclusion of the phrase "at doses below levels that do not result in PPARα activation (KE1)." This infers that DINP *is* likely to be carcinogenic to humans at doses *above* levels that do activate PPARα. The Committee's disagreement with EPA is based, in good measure, on the preponderance of the evidence that PPARα activation in the human does not trigger, at any dose, the obligatory key events that would lead to the liver tumors observed in rodents. However, a few members of the Committee agreed with EPA that the inclusion of the phrase "at doses below levels that do not result in PPARα activation" was appropriate.

Table 3. Overlap of the key characteristics (KC) of cancer with non-cancer endpoints of toxicity

Endpoint of concern:	Cancer[a]	Cardiovascular Disease[b]	Endocrine Disruption[c]	Female reproductive effects[d]	Hepatotoxicity[e]	Immunotoxicity[f]	Male reproductive effects[g]	Aging[h]
Key Characteristics:								
1. Electrophilic or can be metabolically activated	X							
2. Genotoxic	X			X			X	
3. Alters DNA repair/ causes genomic instability	X							X
4. Induces epigenetic alterations	X		X	X			X	X
5. Induces oxidative stress	X	X		X	X		X	
6. Induces chronic Inflammation	X	X					X	
7. Is immune-suppressive	X			X	X			
8. Modulates receptor-mediated effects: - Agonism - Antagonism - Expression	 X X X		 X X X					
9. Causes immortalization	X							
10. Alters cell proliferation, cell death or nutrient supply	X	X		X	X	X		

[a] Smith *et al*. (2016) [b] Lind *et al*. (2021) [c] La Merril *et al*. (2020) [d] Luderer *et al*. (2019) [e] Rusyn *et al*. (2021)
[f] Germolec *et al*. (2022) [g] Arzuaga *et al*. (2019) [h] Lopez-Otin *et al*. (2013)

In the EPA cancer guidelines section that expands upon the discussion of the "*Not Likely*…" descriptor, it states that this descriptor is appropriate for agents for which there is "convincing and extensive experimental evidence showing that the carcinogenic effects observed in animals are not relevant to humans." Most Committee members assessed this applies to be applicable to DINP because 1) the rat kidney tumors could be explained as occurring in accordance with the male rat specific alpha 2μ-globulin (α2μ-globulin) MOA; and thus are irrelevant to humans, 2) the Fischer rat MNCL tumors were determined to be inappropriate for predicting human cancer potential (see discussion of this tumor type under DIDP Charge Question 3b, and 3) the liver tumors seen in rodents also are not likely to be or are not relevant to humans for the reasons described below.

Beginning with Klaunig *et al*. (2003) which proposed a mode of action (MOA) for PPARα activation in rodents resulting in liver tumors as the case study in the application of the Mode of action/human relevance framework for the first time, followed by reviews, updates and refinements by, for instance, Peters *et al*. (2012), Corton *et al*. (2014), Felter, et. al. (2018) and Corton, *et al*. (2018), there is a body of convincing and extensive experimental and epidemiological evidence that the PPARα activation MOA for liver tumors in rodents is not operative humans. Therefore, humans are not responsive to the carcinogenic effects of PPARα activators. Thus, the observation of rodent liver tumors occurring following PPARα activation is not relevant when evaluating DINP's human carcinogenic potential.

This conclusion is further reinforced by Bonavas *et al*. (2012) which describes a meta-analysis of 17 randomized controlled trials (RCTs) involving nearly 45,000 participants treated with drugs in the fibrate chemical class which are PPARα activators that lower cholesterol and triglycerides and can help protect from heart disease, heart attack, and stroke. The follow-up period averaged 5.2 years. The authors observed that the quantitative synthesis of data retrieved from the RCTs was not indicative of a fibrate effect on cancer incidence or death. They also found no evidence of differential effects by length of follow-up or type of fibrate. The authors concluded that fibrates have a neutral effect on cancer outcomes, which include those in the liver. "In summary, fibrate drugs have been on the market since 1977 without an apparent increase in liver cancer in people taking them chronically."

In conclusion, the majority of the committee recommends that it would be more appropriate to say that DINP is "*Not Likely to be Carcinogenic to Humans*."

Most of the committee members supported the position, given that there is no reason to conduct any dose response assessments for any tumor-related key events or endpoints, as related to the rat kidney, MNCL or liver tumors, the POD/HED determined from data representing human-relevant non-cancer endpoints of concern is the appropriate one to use going forward when deriving risk estimates and making unreasonable risk determinations.

Alternative opinions and clarifying comments

Most committee members thought that the agency did provide significant and relevant information, seemingly all that exists for DINP in Section 4.1 and its subsections, Section 4.2, Section 4.3, Section 4.4, Section 4.5 and Section 4.6. A detailed discussion of Uncertainties and Limitations is found in Section 4.7 and Section 4.8 includes a brief summary of the WOE in bullet points. The length of the WOE summary is intentional as it is required to be included in every cancer hazard assessment that the agency conducts. As EPA's cancer guidelines state, "the narrative is to be a short summary of the detailed analysis completed for the agent under evaluation that explains the agent's human carcinogenic potential and

the conditions that characterize its expression" and is "to include the selection of a descriptor that sums up the agency's conclusions about the agent's human carcinogenic potential." The committee did make the recommendation in its response to charge question 2.d, that the analysis in Section 4 would benefit from inclusion of a discussion of relevant material on other PPARα activators.

It would be worthwhile if EPA were to enhance Section 4.9 Human Relevancy with a more detailed summation of information supporting the agency's decision on this question, rather than simply referring to other parties' efforts without providing any detail of their decision logic.

With regard to one committee member's comment that EPA does not "appear to make any sort of connection between how the evidence from animal models could be translated to human studies.," that, too, was addressed in the committee's response to DINP charge question 2d. Recommendation 4 (listed below) states that "Section 4 would benefit from a more substantial discussion of species differences, structurally and functionally, in the behavior of the PPARα nuclear receptor itself." This is the pivotal question for this assessment. Activation of it (the PPARα receptor) in rodents may lead to liver tumors via the described MOA. Activation in humans does not, based upon the available epidemiology studies which explored the relationship between exposure to PPARα agonists and cancer outcomes. (See e.g., Bonavas *et al*. (2012) and Tan *et al*. (2021)).

Recommendations

1. The majority of the committee members support a revision of the cancer classification to "*Not Likely to be Carcinogenic to Humans."*
2. Section 4 would benefit from inclusion of a discussion of relevant material on other PPARα activators (a recommendation also made in the response to DINP charge question 2d).
3. Section 4.9 Human Relevancy should be enhanced with a more detailed summation of information supporting the agency's own decision on this question, rather than simply referring to other parties' efforts without providing any detail of their decision logic.
4. Section 4 would benefit from a more substantial discussion of species differences, structurally and functionally, in the behavior of the PPARα nuclear receptor itself (a reprise of the recommendation made in the response to DINP charge question 2d).
5. The analysis would be made more robust if there were the inclusion of additional human epidemiology studies which examine the relationship between exposure to *any* PPARα agonist and cancer, not just DINP.

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