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Office of Chemical Safety and
Pollution Prevention

Summary of and Response to External Peer Review on the Risk Evaluations and Technical Support Documents for Di(2-ethylhexyl) Phthalate (DEHP), Dibutyl Phthalate (DBP), Butyl Benzyl Phthalate (BBP), Diisobutyl Phthalate (DIBP), Dicyclohexyl Phthalate (DCHP), and Diisononyl Phthalate (DINP)

CASRNs: 17-81-7 (DEHP), 84-74-2 (DBP), 85-68-7 (BBP), 84-69-5 (DIBP), 84-61-7 (DCHP), 28553-12-0 (DINP), 68515-48-0 (DINP)

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KEY ACRONYMS AND ABBREVIATIONS

AOP	Adverse Outcome Pathway
ATSDR	Agency for Toxic Substances and Disease Registry
BBP	Butyl Benzyl Phthalate (or Benzyl Butyl Phthalate)
BMD	Benchmark Dose
BMDxx,	BMD at the xx% response level
BMDL	Benchmark Dose (lower confidence) Limit
BMDS	Benchmark Dose Software
BMR	Benchmark Response
bPOD	Benchmark (or Biological) Point of Departure
CBI	Confidential Business Information
CDR	Chemical Data Reporting
CEHD	Chemical Exposure Health Data
CEM	Consumer Exposure Model
CoC	Concentration of Concern
COU	Conditions Of Use
CQ	Charge Question
CRA	Cumulative Risk Assessment
DBP	Dibutyl phthalate
DCHP	Dicyclohexyl phthalate
DEHP	Di(2-ethylhexyl) phthalate
DIBP	Diisobutyl phthalate
DIDP	Diisodecyl phthalate
DINP	Diisononyl phthalate
DMR	Discharge Monitoring Reporting
DBP	Di(n-butyl) phthalate
ECHA	European Chemicals Agency
ECOTOX	Ecotoxicology
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
F2	Second filial generation
HC	Hazard Concentration
HC05	Fifth centile hazard concentration
HEC	Human Equivalent Concentration
HED	Human Equivalent Dose
HESI	Health and Environmental Sciences Institute
ICSI	Intracytoplasmic Sperm Injection
IVF	in vitro Fertilization
LC50	Lethal Concentration 50%
LOAEC	Lowest-Observed-Adverse-Effect-Concentration
LOAEL	Lowest-Observed-Adverse-Effect-Level
LOEC	Lowest-Observed-Effect-Concentration
MATC	Maximum Acceptable Threshold Concentration
MCOP	Monocarboxyisooctyl Phthalate
MEHP	Mono-2-ethylhexyl phthalate
MOE	Margin of Exposure
mPOD	Metabolomic Point of Departure
MSDS	Material Safety Data Sheet
NAM	New Approach Methodologies

NASEM	National Academies of Sciences, Engineering, and Medicine
NEI	National Emissions Inventory
NHANES	National Health and Nutrition Examination Survey
NLM	National Library of Medicine
NOAEC	No-Observed-Adverse-Effects-Concentration
NOAEL	No Observed Adverse Effects Level
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level
NPDES	National Pollutant Discharge Elimination System
OECD	Organisation for Economic Co-operation and Development
OES	Occupational Exposure Scenario
OPP	Office of Pesticides Program
OPPT	Office of Pollution Prevention and Toxics
ORD	Office of Research and Development
OSHA	Occupational Safety and Health Administration
PACT	Pancreatic Acinar Cell Tumor
PBPK	Physiologically Based Pharmacokinetic
PESS	Potentially Exposed or Susceptible Subpopulation(s)
PNOR	Particulates Not Otherwise Regulated
POD	Point of Departure
PPAR	Peroxisome Proliferator-Activated Receptor
PV	Production Volume
RAGS	Risk Assessment Guidance for Superfund
ReCAAP	Rethinking Chronic Toxicity and Carcinogenicity Assessment for Agrochemicals Project
ROS	Reactive Oxygen Species
RPF	Relative Potency Factor
SACC	Science Advisory Committee on Chemicals
SSD	Species Sensitivity Distributions
tPOD	Transcriptomic or Toxicogenomic Point of Departure
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TSD	Technical Support Document

1 INTRODUCTION

Below are the detailed committee discussions and recommendations by the 2025 Science Advisory Committee on Chemicals (SACC) review of High Priority Phthalates, followed by EPA response.

On January 7, 2025, EPA sought public comment on the draft risk evaluation of DCHP (90 FR 1125 (FRL-12481-01)). On June 5, 2025, EPA sought public comment on the draft risk evaluation of DBP and DEHP (90 FR 23931 (FRL-12808-01-OCSPP)). On August 6, 2025, EPA sought public comment on the draft risk evaluation of BBP and DIBP (90 FR 14882 (FRL-12897-01-OCSPP)). A preparatory virtual public meeting was held on July 21, 2025, for reviewers and the public to comment on and ask questions regarding the scope and clarity of the draft charge questions for the Science Advisory Committee on Chemicals (SACC). On August 4–8, 2025, the SACC conducted an external peer review of the draft risk evaluations for DBP, DCHP, and DEHP, as well as the hazard assessments for BBP and DIBP (90 FR 24400 (FRL-12418-02-OCSPP)). Materials on the draft risk evaluations and other supporting documents, and public comments are available at www.regulations.gov in the dockets:

- BBP Docket: EPA-HQ-OPPT-2018-0501;
- DBP Docket: EPA-HQ-OPPT-2018-0503;
- DCHP Docket: EPA-HQ-OPPT-2018-0504;
- DEHP Docket: EPA-HQ-OPPT-2018-0433;
- DIBP Docket: EPA-HQ-OPPT-2018-0434;
- 2023 SACC Meeting Docket: EPA-HQ-OPPT-2022-0918; and
- 2025 SACC Meeting Docket: EPA-HQ-OPPT-2024-0551.

This document summarizes the SACC comments that the EPA's Office of Pollution Prevention and Toxics (OPPT) received for the draft risk evaluations of BBP, DBP, DCHP, DEHP, and DIBP including all technical support documents (TSDs) and supplemental files in EPA-HQ-OPPT-2024-0551. In addition, this document provides EPA/OPPT's response to the comments received from the SACC peer reviewers. Throughout the Section 2 Summary of *SACC Comments Organized by Charge Questions*, readers will see items labeled "SACC Recommendation," "SACC Comment," and "SACC Request for Minor or Editorial Comment." These sections of text are direct quotes from the SACC report. Regarding responding to peer review comments, this response to comments focuses generally on the main bulleted recommendations provided by the SACC. The bulleted recommendations, generally, represent the most important consensus comments from the peer reviewers. Nevertheless, throughout the individual risk evaluations, EPA has considered and appropriately addressed all the comments raised by the peer reviewers and public commenters.

Stakeholder and public comments received to the SACC meeting docket (EPA-HQ-OPPT-2024-0551) and responses to those comments, which includes comments received during public comment for BBP, DBP, DCHP, DEHP, and DIBP, are summarized in a separate document titled *Response to Public Comments on the Draft Risk Evaluations for Butyl Benzyl Phthalate (BBP); Dibutyl Phthalate (DBP); Dicyclohexyl Phthalate (DCHP); Diethylhexyl Phthalate (DEHP); and Diisobutyl Phthalate (DIBP)*. The separate response to public comment document includes summaries of all received comments as well as EPA's responses to received public comments. The consolidated response to public comments document has been added to the SACC meeting docket (EPA-HQ-OPPT-2024-0551) as well as each individual chemical docket: BBP (EPA-HQ-OPPT-2018-0501) , DBP (EPA-HQ-OPPT-2018-0503), DCHP (EPA-HQ-OPPT-2018-0504), DEHP (EPA-HQ-OPPT-2018-0433), DIBP (EPA-HQ-OPPT-2018-0434).

EPA/OPPT appreciates the valuable input provided by the public and peer review. The input resulted in revisions to the draft risk evaluations of BBP, DBP, DCHP, DEHP, and DIBP.

2 Summary of SACC Comments Organized by Charge Questions

The High Priority Phthalates SACC recommendations and responses are summarized in the subsections below. The SACC meeting minutes and final report are located at https://www.regulations.gov/document/EPA-HQ-OPPT-2024-0551-0167

2.1 Charge Question 1

For DCHP, EPA relied on data from several sources to derive water solubility estimates, as described in Section 2.4.8 of the *Draft Physical Chemistry, Fate, and Transport Assessment for DCHP*. EPA is requesting feedback on the weight of the scientific evidence approach describing the water solubility range for DCHP and the use of a single value as input to exposure models.

2.1.1 SACC Recommendations and EPA Responses (Charge Question 1)

1. **SACC Recommendation:** EPA should provide detailed justifications for selecting or excluding property data and clearly document the rationale for prioritizing some numbers over alternative values.

   EPA Response: EPA included justifications for the selection or exclusion of proprietary data within the TSD and as described in the Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP) (U.S. EPA, 2025).

2. **SACC Recommendation:** EPA should conduct a systematic quality review of data sources (especially for water solubility data) with careful scrutiny of the appropriateness and applicability of the test methods.

   EPA Response: EPA reviewed the available data sources as described in the Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP) (U.S. EPA, 2025). During this process the available data sources are screened and evaluated to select the most relevant evidence for inclusion in the assessment. This includes a framework used to formulate criteria about those characteristics that should be present in the data or information source in order to be eligible for inclusion or exclusion in the review. EPA includes data or information sources that identify measured or estimated physical and chemical properties or endpoints under standard conditions for the chemical substance of interest, including mixtures of isomers as appropriate. Highly theoretical studies are excluded from further consideration. Upon meeting screening criteria during full-text screening, data or information sources then undergo data quality evaluation and extraction. During this process the information obtained from data sources is carefully evaluated based on the appropriateness and applicability of the test methods, experimental and analytical conditions, and expert judgement.

3. **SACC Recommendation:** EPA should perform a sensitivity analysis using a solubility range of 0.03–4 mg/L for DCHP in exposure models to assess impacts on exposure outcomes and avoids reliance on a single, inadequately justified value.

   EPA Response: EPA selected a DCHP water solubility range of 0.03 mg/L to 1.48 mg/L. EPA used the upper bound solubility value in the exposure models. EPA selected the use of the upper bound water solubility value as a reasonable and responsive approach based on the SACC recommendation that best protects human health and the environment.

4. **SACC Recommendation:** EPA should evaluate DCHP's water solubility in conjunction with related properties (*e.g.*, vapor pressure, HLC) using thermodynamic relationships.

   EPA Response: EPA currently implements an alternative approach to those recommended by SACC. For example, for DCHP EPA used the WSKOWWIN model to estimate DCHP's water solubility. WSKOWWIN is a model within EPISuite. The model estimates water solubility values from K_{OW} values, molecular weight, and melting points using two QSPR models developed with 1450 training compounds and externally validated on 817 compounds. The estimated water solubility values were used for the validation and justification of selected values.

5. **SACC Recommendation:** EPA should correct scientifically incorrect language about volatility, trophic transport, and partitioning behavior.

   EPA Response: EPA revised the scientifical language describing DCHP volatility, trophic transport, and partitioning behavior as recommended by SACC.

6. **SACC Recommendation:** In the absence of robustly measured phthalate concentrations in US waters, EPA should include measured water quality data from other countries.

   EPA Response: EPA included US and international monitoring information as reasonably possible. The available data sources obtained during the systematic review process contained monitoring information from the US and other countries. This information is discussed in section 3.4.2.1 of the DCHP Physical Chemistry and Fate and Transport Assessment. As described in this TSD, the international studies support that DCHP may be present in surface water, but the specific values may not be a viable direct comparison to the United States. Detail information about these studies is included in Appendix B.3 of the TSD.

7. **SACC Recommendation:** The EPA should correct the cited value of 1.04 mg/L to 1.01 mg/L, consistent with the original data from the European Chemicals Agency (ECHA) registration dossier and the EC/HC (2017) report.

   EPA Response: EPA has corrected the cited water solubility value to 1.01 mg/L in the DCHP Physical Chemistry and Fate and Transport Assessment.

2.1.1.1 SACC Minor or Editorial Comments and EPA Responses (Charge Question 1)

1. **SACC Comment:** As a comparison, the *Draft Chemistry, Fate, and Transport Assessment for Butyl Benzyl Phthalate* (Section 2.2.6 "Water Solubility," provides the uses of the water solubility value. It would be helpful to repeat the information about uses of the water solubility value in the *Draft Physical Chemistry, Fate, and Transport Assessment for DCHP*. For example, water solubility is used in understanding fate and transport of BBP in the environment, but also when modeling for industrial processes, engineering, human and ecological hazard, and exposure assessments.

   EPA Response: EPA has included the recommended descriptive language for all relevant endpoints as presented in the *Final Chemistry, Fate, and Transport Assessment for BBP.* This language has been adopted in the corresponding Chemistry, Fate, and Transport Assessments for DCHP, DBP, DIBP, and DEHP.

2. **SACC Comment:** Section 2.4.8 of the *Draft Physical Chemistry, Fate, and Transport Assessment for DCHP* states, "Co-solvation such as that demonstrated in Hollifield may allow for the entry of phthalates into surface water and ground water at otherwise achievable concentrations." Since the water solubility of 4.0 mg/L is not used based on justification from EPA, a question arises about whether this sentence is appropriate for this section; if the EPA determines so, it should be clarified. Also, the word "achievable" seems to be "unachievable" based on this sentence's meaning.

   EPA Response: EPA selected 0.03 to 1.48 mg/L as the applicable water solubility range for DCHP solubility in water for use in the draft risk evaluation. EPA has revised the language to clarify that DCHP surface water and groundwater concentrations closer to the upper range of reported water solubilities could be possible. EPA recognizes that concentrations closer to the upper range are not likely to occur in the environment, based on environmental monitoring data, but is suitable for screening purposes.

3. **SACC Request for Minor or Editorial Comment:** Section 2.4.8 of the *Draft Physical Chemistry, Fate, and Transport Assessment for DCHP* states, "the true solubility of DCHP may be lower than the 1.48 mg/L, with concentrations in the environment expected to be lower based on environmental monitoring data." However, no such "environmental monitoring data" were included in the SACC review package.

   EPA Response: EPA has included the citation containing the monitoring data. This information is discussed in section 3.4.2.1 of the Final Chemistry, Fate, and Transport Assessment for DCHP. The data source reported the presence of DCHP in seawater samples with column concentrations of up to 15 ng/L DCHP in samples collected in Puget Sound, WA and Barkley Sound, BC.

4. **SACC Request for Minor or Editorial Comment:** In Section 3.4.2.1, the EPA wrote that DCHP "may be released to surface water from TSCA conditions of use (COUs) but is generally released in low quantities It then points to the Environmental Releases in the *Draft Environmental Release and Occupational Exposure Assessment* document), which, however, does not contain such data related to releases.

   EPA Response: Information related to DCHP releases to surface water is discussed in section 3 of the *Environmental Release and Occupational Exposure Assessment* document.

5. **SACC Request for Minor or Editorial Comment:** Properties such as flashpoint, viscosity, and refractive index are irrelevant to this review and should be consolidated into a brief section.

   EPA Response: EPA is retaining the flashpoint, viscosity, and refractive index information as it might be relevant to alternate assessments.

2.2 Charge Question 2

In the ecological hazard characterization described in Sections 4 and 5.1 of the *Draft Environmental Hazard Assessment for DEHP*, EPA determined the avian hazard value based on an egg injection study employing a single dose resulting in a lowest observed adverse effect level (LOAEL) of 100 mg/kg (Abdul-Ghani, 2012). This LOAEL was based on a behavioral change, a decrease in imprinting preference scores, in the newly hatched chicks (14 to 24 hours old). For the risk characterization, EPA

determined risk by comparing the avian hazard value to exposure levels in eggs from monitoring studies. Specifically, Schwarz *et al*. (2016) collected samples from failed peregrine falcon (Falco peregrinus) eggs within Germany as part of a large survey of pollutants. Concentrations of DEHP within peregrine falcon eggs were reported as "traces of DEHP" with no quantitative concentration values (limit of detection = 0.001 mg/kg dw). A more comprehensive study on environmental pollutants within egg samples was conducted on seabird species within coastal Norway (Huber *et al*. 2015). Concentrations of DEHP of 0.011 to 0.024 mg/kg ww for the European herring gull (*Larus argentatus*), and 0.003 to 0.042 mg/kg ww for the European shag (*Phalacrocorax aristotelis aristotelis*) were reported in pooled eggs samples (Huber, 2015). These measured phthalate concentrations found in the wild bird populations are four orders of magnitude lower than that used in the laboratory administered injection treatment of 100 mg/kg DEHP in chicken eggs (Abdul-Ghani, 2012). Please comment on the strengths and uncertainties of this avian hazard value, including relevance and proposed screening approach for quantitative risk characterization.

2.2.1 SACC Recommendations and EPA Responses (Charge Question 2)

1. **SACC Recommendation:** Given the confidence in the data produced in the Abdul-Ghani *et al*. (2012) study, other technical studies using an egg injection approach should be utilized to determine the LOAEC based on evidence of damage to physiological and endocrine systems across a range of physiological and molecular markers. More recent studies also more completely explain physiological mechanisms of action that stem from DEHP exposure and provide more precise data for estimating hazard and risk to birds and other wildlife.
2. **SACC Recommendation:** Additional measurement end points should be considered based on the Abdul-Ghani *et al*. (2012) study and from other studies, given that egg injection experiments provide valuable information on the administration of known concentrations and for assessing potential risk and hazard from exposures to wild birds.
3. **SACC Recommendation:** Consider 10 mg DEHP/kg or lower as the LOAEL and 5 mg/kg as the NOAEL for increased developmental defect rate in the Abdul-Ghani *et al*. (2012) study. A geometric mean of 5 and 20mg/kg may be an appropriate avian hazard value based on Abdul-Ghani *et al*. (2012), but it is also critical to note that the developmental malformations of the abdominal organs observed in this study constitute a severe, gross, endpoint. If an adverse outcome pathway were available for this finding, it is nearly certain that initiating events would be seen at much lower doses.

   EPA Response to Recommendations 1–3: The risk evaluation has been updated with language and justification for the modified avian hazard threshold value. The study used for avian hazard threshold determination was from Abdul-Ghani (2012) and the hazard threshold was revised and based on developmental malformations including gastroschisis and omphalocele in the chicken from pre-hatch single dose egg injections into the albumen of 0, 5, 20, 50, and 100 mg DEHP resulting in a no-observed-adverse-effect-level (NOAEL)/LOAEL of 5/20 mg/kg of egg from the resulting DEHP injected into the albumen of the egg. Although it was recommended to perform benchmark dose (BMD) modeling on the data from Abdul-Ghani (2012), EPA has derived an avian hazard threshold of 10 mg/kg of egg from the geometric mean of the NOAEL/LOAEL. This hazard threshold has been added to the list of environmental hazard thresholds for DEHP and integrated into the Environmental Risk Characterization for Terrestrial Species (Section 5.3.3) for the Final Risk Evaluation for DEHP.

4. **SACC Recommendation:** EPA should reassess the data in the Abdul-Ghani paper relative to additional measures and current findings of molecular and system level adverse effects and use these data to develop an avian hazard value and to characterize avian risk.
5. **SACC Recommendation:** For reasons of severity of the endpoint, 5mg/kg may be more appropriate and an adjustment factor for severity should be utilized. Alternatively, modeling the dose response trend in developmental malformations could be done to find a POD, but, again, due to severity, some adjustment is appropriate.
6. **SACC Recommendation:** Reconsider the use of the Wood and Bitman (1980) data, with a reasonable estimate of food intake based on the graphically presented data.

EPA Response to Recommendations 4–6: Additional supporting studies have been introduced to the *DEHP Environmental Hazard Assessment* to further characterize the effects of DEHP on avian species via the oral route. Four avian based feeding studies on quail with chronic duration exposures of DEHP span cardiac (Wang et al. 2019), kidney (Wang et al. 2020), intestinal (Yang et al. 2022), and ovarian (Ma et al. 2024) organ systems. The supplemental information provide within Wang et al. (2020) indicates that dose regimes were conducted at non-lethal concentrations designed to specifically elicit possible target organ effects from chronic oral doses of 250, 500, and 750 mg/kg-day. Among these studies, authors report few apical level impacts (*i.e.*, survival, growth, reproduction, etc.) but do report mechanistic endpoints, however, the lowest concentration in all the studies is 250 mg/kg-day, with no lower DEHP concentrations between that and control treatments.

The effects of DEHP on cardiac histology, heat shock proteins, and heat shock transcription factors within juvenile male quail were investigated at 0, 250, 500, and 750 mg/kg-day via gavage for 45-days (Wang et al., 2019). At the end of the treatment period, histology indicated cardiac muscle fiber dilation (expansion) and cell necrosis which was accompanied by myocardial disorganization at the 500 and 700 mg/kg-day treatment groups. Abnormal myocardial cells were seen in the 500 mg/kg-day group, with authors indicating severe myocardial injury induced from DEHP exposure at this dose. Authors did not report the sample size of representative histology slides examined and did not report if one or two people scored the slides (Table S2). The NOAEL and LOAEL were less than 250 and 250 mg/kg-day, respectively, based on effects on swelling and dilation of cardiac cells (Wang et al., 2019).

Another study by the same laboratory evaluated the effects of DEHP nephrotoxicity on juvenile female quail at concentrations of 0, 250, 500, and 1000 mg/kg-day via gavage for 45-days (Wang, 2020). At the end of the treatment period, histological changes occurred at all concentrations including a disorganized renal structure, a partially dilated glomerulus, renal interstitial congestion, and an atrophied Bowman's space. Renal tubular epithelial cells were unclear, and the study authors observed swelling of columnar epithelial cells. Similar to Wang et al. (2019), sample size for the histopathological analysis and observer details were not described (Table 1). Cytochrome P450 (CYP450) activity was significantly affected for different types (increased or decreased expression) (Wang et al., 2020). These studies on Japanese quail indicate an unbounded LOAEL of 250 mg/kg, but given the effects are subapical, the NOAEL is likely not much lower.

Apical reproductive and growth endpoints are presented within a study on DEHP impacts to ovarian development (Li et al. 2020) administered by oral DEHP exposures to quail from 15 to 60 days of age and followed similar DEHP treatment concentrations to Ma et al. (2024). Li et al.

(2020) reported no significant differences between control treatments and the 250 mg/kg treatment with mean age of first egg laying at approximately 45 days as compared to significant delays for the 500 and 1000 mg/kg treatments (Figure 1b). Mean body weight was recorded for all treatment groups at 5-day intervals with no significant differences observed between treatment controls and the 250 mg/kg-day DEHP treatment (Li et al. 2020). Although ovary weight for the 250 mg/kg-d treatment was not significantly different from controls, the resulting gonadosomatic index (coefficient of body and ovarian weight) was significantly different from control groups. Similarly, although ovarian histology showed no significant difference in the thickness of the granulosa cell layer, authors reported the numbers of primordial and perivitelline follicles were greater in DEHP treatments compared to control. Potentially limited with a sample size of four, serum concentrations of hormones associated within ovarian development indicated significant differences in luteinizing hormone and estradiol with no significant differences in testosterone, follicle stimulating hormone, prolactin, and progesterone for the 250 mg/kg-day treatment group compared to controls. Like previously described studies within quail, the evidence from Li et al. (2020) demonstrates an unbounded LOAEL of 250 mg/kg-day.

In both Wang et al. studies, the NOAEL/LOAEL were <250/250 mg/kg-day based on swelling and dilation of cardiac cells (Wang, 2019), and disorganized renal structure, a partially dilated glomerulus, renal interstitial congestion, and an atrophied Bowman's space (Wang, 2019). Apical and mechanistic endpoints examined within Li et al. (2020) similarly indicate a NOAEL/LOAEL of <250/250 mg/kg-day for DEHP. These studies further characterize the effects of DEHP on avian species. The terrestrial mammalian hazard threshold was derived from the NOAEL/LOAEL of 48.58/140.15 mg/kg-day (based on a decrease in pup survival during lactation [Tanaka et al. 2002]), which resulted in a geometric mean of 80.79 mg/kg-day as the hazard value for terrestrial mammals. Although an oral avian hazard threshold has not been derived by EPA within the *Environmental Hazard Assessment for Diethylhexyl Phthalate (DEHP)* a hazard threshold was derived from pre-hatch DEHP egg injections in the chicken which resulted in developmental malformations including gastroschisis and omphalocele in the hatched chicks resulting in a NOAEL/LOAEL of 5/20 mg DEHP/kg of egg (Abdul-Ghani et al., 2012).

7. **SACC Recommendation:** EPA should consider DEHP and other cross-phthalate effects on physiological systems; many of these adverse effects are conserved across vertebrate species.

   EPA Response to Recommendation 7: The Wood and Bitman (1980) study examined the effects of DEHP on feed consumption, growth, and reproduction in the chicken (*Gallus gallus domesticus*), where individual animals were fed a single concentration of 1 percent DEHP (10,000 mg/kg feed) incorporated into their diet for 4 weeks. In the *Draft Environmental Hazard Assessment* TSD for DEHP the EPA did not calculate an achieve dose from the data presented in tables on hen weight and graphical representations of mean feed consumed per week. The *DEHP Environmental Hazard Assessment* has revised this to represent an approximate achieve dose for this study. Specifically, the graphical representation of mean feed intake (grams/hens/day; Figure 1) and mean final weight of treatment groups (Table 1) allowed for the derivation of the DEHP feeding dose of approximately 578 mg/kg-day for this 28-day study. Overall, feed consumption was significantly decreased by 10% compared to controls over the 4-week period. This effect was most prominent during the first 3 weeks of the study, whereby differences in mean feed consumption of the DEHP treated feed was 6, 20, and 9% at days 7, 14, and 21, respectively. Egg production in the DEHP treated group was reduced by 5 percent but was not significantly different from controls over the 4-week period with no differences in egg weight, percent

weights of shell, white or yolk. Although there was an increase in liver lipids and cholesterol in the DEHP treated group compared to controls, no significant effects were observed in chicken growth. Although this study demonstrated no significant differences in apical endpoints with an achieved feeding dose of 578 mg/kg-day, there are concerns with the potential role of food aversion confounding the administration of the DEHP treated feed. The details of the feeding dose and endpoints have been added to the *DEHP Environmental Hazard Assessment*.

8. **SACC Recommendation:** Consider that additional sources of phthalates, DEHP, and microplastics can enter the environment from consumer products and plastics in landfill leachate. Figure 1 captures some of the environmental sources and potential effects in birds.

   EPA Response to Recommendation 8: The *Environmental Media Concentrations, General Population, and Environmental Exposure Assessment for DEHP* performs a qualitative assessment of Landfills as a potential source of DEHP in the environment. This same TSD also presents revised information on DEHP within surface water and ground water from the EPA's Six-Year Review of Drinking Water Standards. DEHP has been measured in landfill leachate at concentrations ranging from 0.01 to 200 µg/L and in stormwater runoff from municipal landfills at concentrations ranging from 7 to 39 µg/L (IARC, 2013). DEHP is monitored at drinking water facilities across the U.S. since a national maximum contaminant level has been set for DEHP within drinking water by public water systems (U.S. EPA, 2025). The EPA's Six-Year Review of Drinking Water Standards from 2012–2019 includes 202,420 sample records from over 36,400 public water systems, ranging up to 52.2 µg/L DEHP detected in finished drinking water at a Pennsylvania facility sourcing surface water, and up to 130 µg/L at a Massachusetts groundwater facility. Although the proportion of microplastics contributing to monitored landfill leachate is unknown, concentrations of DEHP from landfill leachate and groundwater sampling indicate that this compound contributes to the unreasonable risk to the environment for aquatic species. Specifically, EPA determined that the disposal COU contributes to the unreasonable risk of DEHP to both aquatic vertebrates and sediment-dwelling invertebrates through both surface water and pore water. This risk determination is further supported with the concentrations of concern for DEHP indicating impacts to aquatic vertebrates and sediment dwelling aquatic invertebrates at 0.0032 µg/L and 0.03 µg/L, respectively.

   The revised Terrestrial Risk Characterization section within the DEHP Risk Evaluation performed a screening level trophic transfer analysis to examine DEHP concentrations and ingestion rates for a bird species with maximum DEHP concentrations within biosolid amended soils and resulting prey items. Estimated DEHP soil concentrations following application of biosolids are detailed within EPA's *Environmental Media and General Population and Environmental Exposure for DEHP*. Using the highest calculated topsoil concentration of 6.25 mg/kg following an agricultural application of biosolids on soybeans, EPA assumed 100 percent uptake by a worm, so that the concentration of DEHP in the earthworm is equivalent to the soil concentration. The role of DEHP within water versus DEHP within sediment and prey can be examined using a maximum DEHP concentration from a groundwater sample within the EPA's Six-Year Review of Drinking Water Standards. The EPA Wildlife Exposure Factor Handbook (U.S. EPA, 1993) provides an estimated water ingestion rate (g/g-day) is 0.10, which would result in a total daily intake of DEHP from water of 1.3×10^{-2} mg/kg-day with a maximum absorption fraction of 1 as a screening level assumption. The contribution of potential DEHP from water is significantly less than intake from DEHP contaminated prey and incidental soil ingestion. Using the insectivorous Woodcock as a representative species with a daily feed intake rate (FIR) of 0.77 and incidental soil intake rate (SIR) of 0.16 as wildlife exposure factors (U.S.

EPA, 1993) and assuming a 100% absorption fraction of that soil and the prey items (earthworms) resulted in a maximum daily concentration for oral uptake of DEHP of 6.22 mg/kg-day. This DEHP from soil and prey for the insectivorous bird is two orders of magnitude (~40 times) lower than concentrations resulting in subapical effects (250 mg/kg-day) from chronic feeding studies in Japanese qual (Wang et al. 2019; Wang et al. 2020) and one order of magnitude less than the DEHP mammal hazard threshold of 80.79 mg/kg-day from Tanaka et al. (2002).

2.3 Charge Question 3

Chronic hazard values for DEHP, as outlined in the *Draft Environmental Hazard Assessment for DEHP*, were identified for aquatic invertebrates and vertebrates. Among the high-priority phthalates currently under review, DEHP exhibits the highest chronic potency to aquatic organisms. Significant effects were observed, in fish exposed to chronic levels of DEHP, including reduced growth (in terms of length and weight) and decreased reproduction exhibited by specific effects such as reduced gonadal weight, lowered sperm motility, and fewer offspring (Chikae *et al*. 2004a; Chikae *et al*. 2004b; Zanotelli *et al*. 2010; Corradetti *et al*. 2013; Golshan *et al*. 2015). Similarly, chronic exposure to DEHP in invertebrates affected growth and reproductive endpoints (Sanders *et al*. 1973; Kwak and Lee, 2005; Heindler *et al*. 2017). The EPA selected no observed adverse effect concentration (NOAEC) and lowest observed effect concentration (LOAEC) values from the Chikae *et al*. (2004a, 2004b) studies as the most sensitive endpoints, though similar effect concentrations were noted in other fish studies. By using the geometric mean of NOAEC and LOAEC values and applying an assessment factor of 10, a concentration of concern (CoC) for chronic aquatic vertebrates was determined to be 0.0032 µg/L, which is below the detection limit for DEHP as reported by Liu *et al*. (*2014*). Please review and comment on the strengths and uncertainties of the methodology and data used to derive a chronic CoC for aquatic invertebrates and vertebrates.

2.3.1 SACC Recommendations and EPA Response (Charge Question 3)

1. **SACC Recommendation:** EPA should reference recent publications with newer technology for quantification of DEHP and other phthalates and note that sensitive methods can be used to quantify these compounds.

   Additional detail from SACC report narrative: Hong *et al*. (2024) used SSDs to determine HC5s for aquatic species exposed to multiple phthalates. The HC5 for HEDP was 1.05 µg/L. Hong *et al*. (2024) did not include data from Chikae *et al*. (2004a; 2004b). These data are still not in the ECOTOX database. This absence of data identifies a deficiency in the compilation of toxicity data in the ECOTOX database, which has traditionally been maintained by the EPA. This database comment goes specifically to the ability of EPA risk assessors to rapidly and effectively gather data that are needed for exposure, hazard, and risk evaluations. Lack of proper curation of such databases also diminishes the public's ability to readily and transparently access available toxicity data used in regulatory decisions.

   Additional detail from SACC report narrative: Data from Hong *et al*. (2024) included mortality as an endpoint. This data set was reevaluated by removing mortality data, converting all LOECs and MATC values to NOECs, and adding the Chikae chronic toxicity value of 0.032 µg/L, based on decreased body weight, with no assessment factor. The resulting species sensitivity distribution was placed into the EPA SSD toolbox and modeled without body allometric scaling. That process produced a best fit to the data with a logistic function and an HC5 of 159 ng/L (Figure 2). The predicted fifth centile Hazard Concentration (HC5) value for

this single regression is 0.159 µg/L (159 ng/L) and a standard error of 0.151 ug/L. A reasonable lower bound for hazard from this single graph would be 0.008 ug/L.

EPA Response: The SACC provided additional references to EPA on the detection capabilities of DEHP and the derivation of an HC05 using a species sensitivity distribution (SSD) for chronic aquatic hazard data. The two Chikae et al. (2004) papers are available within the ECOTOX Knowledgebase with ECOREF numbers of 95936 and 180986. EPA acknowledges the predicted fifth centile HC05 value of 0.159 µg/L with a reasonable lower bound hazard value of 0.008 µg/L. Compared to this probabilistic approach, EPA used a deterministic method to establish a hazard value (geometric mean) of 0.032 µg/L. When incorporating an assessment factor of 10, the resulting COC was 0.0032 µg/L. The resulting deterministic and probabilistic approaches for deriving a COC for chronic DEHP exposure in vertebrates are both the same order of magnitude. Within the final DEHP risk characterization, the EPA applied the previously derived COC for chronic exposure within aquatic vertebrates of 0.0032 µg/L.

2. **SACC Recommendation:** EPA should consider BMD modeling of Chikae *et al*. (2004b) data to determine POD. EPA should consider alternate computational approaches to deriving the CoC for chronic aquatic vertebrate hazard threshold.

   EPA Response: SACC provided EPA with an SSD that predicted the fifth centile Hazard Concentration (HC05) value for a single regression of 0.159 µg/L (159 ng/L) and a standard error of 0.151 ug/L with a lower bound of 0.008 ug/L using data from Hong et al. (2024), the Chikae chronic toxicity value of 0.032 µg/L, and converting all LOAEC and maximum acceptable threshold concentration (MATC) values to NOAECs. The SSD software also generated a list of fits to six functions with the Weibull model generating a highly significant prediction of 0.003 ng/L. The predicted HC05 using all model fits (weighted based on each model's goodness of fit) was 216 ± 186 ng/L (mean ± SE) and provides a "lower bound" of the mean at 30 ng/L.

   The SACC indicated the HC05 approach could be further refined with additional data from the second Chikae study (2004b) combining the HC05 estimate using the most sensitive species and an assessment factor, resulting in the MATC of DEHP between of 3.2 and 32 ng/L (with 3.2 ng/L being highly conservative). The method used by SACC to calculate a MATC using a probabilistic approach results in a lower bound of 0.0032 µg/L (3.2 ng/L). The EPA did not perform BMD modeling on data within Chikae et al. (2004) for a POD and represents the chronic aquatic vertebrate COC for DEHP with a ChV from the NOAEC and LOAEC with the application of an assessment factor (10). BMD modeling was not conducted for any of the chronic aquatic vertebrate studies showing definitive effects less than the limit of solubility. These studies reported effects on mortality, growth, reproduction and development at reported concentrations ranging 0.01 up to 3.0 µg/L. In both studies by Chikae et al. (2004a,b) a dose-response gradient was established using nominal concentrations of 0.01, 0.1, 1.0, and 10.0 µg/L with definitive NOAEC/LOAEC values established, representing effects of growth and development of embryo and fry of *O. latipes.* Given the diversity of effects and inconsistency of these effects between studies (e.g., the sexes affected for each endpoint), BMD modeling does not provide additional certainty in the response. Calculating the ChV from the NOAEC and LOAEC provides an estimate of hazard that considers the uncertainty in where the response occurs in the concentrations tested (i.e., where the effect may occur between the NOAEC and LOAEC).

The values generated by the SACC using SSDs/refined SSDs are identical, nearly identical, and less than an order of magnitude different to 0.0032 µg/L (32 ng/L) value modeled by the EPA based on a deterministic approach with the addition of an assessment factor.

3. **SACC Recommendation:** The comment and further analysis presented above relative to obtaining data that are sufficient to produce accurate assessments and SSDs could pertain to EVERY data quality and hazard assessment document in the phthalate docket. EPA should check each such document to ensure that the documents are not biased toward low/no risk when in fact higher risks are predicted than are being portrayed in the documents.

   EPA Response: EPA has incorporated probabilistic approaches for hazard threshold determination for acute duration of exposure with the utilization of EPA tools such as SSD Toolbox and Web-ICE. Incorporation of a probabilistic approach for chronic hazard data is possible, however, there are concerns about the application of this method from the Hong et al. (2024) paper in which a chronic SSD was applied for DEHP and other phthalates. The data used for the chronic SSD within Hong et al. (2025) are presented in the fourth tab of the supplemental data. In this tab titled "Table S3" the durations do not always align with a chronic exposure for a specific species; however, they were incorporated into a chronic SSD calculation. Many of the endpoints used Hong et al. (2024) are on a molecular, cellular, and sub-organ level, whereas the current deterministic approach for chronic hazard threshold identification within the DEHP Risk Evaluation are represented by ecologically-relevant apical endpoints such as morality, growth, development, and reproduction.

   Chronic toxicity data are not as amenable to Species Sensitivity Distributions (SSD) model fitting and other probabilistic procedures as are toxicity data from acute experiments. Chronic toxicity data encompass different endpoints (*e.g.*, reproduction, growth, development, molecular, cellular, etc.), different exposure durations, and nonequivalent statistical estimates. EPA is unaware of any scientifically validated procedures for standardizing across these endpoints, durations, and statistics. Also, the available chronic endpoint data have less taxonomic coverage and may have different modes of action acting across different physiological effects. Using SSDs derived from chronic endpoints would introduce myriad additional uncertainties that might obscure the interpretations needed for clear risk characterizations. Thus, EPA relied on population-level and relevant endpoints from studies with clear dose-responses, exposure durations, and adverse effects to determine protective chronic COCs.

2.4 Charge Question 4

In the *Draft Environmental Hazard Assessments* for DBP (Section 2.1.1), BBP (Section 3), and DIBP (Section 3), transcriptomic points of departure (tPODs) for aquatic vertebrates derived from studies conducted by EPA's Office of Research and Development were included in the weight of scientific evidence with concentrations of concern (CoCs) derived from *in vivo* apical studies for acute exposures in aquatic vertebrates and/or Species Sensitivity Distributions. Please comment on the current application of the tPOD and metabolomic points of departure (mPODs) in the phthalate draft environmental hazard assessments in a weight-of-evidence manner and if there are any suggestions for improving their comparisons to the corresponding environmental hazard thresholds (acute and chronic) for future application in TSCA chemical risk evaluations. In your response, please include whether tPOD and/or mPOD data presented in DBP, BBP, and DIBP is sufficient to support a chemical specific CoC.

2.4.1 SACC Recommendations and EPA Responses (Charge Question 4)

1. **SACC Recommendation:** EPA should include tPOD data in their weight of evidence analysis and draft risk assessment of BBP and DIBP, in addition to DBP. The tPOD and mPOD data were sufficient to support chemical- specific concentrations of concern for DBP, BBP, and DIBP. For example, given the documented concordance between apical PODs and tPODs in multiple publications, EPA could assess the ratio between apical POD and tPOD and flag situations where this ratio is not within 3-fold or 10-fold for further review.
2. **SACC Recommendation:** EPA should determine whether the detailed transcriptomic data constitute evidence of adverse, sublethal effects related to fitness. Evidence of stress response and/or ROS response may constitute an adverse, sublethal effect related to fitness, sufficient to support a POD for risk assessment.
3. **SACC Recommendation:** EPA should assess the available rodent *in vivo* and *in vitro* omics data and consider whether they would support development of tPODs for terrestrial wildlife and human health.
4. **SACC Recommendation:** EPA should clarify their reasons for choosing different strategies to derive tPOD, mPOD, and bPOD. EPA should establish a systematized approach for derivation of tPOD and mPOD values and should plan to include at least tPOD values for future environmental hazard assessments.
5. **SACC Recommendation:** EPA should include more information about sensitive gene sets in tPOD analyses to establish biological plausibility and relevance of the transcriptomic response to fitness.
6. **SACC Recommendation:** EPA should take steps to make the Bencic, Flick *et al*. (2024) report publicly available, preferably as a peer-reviewed publication.

EPA Response to Recommendations 1–6: EPA has added the recommended discussion on the tPOD, mPOD, and bPOD (hereafter, the NAMs [new approach methodologies]) to the BBP and DIBP weight of scientific evidence sections in the respective *Environmental Hazard Assessments*. For each of these chemicals, the NAMs were compared to the chosen apical point of departure (POD) for acute aquatic hazard, because the NAMs were derived from a 24-hour exposure in zebrafish embryos. For BBP and DIBP, as with DBP, the apical POD for acute aquatic hazard, which was derived from a Species Sensitivity Distribution (SSD) based on acute 50% lethal concentrations (LC50s), was well within an order of magnitude, and in most cases exhibited a threefold or lesser difference, from the NAM endpoints. This concordance between endpoints was used to bolster confidence in the SSD approach with additional discussion in the weight of scientific evidence portion of the assessments.

For these transcriptomic points of departure (tPODs), the data were used to support the weight of scientific evidence underlying PODs that were derived from apical, whole-animal toxicity studies as has historically been the basis for Toxic Substances Control Act (TSCA) environmental hazard assessment. In the case of DBP, BBP, and DIBP, the affected Gene Ontology processes were related to nonspecific cellular responses to xenobiotic stimulus and oxidative stress. While the study underlying the tPOD establishes that the exposure level leading to transcriptomic changes is closely linked to the exposure level associated with apical adverse outcomes, EPA did not identify an Adverse Outcome Pathway (AOP) that clearly linked the specific affected processes to the observed apical outcomes related to fitness in the organisms studied. While it is encouraging that the tPODs were similar to the hazard values from an SSD based on acute LC50 data for all three chemicals, EPA has, in this case, chosen to base hazard

values on apical outcomes where available in the existing data, if there is no clear AOP for the affected genetic pathways.

EPA appreciates the SACC's support of further developing tPODs and related points of departure, and notes that the development of these methods is progressing under the research group identified in the Bencic et al. (2024) paper. The SACC's comments, including the suggestion to establish a systematized approach for quantifying the various PODs and to investigate rodent data for applicability to terrestrial wildlife, have been shared with the research group and will be taken into account in future work. EPA plans to make the Bencic et al. 2024 report publicly available as requested by SACC. The SACC's editorial comments have been incorporated into the final *Environmental Hazard Assessments,* including standardizing the document structure, including a version of the draft DBP Table 2-11 in all three documents and adding discussion of the tPOD and mPODs in the main body text.

2.5 Charge Question 5

EPA has developed *Draft Non-cancer Human Health Hazard Assessments* for DCHP, BBP, DBP, DIBP, and DEHP, as well as the *Draft Meta-analysis and Benchmark Dose Modeling of Fetal Testicular Testosterone for DEHP, DBP, BBP, DIBP, and DCHP,* which supports the dose-response assessment presented in the non-cancer human health hazard assessment for each phthalate.

2.5.1 Charge Question 5.a

In the *Draft Non-cancer Human Health Hazard Assessment for DEHP*, EPA discusses the weight of scientific evidence for effects of DEHP on nutritional/metabolic effects related to glucose/insulin homeostasis and lipid metabolism (Sections 3.2 and 3.9) and effects on the female reproductive tract (Section 3.1.2.3, Section 3.1.3.2, and Section 3.9). Although these hazards may inform potentially sensitive PODs, EPA identified substantial deficiencies and limitations in the evidence, including lack of replication and inconsistencies regarding the dose-response, temporality, directionality, and magnitude of changes in parameters examined, which reduces EPA's confidence in using these hazards for the quantitative dose-response assessment. Therefore, EPA has preliminarily concluded that there is too much uncertainty associated with these hazards to support quantitative dose-response assessment and POD determination

2.5.1.1 Charge Question 5.a.i

Please comment on the strengths and uncertainties pertaining to EPA's preliminary conclusions on the nutritional/metabolic effects related to glucose/insulin homeostasis and lipid metabolism.

2.5.1.1.1 SACC Recommendations and EPA Responses (Charge Question 5ai)

1. **SACC Recommendation:** The title of Sections 3.2 and 3.2.3 should be changed to remove "metabolic syndrome" in keeping with the lack of established "syndrome" for exposure to DEHP.
2. **SACC Recommendation:** The Committee agrees with Agency's conclusion that the current evidence is insufficiently clear and consistent to support/conduct a quantitative dose-response assessment to develop a POD.

EPA Response to Recommendations 1-2: EPA revised the title of Sections 3.2 and 3.2.3 in the DEHP non-cancer human health hazard assessment to remove reference to "metabolic syndrome" and instead refer more broadly to "Glucose/Insulin Homeostasis and Lipid

Metabolism" to more accurately capture the suite of endpoints examined in these studies, without implying the more specific criteria for "metabolic syndrome" in humans. EPA also revised the text within Sections 3.2.2.1, 3.2.2.2, and 3.2.3 of the DEHP non-cancer human health hazard assessment accordingly to reflect this change.

2.5.1.2 Charge Question 5.a.ii

Please comment on the strengths and uncertainties pertaining to EPA's preliminary conclusions on the potential hazard DEHP poses to the female reproductive tract.

2.5.1.2.1 SACC Recommendations and EPA Response on Animal Studies (Charge Question 5.a.ii)

1. **SACC Recommendation:** Clarification should be made to include appropriate evidence of a potential non-monotonic dose response. There have been phthalate studies that have reported reproductive/endocrine effects following exposure to low doses but no effects or opposite effects following exposure to high doses (examples include Andrade *et al*. 2006; Pocar *et al*. 2017; Kim *et al*. 2018; Kim *et al*. 2019). Specifically, application of the European Food Safety Authority (EFSA 2021) approach is recommended in cases of apparent non-monotonicity and a discussion that females have potential low-dose effects, but more research is needed to clarify the dose response.

    - The Committee recommends that EPA consider results of the recent meta-BMD analysis of data from Silva *et al*. (2025), which calculated $BMDL_5$s of 9.1 mg/kg/day for serum progesterone and 19.5 mg/kg/day for altered follicle count. The analysis encompassed four studies with a dose range of 0.02 to 250 mg/kg/day for studies in adult rats with exposure duration of 10–30 days.

    - The Silva *et al*. (2025) provides a benchmark dose modeling analysis with POD for female reproductive toxicity in response to DEHP exposure. Data from four studies involving sexually mature female mice exposed to DEHP (0.02 to 240 mg/kg/day) via oral administration for 10 or 30 days, or through diet for 30 days, were modeled. Some Committee members recommend this publication for a review and ask EPA to consider using adding a modeling approach focused on adverse effects in females for a thorough, integrated analysis.

    - Studies published by scientists from the University of Illinois College of Veterinary Medicine have investigated the effects of DEHP exposure on the female reproductive system. These papers present high-quality research describing the adverse effects following administration of phthalate mixtures, which have not been considered. Specifically, the Committee recommends that a discussion of low-dose effects of environmentally relevant doses to phthalate mixtures may not have been evaluated and warrants further investigation. The following bullets provide examples of studies from this group.

        - A 10-day exposure to DEHP (20-500 mg/kg/day) in adult female CD-1 mice accelerated follicular recruitment nine months later (Hannon *et al*. 2016). The accelerated follicular recruitment disrupted estrus cyclicity and altered hormone levels. Further, there was a significant loss of primordial follicles, that reduced ovarian reserve and ultimately potential early reproductive senescence. The NOAEL could be based on proportional follicle counts (stages), with the 20 µg/kg/day group being significant.

Table 2-1. Overview of the Four Selected Studies Analyzing the Effects of Short-Term Exposure to DEHP on Female Reproductive Toxicity Endpoints[1]

Study	Reference	Doses	Group Size	Endpoints Measured
10-d oral exposure, study I	Hannon *et al.* (2014)	0, 0.02, 0.2, 20, and 200 mg/kg/day	n = 8 per dose group, female mice only	Estrous cyclicity, serum hormones, and ovarian follicle number
10-d oral exposure, study II	Chiang and Flaws (2019)	0, 0.02, 0.2, 20, and 200 mg/kg/day	n = 6 per dose group, female mice only	Body and organ weights
30-d oral exposure	Hannon *et al.* (2014)	0, 0.02, 0.2, 20, and 200 mg/kg/day	n = 8 per dose group, female mice only	Estrous cyclicity, serum hormones, and ovarian follicle numbers
30-d dietary exposure	Laws *et al.* (2023), Safar *et al*. (2023), Santacruz-Márquez *et al*. (2024)	0, 0.024, 0.24, 24, and 240 mg/kg /day	n = 10 per dose group, female mice only	Estrous cyclicity, serum hormones, and ovarian follicle numbers

  - Gestational exposure in mice reduced the time in proestrus and reduced rate of term pregnancy (delivery) at 11 and 13 months (Brehm and Flaws, 2021). These and other data, especially those with measured hormone and molecular endpoints may require analyses appropriate for non-monotonic data. Embryo fragmentation followed oral administration of 2 mg/kg/day (1 month exposure duration), and decreased implantation rate and blastocyst development was observed following oral administration of 0.2 to 2 mg/kg/day (Magosso *et al*. 2025).
  - Decreased ovarian cytokines were observed at 6 months postnatal following prenatal exposure to a phthalate mixture. Most effects were observed following administration of 200 mg/kg/day, but a few changes occurred as low as administration of 20 ug/kg/day. The dose-response relationship for some of these changes were non-monotonic (Fletcher *et al*. 2024).

- The Committee recommends EPA include a table to summarize both studies that provide evidence of adverse effects as well as studies that do not demonstrate adverse effects, including endocrine status. EPA should include a table of results for the female reproductive toxicity endpoints described in the text of section 3.1.2.3 and use the information available to determine if a consensus NOAEL and LOAEL emerge.

The risk for adverse outcomes will vary with the endocrine status (age, reproductive stage such as pubertal, adult, aging, menopausal), which could affect the susceptibility of individuals to exposure to DEHP. The variable responses in the studies mentioned above reinforce the difficulties in identifying a specific POD for adverse female reproductive system effects. However, the inclusion of these studies is warranted.

[1] This table was included as part of the SACC consensus recommendation in the final report from the SACC located at https://www.regulations.gov/document/EPA-HQ-OPPT-2024-0551-0167.

EPA Response: During the August 2025 peer-review meeting, the SACC recommended that EPA consider potential non-monotonic dose responses for female reproductive/endocrine endpoints. EPA consulted the European Food Safety Authority (EFSA) approach as recommended by SACC and included the following discussion in the human health hazard TSD for DEHP in Section 3.2.2.3:

> EFSA's *Opinion on the impact of non-monotonic dose responses on EFSA's human health risk assessments* included DEHP as one of the two case studies examined (EFSA, 2021). EFSA noted that non-monotonic dose-response (NMDR) has been reported for aromatase activity in studies, and that changes in aromatase activity resulting in differences in testosterone metabolism are a possible mechanism to support the biological plausibility of the observed NMDR for postnatal testosterone with exposure to DEHP. In a subsequent review of this evidence, Astuto et al. (2023) summarized the conclusions from that Opinion and applied an AOP framework to assess the biological plausibility DEHP's effect on testosterone, noting the effects on brain aromatase (CYP19) in the study by Andrade et al. (2006). Astuto et al. (2023) noted that, because aromatase is responsible for the catalysis of testosterone to estradiol, a non-monotonic disruption of brain aromatase homeostasis could be directly caused by the disruption in testosterone homeostasis, or secondary to the hormonal imbalance caused by a disruption of testosterone homeostasis. However, in their overall assessment, the authors concluded that the "available evidence is inconclusive regarding the assessment of possible NMDR for testosterone levels" and cited the need for studies with sufficient number of doses and appropriate exposure windows.
>
> EPA acknowledges that a NMDR for aromatase activity cannot be ruled out but does not consider the nonmonotonic statistically significant differences in aromatase reported in the study by Andrade et al. (2006) to sufficiently explain the monotonic dose-related effects described in the other publications by Andrade and Grande et al. (2006a,b,c) which were more definitively due to treatment with DEHP. Overall, EPA considers there to be too much scientific uncertainty associated with the apparent NMDR effects to use these endpoints quantitatively in risk characterization.

The SACC recommended that EPA consider results of the recent Bayesian BMD analysis of data of the effects of DEHP on female reproductive tract endpoints reported by Silva et al. (2025), which encompassed four studies with a dose range of 0.02 to 250 mg/kg-day in adult mice with exposure duration of 10–30 days. In response to the Committee's recommendation, EPA reviewed this study and confirmed that this meta-BMD analysis resulted in a BMD_{10} of 36.6 mg/kg-day and a $BMDL_{10}$ of 9.1 mg/kg-day for serum progesterone and a BMD_{10} of 31 mg/kg-day and $BMDL_{10}$ of 19.5 mg/kg-day for altered follicle count. However, EPA notes that these BMDL estimates are higher and therefore less sensitive than the POD of 4.8 mg/kg-day that EPA selected based on male reproductive outcomes in the three-generation reproduction study of rats (TherImmune Research Corporation, 2004; Blystone et al., 2010). Furthermore, EPA considers a POD based on the meta-analysis and BMD modeling of female reproductive endpoints in the study by Silva et al. (2025) to have greater uncertainty because it focused on the magnitude of the responses, whereas the directionality differed across studies and durations. Specifically,

serum progesterone was increased in the 10-day study but decreased in the 30-day oral gavage and dietary studies; and ovarian primordial follicle count was increased in the 30-day dietary study but decreased in the 10-day and 30-day oral gavage studies.

EPA further examined the individual studies underlying the BMD analysis in the publication by Silva et al. (2025). Studies are summarized below:

> Two of these studies were already considered by EPA in the draft human health hazard technical support document, including studies by Hannon et. al (2014) and Chiang and Flaws (2019). In the study by Hannon et al., CD-1 mice were orally exposed to 200 mg/kg-day for 30 days resulting in a NOAEL of 20 mg/kg-day and a LOAEL of 200 mg/kg-day based on significant differences in estrous cyclicity (increased percentage of days spent in estrus). This study was included in the Agency for Toxic Substances and Disease Registry's (ATSDR) Table 2-2 LSE; however, the LOAEL was an order of magnitude higher than EPA's inclusion criteria of 20 mg/kg-day or lower and was therefore not sensitive enough for consideration in dose-response analysis to derive a POD. The study by Chiang and Flaws (2019) reported reduced fertility 3 months post-exposure to 0.02 mg/kg-day, but no effects on fertility at higher doses and no effects at 0.2 mg/kg-day at any other time point (0, 3, 9, or 12 months post-exposure), and the assessment by ATSDR (2022) excluded this study from the LSE table "based on the lack of clearly adverse, dose-related findings" (ATSDR, 2022).
>
> Three studies included in the analysis by Silva et al. (2025) were published after the publication of ATSDR (2022) and were therefore not available for EPA's consideration in the draft human health hazard TSD, including studies by Laws et al. (2023), Safar et al. (2023), and Santacruz-Márquez (2024). The study by Safar et al. (2023) examined the effects on female reproductive endpoints in mice given a mixture of 6 phthalates in the diet for up to 6 months; however, this study was excluded because the study design did not include exposure to individual phthalates separately. In the study by Laws et al. (2023), female CD-1 mice were fed DEHP in the diet at 0 (corn oil control), 0.15, 1.5, and 1500 ppm (approximately equivalent to 0, 0.024, 0.24, and 240 mg/kg-day, respectively) for up to a year exposure. In this study, significant differences in the percentage of days in estrus were noted at the low dose at 3- and 6-months; however, these findings were transient and unrelated to dose, and there were no effects on body weight, food consumption, or reproductive indices. Similarly, in the study by Santacruz-Márquez (2024), adult female CD-1 mice were fed test diets at the same concentration as the study by Laws et al. (2023), for a short-term exposure (1 month) or a long-term exposure (6 months) to examine ovarian follicle growth and hormone levels. Serum FSH was decreased at 0.024 mg/kg-day at 1 month but was increased at 240 mg/kg-day at 6 months; and luteinizing hormone (LH) was decreased at 0.024 and 0.24 mg/kg-day at 6 months. At 240 mg/kg-day, the percentage of primordial follicles was increased and the percentages of preantral and antral follicles were decreased at 6 months, but were comparable to controls at 1 month. Again, these differences did not show concordance with dose and/or time, and the effects at 240 mg/kg-day were over an order of magnitude higher (e.g., less sensitive) than the cut-off criteria that EPA established for inclusion in dose-response analysis.

The SACC recommended that EPA discuss the low-dose effects of environmentally relevant doses to phthalate mixtures and provided references for several studies published by scientists from the University of Illinois College of Veterinary Medicine (Brehm and Flaws, 2021; Magosso et al. 2025; Fletcher et al. 2024. EPA reviewed these studies and confirmed that they

only examine the effects from dosing with a mixture of six phthalates, without including any groups with exposure to individual phthalates. Therefore, EPA did not consider these studies appropriate for derivation of a hazard POD specific to DEHP or any other individual phthalate. EPA notes that it is considering risk from cumulative exposure to phthalates in the *Revised Draft Technical Support Document for the Cumulative Risk Analysis of DEHP, DBP, BBP, DIBP, DCHP, and DINP Under the Toxic Substances Control Act (TSCA)*. Among this list of studies, the SACC report also recommended that EPA consider the study by Hannon *et al.* (2015), and this study entailed oral dosing of adult CD-1 mice with vehicle or DEHP at doses ranging from 20 μg/kg-day to 500 mg/kg-day for 10 days and assessing reproductive outcomes at 6 months and 9 months post-dosing. However, in this study, the only dose-related findings were increased progesterone and a decrease in the percentage of days in estrus at 9 months at 500 mg/kg-day, which is two orders of magnitude higher than the POD selected by EPA, based on effects on the developing male reproductive system.

The SACC also recommended that EPA include a table to summarize both studies that provide evidence of adverse effects as well as studies that do not demonstrate adverse effects and include a table of results for the female reproductive toxicity endpoints described in narrative in Section 3.1.2.3 and determine if a consensus NOAEL and LOAEL emerge. EPA notes that Section 3 is focused on hazard identification, and given the limitations and uncertainties in the data supporting an effect on the female reproductive tract (e.g., non-monotonic dose response and lack of concordance regarding dose- and time-dependence of effects across studies), EPA did not consider it appropriate to carry this hazard forward to the dose-response analysis in Section 4, which includes a presentation of the data in a table.

2.5.1.2.2 SACC Recommendation and EPA Response on MOA (Charge Question 5.a.ii)

SACC Recommendation: With respect to the biological plausibility statement beginning on line 2101, the Committee recommends that EPA consider that (1) a complete AOP is not required to establish biological plausibility; and (2) the proposed effects of phthalates on the female reproductive system occur through analogous methods to the male reproductive system, including suppression of steroid hormone biosynthesis and the expression of genes required for steroidogenesis. Although there is less consistency in endpoints and study designs in the female studies than in the male studies, there is an argument for biological plausibility.

For example, DEHP has been mapped to the human female reproductive toxicity–adverse outcome pathway (HFRT-AOP) network (Pogrmic-Majkic *et al*. 2022), identifying divergent paths by which DEHP can cause female reproductive dysfunction. This approach has allowed identification of potentially relevant Molecular Initiating Event(s) (MIEs), Key Events (KEs), data gaps, and emergent paths where the experimental efforts should be focused to advance the mechanistic understanding of DEHP-induced female reproductive dysfunction.

EPA Response: With respect to biological plausibility, the Committee recommended that EPA consider that (1) a complete AOP is not required to establish biological plausibility; and (2) the proposed effects of phthalates on the female reproductive system occur through analogous methods to the male reproductive system, including suppression of steroid hormone biosynthesis and the expression of genes required for steroidogenesis. In response, in the *Biological plausibility and coherence* discussion in Section 3.1.3.2, EPA added additional characterization of the effects on the female reproductive tract, including the addition of the study by Parra-Forero et al. (2019) and noted that it may be possible that

oral exposure to DEHP could delay meiotic progression of germ cells in fetal ovaries and accelerate folliculogenesis , as reported in the study by (Zhang et al. 2015), decrease oocyte maturation and increase oocyte degeneration (Pocar et al. 2012), and/or arrest zygote development in young sexually mature mice (Parra-Forero et al. 2019). However, there is no proposed adverse outcome pathway that establishes a mechanism through which these effects may occur, and these endpoints were either not examined in other oral studies in rodents or they were not consistently observed in studies in which they were examined. EPA also notes that the above-mentioned discussion on NMDR speaks to the biological plausibility for these effects on the developing female reproductive tract for which a complete AOP is not currently available.

2.5.1.2.3 SACC Recommendations and EPA Response on Human Effects Considering the Female Reproductive Studies (Charge Question 5.a.ii)

1. **SACC Recommendation:** Exposure to MEHP, a metabolite of DEHP in the human body, has been linked to adverse effects and should be considered in assessing potential risk from exposure (see pp 28, 33). For example, urinary DEHP metabolites were positively associated with increased serum lipid profiles (Lin *et al*. 2024).

   EPA Response: The EPA acknowledges the importance of considering MEHP, a primary metabolite of DEHP, in assessing potential risk. The EPA was able to locate a publication by Lin et al., 2024 "The Association Among Urinary Di-(2-ethylhexyl) Phthalate Metabolites, Serum Lipid Profiles, and Serum Apoptotic Microparticles in a Young Taiwanese Population' which the EPA believes the commenter was referencing; however the results presented in this publication did not change the EPA's epidemiological conclusions and does not add to the quantitative weight of scientific evidence. The adverse effects highlighted in Lin et al. 2024, as well as other effects noted in other epidemiology publications on DEHP, were included in the qualitative assessment of the effects of DEHP on female reproductive endpoints in the human health hazard TSD.

2. **SACC Recommendation:** Include the Health Canada (2018a and 2018b) data rather than discarding it; the paucity of studies (lines 123–1236) and the findings of lower fertility, diminished egg production, ovarian antral follicle counts, as well as increases in preterm birth is strong evidence that EPA should consider these effects for female health rather than dismissing them. The Health Canada work preceded many of these studies.

   EPA Response: The DEHP human health hazard TSD includes findings from Health Canada (2018a and 2018b) that the EPA has reviewed and incorporated as part of the qualitative weight of evidence.

3. **SACC Recommendation:** Although the assumption that the male POD is sufficiently conservative to apply to females, the Committee recommends that other studies should be evaluated sufficiently to confirm this at reproductive and other life stages (*e.g.,* menopause).

   EPA Response: As described further in the *Systematic Review Protocol for Diethylhexyl Phthalate (DEHP),* EPA identified 50 animal toxicology studies that provided information pertaining to hazard outcomes associated with exposure to less than or equal to 20 mg/kg-day, including 25 studies on male and female reproduction/development. The evidence supporting each of these hazards was thoroughly evaluated as described in Section 3 of the DEHP Non-cancer Human Health Hazard Assessment, including a detailed evaluation of the individual

studies and a discussion of the evidence across studies in evidence synthesis and integration. This weight of evidence analysis was organized around modified Bradford-Hill criteria, including examination of concordance regarding dose-response, temporality, strength, consistency, specificity, and biological plausibility.

Although there are a growing number of studies examining the female reproductive tract as a target of DEHP toxicity, there is uncertainty given the limited strength, consistency, specificity, dose concordance, biological coherence, and established adversity associated with effects in many of these studies (Parra-Forero et al., 2019; Shao et al., 2019; Zhang et al., 2014; Pocar et al., 2012), or the fact that they do not provide a sex-specific endpoint that is more sensitive than the well-established effects on developing male reproductive tract (Andrade et al., 2006a; Grande et al., 2006). EPA concluded that there is too much variability in the adverse outcomes in these studies to use them quantitatively for risk characterization. Notably, SACC ultimately agreed with this conclusion, noting that this variability may be due to differences in endocrine status (age, reproductive stage such as pubertal, adult, aging, menopausal) which "reinforces the difficulties in identifying a specific POD for adverse female reproductive system effects" (U.S. EPA, 2025o). In conclusion, EPA considered the evidence supporting an effect of DEHP on the developing male reproductive tract to be the most robust and provide the most sensitive and appropriate POD for use in risk assessment and therefore carried this evidence forward to dose-response analysis.

2.5.1.2.4 SACC Minor or Editorial Comments and EPA Response (Charge Question 5.a.ii)

SACC Comment: The following comments refer to *Draft Non-cancer Human Health Hazard Assessment for DEHP* Page 37, lines 1260–1261, it states "... women undergoing *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) therapy"; these are not different treatments; ICSI is a possible type of fertilization in IVF. Fertilization is conducted in one of two ways: standard (sperm and eggs are combined in the petri dish and allowed to fertilize "naturally"); and ICSI (a single sperm is injected into an egg). Hence, it is not IVF or ICSI.

- In page 38 line1299, there is an extra "was."
- Reporting the sample number for the different dose groups by Shao *et al*. (2019) is needed.

EPA Response: EPA clarified that ICSI is a specific subset of IVF; EPA deleted the extra "was" on page 38 line 1299; EPA specified the sample size in the study by Shao et al. (2019), noting in Section 3.1.2.3 that the study in female Wistar rats included 12 per dose group.

2.5.2 Charge Question 5.b

In Sections 4.2 and 4.3 of the *Draft Non-cancer Human Health Hazard Assessment for DEHP,* EPA has preliminarily selected the NOAEL of 4.8 mg/kg/day (HED = 1.1 mg/kg/day) as the POD to estimate non- cancer risks from oral exposure to DEHP for acute, intermediate, and chronic durations of exposure. This POD is based on the NOAEL from a multi-generation reproductive toxicity study in which reproductive tract malformations were observed in male offspring at 14 mg/kg/day (Blystone *et al*. 2010; TherImmune Research Corporation, 2004) and the study by Andrade and Grande *et al*. (2006c; 2006a; 2006) with a similar NOAEL (5 mg/kg/day) and LOAEL (15 mg/kg/day), along with 13 additional studies reporting effects on the developing male reproductive system consistent with disrupted androgen action and phthalate syndrome at LOAELs in a narrow range of 10 to 15 mg/kg/day. Please comment on

the strengths and uncertainties in the selected HED, including EPA's selection of co-critical studies, and the weight of scientific evidence from the studies supporting a refined consensus LOAEL.

2.5.2.1 SACC Recommendations and EPA Response (Charge Question 5b)

1. **SACC Recommendation:** Provide citations or references to support the concept of the "consensus NOAEL" and provide clear justification for dismissing non-male reproductive endpoints in selection of the NOAEL/LOAEL.

2. **SACC Recommendation:** Provide additional evaluations to determine the potential limitations and/or uncertainties in relying upon a consensus NOAEL/LOAEL approach when the BMD approach is the preferred approach for the meta-analysis and could be used to estimate a NOAEL-equivalent POD.

3. **SACC Recommendation:** EPA should follow its own well-established guidance, the recommendations of the NASEM, and the repeated recommendations of the SACC by conducting BMD modeling. The Committee recommended performing BMD analysis of the Blystone *et al*. (2010) study, rather than using the NOAEL from the study as the POD. The longer duration of exposure in Blystone *et al*. (2010), a 3- generation study, than in the numerous short-term studies, as well as the endpoint of reproductive tract malformations, which are a higher-order effect than reduced testosterone biosynthesis, contribute to confidence in (and justification for) using the Blystone *et al*. (2010) study to derive the POD, rather than the meta-analysis and BMD.

4. **SACC Recommendation:** Extract and use existing data or require determination of rate of metabolism of DEHP to MEHP for dermal and inhalation exposure routes.

5. **SACC Recommendation:** Table 4-1 in the *Draft Non-cancer Human Health Hazard Assessment for DEHP* is very useful. Other end points that are responsive and described in detail above should also be presented separately or as part of this table.

6. **SACC Recommendation:** In the *Draft Non-cancer Human Health Hazard Assessment for DEHP*, lines 4631–4653, the criteria for study selection are for non-cancer health endpoints in general. There needs to a segue or conclusion to support the focus on male reproductive development as well as some criteria for selection of studies on male reproductive development. Generally, studies including exposure during the "critical window" (gestational days 15–21) should be one criterion.

   EPA Response to SACC Recommendations 1-6: Regarding EPA's use of a "consensus NOAEL-LOAEL" approach over BMD modeling: EPA notes that the "consensus NOAEL" approach is not a novel concept, although it may not always be referred to using that terminology. Many risk assessment guidance documents describe the synthesis and integration of evidence across studies that underlie this approach. Simply put, the approach refines the effect threshold by selecting the highest NOAEL below the lowest LOAEL among a suite of studies with similar endpoints. This concept is not limited to human health hazard assessment. In determining ecological hazard, some EPA employs a similar approach in deriving wildlife toxicity reference values in its *Guidance for Developing Ecological Soil Screening Levels (Eco-SSLs)*, which selects the lowest LOAEL above either the highest NOAEL, or the geometric mean of the NOAELs, depending on the weight of evidence across the suite of studies with ecologically relevant endpoints (U.S. EPA, 2007).

EPA acknowledges that, within a given study, BMD modeling of effects is generally preferred when deriving a POD because a BMD is unaffected by dose-selection, and the model takes into account considerations such as variability and sample size. However, in consideration of the extensive evidence supporting effects on DEHP on the male reproductive tract, EPA reaffirms that there is robust confidence in the approach and the resulting POD that EPA selected in the draft human health hazard TSD, for the following reasons, detailed further in Section 4.3 on the weight of scientific evidence: study selection for POD:

> There are 15 studies comprising 19 publications reporting LOAELs in a narrow dose range of 10 to 15 mg/kg-day based on treatment-related effects on the developing male reproductive system consistent with a disruption of androgen action during the critical window of development. The AOP for effects on the developing male reproductive system from exposure to DEHP and other phthalates is well established.
>
> The selected POD is based on effects consistent with phthalate syndrome in two high quality studies, including a three-generation reproductive toxicity study in rats (TherImmune Research Corporation, 2004) and a follow up analysis which examined a larger number of pups from this study in order to have greater power to detect statistically significant increases in reproductive tract malformations (Blystone et al. 2010). Furthermore, the medium-quality studies by Andrade and Grande et al. (2006a,b,c), which exposed rats starting at implantation and throughout the remainder of gestation and lactation, established a LOAEL of 15 mg/kg-day and a NOAEL of 5 mg/kg-day, which are similar to the NOAEL (4.8 mg/kg-day) and LOAEL (14 mg/kg-day) in the three-generation reproduction study (TherImmune Research Corporation, 2004; Blystone et al. 2010). Therefore, consideration of these studies as co-critical studies provides additional strength and confidence in the selected POD, in both the outcomes and the dose at which they occur.
>
> In addition to the principal and co-critical studies, 13 other studies indicated similar effects on the developing reproductive system in a narrow dose range supporting LOAELs of 10 to 14 mg/kg-day. Eleven of the 13 studies did not test low enough doses to establish a NOAEL. The two remaining studies support NOAELs of 1 and 3 mg/kg-day (Akingbem et al. 2001; Christiansen et al. 2010). Although these NOAELs are lower than the selected POD (NOAEL of 4.8 mg/kg-day), this is merely a reflection of dose-selection, and EPA has higher confidence in the POD (NOAEL of 4.8 mg/kg-day) as a robust consensus NOAEL based on a high quality three-generation reproduction study (TherImmune Research Corporation, 2004; Blystone et al. 2010) co-critical with the studies by Andrade and Grande et al. (2006).
>
> EPA also added discussion of BMD modeling of reproductive tract malformations (RTMs) conducted by Blystone et al to Section 4 of the DEHP non-cancer human health hazard assessment. Blystone et al. (2010) also conducted BMD modeling on the RTM data, which supports BMD_5/$BMDL_5$ estimates of 11.6/7.0 mg/kg-day for the F1 generation, 10.4/2.2 mg/kg-day for the F2 generation, and 8.5/5.6 mg/kg-day for combined F1 and F2 generations. BMD_5 estimates from this analysis range from 8.5 to 11.6 mg/kg-day and are slightly lower than the LOAEL of 14 mg/kg-day supported by

this study, while $BMDL_5$ estimates ranged from 2.2 to 7.0 mg/kg-day and are consistent with the NOAEL of 4.8 mg/kg-day, and support its selection as the POD.

In summary, there are a considerable number of studies supporting an effect of DEHP on the developing male reproductive system in the narrowly refined threshold in which no effects are occuring at doses as high as 5 mg/kg-day and numerous effects are occurring at doses as low as 10 mg/kg-day across the key events in the AOP in 15 studies. EPA has robust confidence that using the entire body of evidence represents the best available science, compared to BMD modeling of any individual endpoint within an individual study.

The SACC also recommended that EPA "provide clear justification for dismissing non-male reproductive endpoints in selection of the NOAEL/LOAEL". EPA disagrees with the characterization that it dismissed non-male reproductive endpoints in the selection of the NOAEL/LOAEL. As detailed in Section 1.2.3 Scope of the DEHP Hazard Assessment, EPA provides a detailed explanation that it further considered the 201 studies included in ATSDR's Table 2-2 of LSEs (ATSDR, 2022) to identify studies with sensitive endpoints (LOAEL <20 mg/kg-day) for new information on human health hazards not previously identified in existing assessments— including information that may indicate a more sensitive POD than established by the regulatory bodies prior to the publication of ATSDR in 2022. As described further in the *Systematic Review Protocol for DEHP*, EPA identified 50 animal toxicology studies that provided information pertaining to hazard outcomes associated with exposure to less than or equal to 20 mg/kg/day, including: 25 studies on male and female reproduction/ development; 16 studies on metabolic endpoints related to glucose/insulin homeostasis and lipid metabolism; 4 studies on cardiovascular/kidney outcomes, 19 studies indicating effects on the liver, 3 studies reporting neurological effects, three studies indicating effects on the immune system, and one study describing effects on musculoskeletal systems, in addition to 5 studies reporting hazards identified by the inhalation route. Importantly, the evidence supporting each of these hazards was thoroughly evaluated as described in Section 3 Non-Cancer Hazard Identification, including a detailed evaluation of the individual studies and a discussion of the evidence across studies in evidence synthesis and integration. This weight of scientific evidence analysis was organized around modified Bradford-Hill criteria, including examination of concordance regarding dose-response, temporality, strength, consistency, specificity, and biological plausibility. Notably, EPA considered the evidence supporting an effect of DEHP on the developing male reproductive tract to be the most robust and provide the most sensitive and appropriate POD for use in risk assessment and therefore carried this evidence forward to dose-response analysis. However, this does not equate to a dismissal of the evidence supporting other hazards.

The SACC also noted that the criteria for study selection are for non-cancer health endpoints in general and recommended that EPA include a conclusion to support the focus on male reproductive development as well as some criteria for selection of studies on male reproductive development (for example, including studies which entailed exposure during the "critical window" (gestational days 15–21) as one criterion. Again, this recommendation speaks to the organization of the hazard assessment. EPA included its criteria for inclusion in the hazard assessment in Section 1.2.3 Scope of the DEHP Hazard Assessment; while Section 3 addresses the strength of the evidence supporting each hazard, and the hazard(s) for which EPA has the strongest evidence of an effect of DEHP relevant to derivation of a POD for human health risk assessment is/are carried forward to Section 4 for dose-response analysis. Therefore, EPA cannot simultaneously consider all hazards providing sensitive endpoints while at the same time narrow the evidence pool with a criterion of exposure only during a critical window of development

relevant to only one of those hazards. EPA interprets this recommendation that SACC supports an organization of the hazard assessment that begins with considering all hazards with sensitive endpoints, and then when a specific hazard such as the effects on the developing male reproductive system is considered, further refining the inclusion criteria to limit the studies to those with exposure during the critical window of development. EPA did not consider the latter criterion to be necessary, as there are several studies represented by exposure of weanling or even adult rodents that indicate effects on the male reproductive system, which may entail effects at different KE in the AOP (*e.g.*, Leydig cells vs Sertoli cells) and may differ depending upon the exposure duration and developmental stage of the animals.

Related to the consideration of other hazards, the SACC considered Table 4-1 in the *Draft Non-cancer Human Health Hazard Assessment for DEHP* to be very useful and recommended that endpoints other those affecting the developing male reproductive tract that are responsive and described in detail above should also be presented separately or as part of this table. Again, EPA has organized the hazard assessment to address hazard identification and the strength of the evidence supporting each hazard in section 3 and reserves Section 4 for the detailed data included in tables for dose-response analysis and POD derivation.

The SACC recommended that EPA extract and use existing data or require determination of rate of metabolism of DEHP to MEHP for dermal and inhalation exposure routes. In response to this recommendation, EPA added a new section to the hazard assessment for DEHP and each of the other phthalates (Section 4.4 Route-to-Route Extrapolation) that describes in further detail the evidence supporting EPA's decision to conduct route-to-route extrapolation from oral to dermal and inhalation routes, including a detailed description of the existing physiologically based pharmacokinetic (PBPK) models for DEHP and their strengths and limitations for quantitative use in a regulatory framework, and a more in-depth discussion of the empirical evidence describing how ADME varies across routes of exposure (oral, dermal, and inhalation).

2.5.3 Charge Question 5.c

In the *Draft Non-cancer Human Health Hazard Assessment for DEHP*, EPA discusses the health hazards identified via the inhalation route of exposure (Section 3.8). EPA has preliminarily determined the weight of scientific evidence does not support the use of hazard data from available animal inhalation studies for quantitative use in determining an inhalation POD (Section 3.9). EPA did not consider any of the five inhalation studies in animals to be suitable for quantitative derivation of a POD due to: limitations and uncertainties related to exposure characterization; inconsistencies in the occurrence, temporality, and directionality of many of the effects; and questionable adversity for effects considered minor and/or transient. Given the lack of specific inhalation epidemiology data and uncertainties associated with the animal toxicity studies, EPA did not consider these studies quantitatively for determining an inhalation POD.

2.5.3.1 Charge Question 5.c.i

Please comment on the strengths and uncertainties of the supporting data.

2.5.3.1.1 SACC Recommendations and EPA Response (Charge Question 5.c.i)

1. **SACC Recommendation:** The Committee recommends that EPA review the DEHP literature published since June 2020 to ensure nothing important or influential was missed.

EPA Response: In response to SACC's recommendation that EPA review the DEHP literature published since June 2020 to ensure nothing important or influential was missed, EPA notes that it revised each of the technical support documents and risk evaluations to update the sections relevant to systematic review, noting that an updated literature search was conducted, which entailed revised PECO or PESO statements to screen all literature submitted in SACC and public comments to determine if any newer studies would quantitatively impact the analyses, and incorporate the data from those studies, as appropriate.

2. **SACC Recommendation:** The Committee recommends that EPA should clarify and revise interpretation of the Kurahashi *et al*. (2005) and Ma *et al*. (2006) studies considering the Committee's comments.

   EPA Response: In response to the SACC's recommendation, EPA clarified and revised interpretation of the Kurahashi *et al*. (2005) and Ma *et al*. (2006) studies regarding the Committee's comments on the exposure characterization (*e.g*., vapor vs aerosol) and other considerations regarding study design. Specifically, EPA added to the narrative that the "test atmospheres were generated by vaporizing DEHP (99.0–99.9%) contained in a flask immersed in oil at 90°C for the low-concentration or 130°C for the high concentration, and DEHP was measured once daily in the exposure chambers with a gas chromatograph with a column temperature of 220°C". EPA deleted the criticism that particle size distribution (MMAD and GSD) were not reported, given that these measurements are relevant to aerosols and not vapors.

3. **SACC Recommendation:** The Committee recommends additional explanation/discussion of the Merkle *et al*. (1988) study in light of the Committee comments about the maternal body weight data and fetal visceral variations.

   EPA Response: The SACC recommended additional explanation/discussion of the Merkle *et al*. (1988) study in light of the Committee comments about the maternal body weight data and fetal visceral variations. The EPA re-examined the narrative and affirmed that it supports the conclusions that the findings are minor, transient, and not adverse. The decreases in maternal body weight at the high concentration were minor (<10% difference from controls), and EPA notes the following regarding the increased incidence of visceral variations at the high concentration:

   > While the incidence of variations was increased over concurrent controls, it was stated that they were within the range of historical controls for this lab.
   >
   > No incidence data were provided for specific visceral variations (just total), although the authors noted that the majority were renal pelvis dilatation.
   >
   > Renal pelvis dilatation is often associated with decreased fetal body weights and delayed development, but no effects on fetal body weight were reported, and there were no differences in offspring development in the satellite group that continued throughout the lactation period.

4. **SACC Recommendation:** The Committee recommends that EPA should conduct a bounding calculation to demonstrate that the route-to-route extrapolation to derive the inhalation POD from the oral data is not an underestimate.

   EPA Response: In response to SACC's consideration of the differences in metabolism of DEHP via different routes of exposure, EPA added a new section to the hazard assessment for DEHP and

each of the other phthalates (Section 4.4 Route-to-Route Extrapolation) that describes in further detail the evidence supporting EPA's decision to conduct route-to-route extrapolation from oral to dermal and inhalation routes, including a detailed description of the existing PBPK models for DEHP and their strengths and limitations for quantitative use in a regulatory framework, and a more in-depth discussion of the empirical evidence describing how ADME varies across routes of exposure (oral, dermal, and inhalation). Because EPA did not consider any of the five inhalation studies identified to be suitable for quantitative derivation of an inhalation POD, EPA did not consider it necessary or appropriate to conduct a bounding calculation to demonstrate that the route-to-route extrapolation to derive the inhalation POD from the oral data is not an underestimate.

2.5.3.2 Charge Question 5.c.ii

Please comment on EPA's decision to perform route-to-route extrapolation from the oral POD to derive an inhalation POD.

2.5.3.2.1 SACC Recommendation and EPA Response (Charge Question 5.c.ii)

SACC Recommendation: The Committee recommends that the EPA reconsider and refine the route-to-route extrapolation to estimate an inhalation POD considering metabolism and absorption differences between the oral and inhalation routes of exposure.

D*raft Non-cancer Human Health Hazard Assessment for DEHP* (section 1.1, line 402): There are numerous instances throughout the various documents (not just this one) of the typo underlined here: "Existing assessments reviewed by EPA are listed below. As described further in 0, most of these…" Please clarify if this is meant to refer to another section of the document?

EPA Response: In response to feedback from the SACC, EPA added a new section (Section 4.4 Route-to-Route Extrapolation) to the Non-cancer Human Health Hazard Assessment for DEHP. This section describes the strengths, weaknesses and limitations of the available published PBPK models for DEHP, including limitations that preclude their use in dosimetry predictions (*e.g.*, attributed all elimination of the metabolite MEHP to liver metabolism, which does not account for urinary excretion) and the lack of validation of these models to support route-to-route extrapolation for regulatory risk assessment. Therefore, EPA conducted route-to-route extrapolation using a combination of empirical absorption data and default assumptions regarding potential route-specific differences in metabolism. The available data accounting for differential absorption across routes (oral, dermal, inhalation) and similarities in metabolism indicate that the hazard derivation from different routes of exposures is reasonably supported. Section 4.4 on Route-to-Route Extrapolation in the Non-cancer Human Health Hazard Assessment for DEHP describes the ADME data in further detail across routes and species.

EPA has fixed the broken cross-reference to '0'. EPA's intent was to reference Appendix A in that instance. Broken cross-references to '0' have also been fixed throughout other documents, as indicated by SACC.

2.5.4 Charge Question 5.d

In Section 4.3 of the *Draft Non-cancer Human Health Hazard Assessment for DCHP*, EPA has preliminarily selected a human equivalent dose (HED) of 2.4 mg/kg/day (NOAEL of 10 mg/kg/day from Li *et al*. (2016)) based on effects on the developing male reproductive system consistent with a disruption of androgen action and phthalate syndrome for assessing risks from acute, intermediate, and chronic duration exposure to DCHP. Please comment on the strengths and uncertainties in the selected acute/intermediate/chronic HED for DCHP.

2.5.4.1 SACC Recommendations and EPA Response (Charge Question 5d)

1. **SACC Recommendation:** The Committee agrees that EPA provided sufficient justification to proceed with the HED of 2.4 mg/kg/day, based on the NOAEL dose of 10 mg/kg/day (rat) in the selected study by (Li, Chen *et al*. 2016).
2. **SACC Recommendation:** However, the Committee also recommends that EPA use the $BMDL_5$ from the meta-analysis as the POD for DCHP, as justified above. This approach would be consistent with other phthalates under consideration and with EPA's cumulative risk assessment guidance. At a minimum, EPA should explicitly state the strengths and weaknesses of both approaches in Section 4.2 of the *Draft Non-cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate*. The Agency should justify its choice based on the balance of those strengths and weaknesses, rather than giving greater weight to the weaknesses of the BMD approach.
3. **SACC Recommendation:** Finally, if EPA chooses to use the BMD approach, the EPA should specify the rationale for the selected benchmark response (BMR) level, taking into consideration the uncertainties described above by the Committee.

EPA Response to SACC Recommendations 1–3: EPA has added additional text to Section 4 of the DCHP Non-cancer Human Health Hazard TSD further describing how EPA utilized the NOAEL/LOAEL and BMD modeling approaches as part of the dose-response assessment for DCHP. This includes additional discussion describing the balance of strengths and weaknesses of both the BMD and NOAEL/LOAEL approaches to determine the proposed POD and HED for DCHP, including acknowledgement of the limitations and uncertainties of the NOAEL/LOAEL approach. Additional text has been added to Section 4 of the DCHP Non-cancer Human Health Hazard TSD and to Table 4-1 to clearly describe which studies EPA considered for additional BMD analysis to refine NOAEL/LOAEL values, the results of any additional BMD modeling that was conducted, and if BMD was not conducted, the reasons why modeling on specific studies was not conducted.

Specifically, EPA conducted additional BMD modeling of fetal testicular testosterone data from the individual studies (Gray et a. 2021; Furr et al. 2014) included in the meta-analysis using EPA's BMD Software (BMDS Online Version 25.1), as well as testosterone data from two studies (Li et al. 2016; Ahbab et al. 2015) in which the outcome was measured in postnatal rats (not fetal rats) and was not included in the meta-analysis of combined data. BMD modeling of individual *ex vivo* fetal testicular testosterone data sets from Gray et al (2021) and Furr et al. (2014) supports BMD_5 and $BMDL_5$ estimates of 9.0 and 5.2 mg/kg-day (Furr et al. 2014) and BMD_5 and $BMDL_5$ estimates of 13.7 and 10.0 mg/kg-day (Gray et al. 2021). Notably, these BMD_5/$BMDL_5$ estimates are nearly identical to the BMD_5/$BMDL_5$ estimates of 8.4 and 6.0 mg/kg-day derived via meta-analysis of the combined data sets. No BMD models adequately fit testosterone data from Ahbab et al. (2015), while BMD analysis of PND 1 testicular testosterone data from Li et al. (2016) supports BMD_5/$BMDL_5$ estimates of 6.9 and 1.2 mg/kg-day. However, as discussed in Section 4 of the DCHP Non-cancer Human Health Hazard TSD, there is uncertainty associated with the $BMDL_5$ estimates because the $BMDL_5$ estimates are approximately 5× to 10× below the lowest dose included in each respective study. Consistent with EPA's *Benchmark Dose Technical Guidance*, the lack of data to inform the low-end of the dose-response curve reduces EPA's confidence in using the $BMDL_5$ estimates for risk characterization. Given the limitations associated with BMD modeling of fetal testosterone data, EPA has retained use of the NOAEL of 10 mg/kg-day from the study by Li et al. (2016) as the acute/intermediate/chronic POD for use in risk characterization.

EPA notes that Appendix E in the DCHP Non-cancer Human Health Hazard TSD provides EPA's rationale for selection of a BMR of 5% as the most appropriate response level for evaluating decreased fetal testicular testosterone when sufficient dose-response data are available to support modeling of fetal testicular testosterone in the low-end range of the dose-response curve. This conclusions was reached based on various biological and statistical considerations. EPA acknowledges that EPA's BMD Technical Guidance (U.S. EPA, 2012) recommends always reporting BMD model results for a BMR of 1 control SD for continuous datasets for comparison purposes. However, BMD technical guidance also clearly states that "The ideal is to have a biological basis for the BMR for continuous data." Since EPA has determined that a BMR of 5 percent is the most appropriate BMR for evaluating decreased fetal testicular testosterone, there is little value added by reporting the results of a BMR of 1 control SD (although EPA did report results for a BMR of 1 control SD for comparison purposes for BMD modeling of individual fetal testicular testosterone datasets of BBP and DIBP). It is also important to note that BMD modeling of decreased fetal testosterone data was not used just for determining the POD, but also for deriving relative potency factors (RPFs). RPFs must be derived at a constant response level so that they are comparable. Since a BMR of 1 control SD does not represent a constant response level (the magnitude of the standard deviation of the control will vary across studies and across phthalates), a BMR of 1 control SD cannot be used to calculate RPFs.

2.5.4.2 SACC Minor or Editorial Comments and EPA Response (Charge Question 5.d)

SACC Comment: Regarding the *Draft Non-cancer Human Health Hazard Assessment for DCHP*:

- There is a typo on line 1091: "considered developed."
- Line 1059 reads: "EPA considered reducing the UFA further to a value of 1 based on apparent differences in toxicodynamics between rats and humans." EPA should clarify that it did not reduce the UFA further.

EPA Response: EPA has addressed the typo described on line 1091 as suggested by SACC. Regarding the clarification requested on Line 1059, EPA already stated that it did not reduce the interspecies uncertainty factor (UFA) further at the end of the paragraph.

2.5.5 Charge Question 5.e

In Section 4.3 of the *Draft Non-cancer Human Health Hazard Assessment for BBP*, EPA has preliminarily selected a HED of 12 mg/kg/day (NOAEL of 50 mg/kg/day) based on effects on the developing male reproductive system consistent with a disruption of androgen action and phthalate syndrome observed across several studies (Tyl *et al*. 2004; Ahmad *et al*. 2014; Furr *et al*. 2014; Aso *et al*. 2005) for assessing risks from acute, intermediate, and chronic duration exposure to BBP. Please comment on the strengths and uncertainties in the selected acute/intermediate/chronic HED for BBP.

2.5.5.1 SACC Recommendation and EPA Response (Charge Question 5.e)

SACC Recommendation: The Committee agreed that reliance upon multiple authoritative reviews of the available data for BBP in drawing conclusions about studies to be relied upon for EPA is a strength and demonstrates consensus with other reviews of the relevant data for BBP, as long as there are no new studies to challenge that conclusion. The Committee also commented that the endpoints of concern are also consistent with endpoints recommended by the SACC (2023) in a previous review of the approach for phthalates. However, the Committee recommended:

- EPA provide justification for the use of a NOAEL/LOAEL approach versus BMD modeling results for selecting a POD for a single phthalate. Especially since the BMD approach is preferred for the development of RPFs.
- EPA should demonstrate no impact if different studies are considered for the individual phthalate POD versus the meta-analysis to derive RPFs. It is possible that the use of different studies may introduce uncertainty or suggest differences that are not currently being considered.
- If EPA relies upon the results of BMD modeling to identify a POD, the approach and BMR selected should be consistent with the *Benchmark Dose Technical Guidance* (US EPA 2012) and, if not, justification needs to be provided.
- The data from Gray *et al*. (2021) should be considered in the derivation of a POD, as well as the results from other studies that provide NOAELs or LOAELs lower than those based on the results from the Tyl *et al*. (2004) study. This may impact the selected POD.

EPA Response: EPA has added additional detail throughout Section 4.2 of the BBP Human Health Hazard TSD describing the consideration of both BMD modeling and NOAEL/LOAEL approaches for studies considered during dose-response analysis to determine the POD for BBP. In revising the dose-response assessment consistent with EPA's *Benchmark Dose Technical Guidance*, EPA considered multiple studies providing potentially sensitive endpoints for BMD modeling to refine the identified NOAEL/LOAEL values for sensitive studies (*e.g.*, testicular histopathology, sperm parameters, organ weights). Studies that were considered were those that showed a NOAEL or LOAEL at 100 mg/kg-day or below, where a consensus LOAEL of 100 mg/kg-day was noted for BBP effects. For many of the endpoints considered for BMD modeling but not modeled, EPA added discussion on why BMD analysis was not appropriate, including data reporting deficiencies, lack of dose-response data (*i.e.*, only high dose effects in histopathology data), or data identified as generally not amenable to BMD modeling. BMD analysis notes were added to Section 4.2 and to the dose-response table (Table 4-1). However, of the sensitive studies, testicular histopathology effects of testes softening and seminiferous tubule atrophy were identified in Aso et al. (2005) as sensitive dose-responsive endpoints suitable for BMD analysis. EPA conducted BMD analysis of these endpoints, which resulted in a $BMDL_5$ of 55 mg/kg-day based on increased incidence of seminiferous tubule atrophy in F1 males (Appendix G was added with BMD analysis details). Overall, in considering and conducting further BMD analysis in revisions, BBP effects still fell within a NOAEL/LOAEL of around 50/100 mg/kg-day. To summarize EPA's conclusions on the additional analysis and considerations, EPA has also added a section (Section 4.2.4) in the dose-response assessment on conclusions of additional BMD analysis.

Also discussed in dose-response assessment, two studies provided effect levels below the NOAEL of 50 mg/kg-day identified in Tyl et al. (2004) based on decreased anogenital distance in F1 and F2 rats. Ahmad et al. (2014) suggested a NOAEL of 20 mg/kg-day based on decreased serum testosterone, decreased epididymis and prostate weight, and sperm effects, and Gray et al. (2021) suggested a no-observed-effect-level (NOEL) of 11 mg/kg-day based upon fetal testicular gene expression decrease in *Insl3*. Grey et al. (2021) was noted to show a gene expression change at the low-dose range, but *ex vivo* fetal testicular testosterone was decreased at a LOAEL of 300 mg/kg-day. However, the low-dose gene expression effect was not considered adverse in isolation of other phthalate-syndrome outcomes (*e.g.*, testosterone production, histopathology, malformations), and the *ex vivo* fetal testicular testosterone from Gray et al. (2021) was included in the BMD analysis of fetal testosterone level meta-analysis and individually (no acceptable model fits were found). Sensitive endpoints reported at the NOAEL in Ahmad et al. (2014) were discussed as well (and considered for BMD analysis), but EPA identified data reporting deficiencies, study limitations, and inconsistencies compared to other studies such that this study was not selected for the BBP POD. Thus, EPA had higher confidence in the next most sensitive

NOAEL of 50 mg/kg-day from Tyl et al. (2004). Additionally, the LOAEL of 100 mg/kg-day from Ahmad et al. (2014) was considered with multiple other LOAELs reported in other studies for sensitive phthalate-syndrome effects.

2.5.5.2 SACC Minor or Editorial Comments and EPA Response (Charge Question 5.e)

SACC Comment: Regarding lines 416–420, the Committee recommended that this sentence specify that the sexual differentiation (masculinization) of the gonads occurs during this time and does not refer to sexual differentiation of the hypothalamus and neuroendocrine systems.

EPA Response: EPA has addressed this editorial comment by specifying the masculinization programming window being referred to is "of the gonads".

2.5.6 Charge Question 5.f

In the *Draft Meta-analysis and Benchmark Dose Modeling of Fetal Testicular Testosterone for DEHP, DBP, BBP, DIBP, and DCHP*, EPA conducted an updated meta-analysis and BMD modeling analysis of decreased fetal testicular testosterone in rats. The analysis represents an update of the analysis conducted by NASEM in 2017. As part of EPA's updated analysis, EPA conducted modeling using Metafor Version 2.0.0 (version originally used by NASEM in 2017) and Version 4.6.0 (most recent version available at the time of EPA's updated analysis); evaluated *benchmark response (BMRs)* of 5, 10, and 40 percent (NASEM evaluated BMRs of 5 and 40 percent); and included newly identified fetal testicular testosterone data.

Overall, EPA selected BMD modeling results obtained using Metafor Version 4.6.0 for use in the single phthalate risk evaluations and phthalate cumulative risk assessment because these results were obtained using the most up-to-date version of the Metafor package available at the time of the updated meta-analysis and BMD modeling analysis. Please comment on the strengths and uncertainties associated with the methods and data used in the updated analysis. In your response, please comment on EPA's preliminary decision to use model results obtained using Metafor Version 4.6.0 vs. Version 2.0.0.

2.5.6.1 SACC Recommendations and EPA Response (Charge Question 5.f)

1. **SACC Recommendation:** Address the limitations previously identified by the SACC in 2023 and as part of the public comments to demonstrate that the approach using Metafor is state of the science and able to sufficiently model the available dose-response information. If not, the application of EPA's BMDS models should be considered. If the EPA BMDS models provide adequate fits, those outputs should be considered.
2. **SACC Recommendation:** Differences in the PODs recommended in individual phthalate assessments and those relied upon for the meta-analysis need further review and discussion to identify any potential uncertainties and the potential impact on the meta-analysis results.

   EPA Response to Recommendations 1-2: EPA has added additional discussion to Section 2.4.1 of the cumulative risk assessment (CRA) TSD to address limitations noted by SACC, including 1) use of additional BMD modeling tools, including use of EPA's BMD Software; 2) appropriateness of combining fetal testicular testosterone concentration data and *ex vivo* fetal testicular testosterone production data; 3) parallel dose-response curves; and 4) use of a new Bayesian Hierarchical Modeling approach for BMD modeling. These four topics are discussed further below.

1. *Use of Additional BMD Modeling Tools: BMD Modeling of fetal testis testosterone data using EPA's BMD Software*. To help address uncertainty associated with the limited number of models included in Metafor, EPA conducted additional BMD modeling of fetal testicular testosterone data from individual studies of DBP, DCHP, DIBP, and BBP using EPA's BMD Software (BMDS). The primary benefit of this analysis is that EPA's BMD Software includes a broader suite of models compared to those included in the meta-analysis approach (*i.e.*, Exponential, Hill, Polynomial, Power, Linear models vs. linear and linear-quadratic models in Metafor). However, a limitation of this additional analysis is that it does not allow for meta-analysis of combined data (*i.e.*, datasets from individual studies are modeled one at a time). Further, it is important to note that EPA's current BMD Software does not incorporate Bayesian model averaging for continuous models (EPA's BMDS only offers Bayesian modeling averaging for dichotomous models).

   A comparison of BMD modeling results using Metafor and EPA's BMD Software for DBP, DCHP, DIBP, and BBP is provided in Section 2.4.1.1 of the CRA TSD and more detailed results from this additional BMD modeling are provided in the individual non-cancer human health hazard assessments for DBP, DIBP, DCHP, and BBP. Notably, in many cases, the linear model in EPA's BMDS provided a viable fit (although typically not the best fit) for the modeled fetal testicular testosterone data from individual studies, suggesting the linear and linear-quadratic models in Metafor would be expected to provide reasonable BMD/BMDL estimates. Consistent with this, EPA obtained similar BMD/BMDL estimates between the two BMD modeling approaches for DBP, DIBP, BBP, and DCHP. This further demonstrates that the linear-quadratic model in Metafor provides reasonable BMD/BMDL estimates, which increases EPA's confidence in use of Metafor for meta-analysis and BMD modeling of fetal testicular testosterone data to support POD and RPF derivation.

2. *Appropriateness of combining fetal testicular testosterone concentration data and ex vivo fetal testicular testosterone production data*. Another uncertainty noted by SACC during the August 2025 peer-review meeting was whether it was appropriate to combine fetal testicular testosterone concentration data with *ex vivo* fetal testicular testosterone production data as part of the meta-analysis and BMD analysis, as was done for DBP and DEHP. For example, the DEHP meta-analysis and BMD analysis included fetal testicular testosterone concentration data from two publications and *ex vivo* fetal testicular testosterone production data from six publications, while the DBP meta-analysis and BMD analysis included fetal testicular testosterone concentration data from five publications and *ex vivo* fetal testicular testosterone production data from three publications. In contrast, only *ex vivo* fetal testicular testosterone production data was included in the meta-analysis and BMD analysis for DIBP, BBP, and DCHP.

   As discussed in Sections 2.4.1.1 and 2.4.1.2 of the CRA TSD, EPA conducted BMD modeling of individual fetal testicular testosterone datasets for DBP using EPA's BMD Software (BMDS Version 25.1). Across the 5, 10, and 40 percent response levels, BMD estimates for fetal testicular testosterone content and *ex vivo* fetal testicular testosterone production were similar (within approximately two-fold or less), indicating similar sensitivity in responses across the two measures of reduced fetal testicular testosterone. Given the similarity in BMD estimates across response levels for both measures of fetal testicular testosterone, EPA concludes that its current meta-analysis and BMD analysis approach that combines data for both measures of fetal testicular testosterone for DBP and DEHP remains appropriate.

3. *Parallel dose-response curves*. As discussed by the National Research Council in 2008 (NRC 2008), there may be challenges associated with the RPF approach because phthalate dose-response curves may lack "parallelism." For parallel dose-response curves the RPF is constant, regardless of the response level (that is, 5%, 10%, or 40%). However, different chemical dose-responses may have differing shape and slope dose-response curves leading to variability in RPFs across different BMRs. This concern was echoed by the SACC during the 2023 peer-review of EPA's *Draft Proposed Approach for Cumulative Risk Assessment (CRA) of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act* and the August 2025 peer-review of this CRA TSD. Although SACC noted that parallel dose-response curves are not required for estimating RPFs, they are preferred, and demonstrating parallel dose-response curves would increase confidence in EPA's derived RPFs.

   Consistently, EPA's *Advances in Dose Addition for Chemical Mixtures: A White Paper* (U.S. EPA, 2023) states "*In the Agency-wide guidance on dose addition, there is an assumption of constant relative potency (U.S. EPA, 1987; U.S. EPA, 2000), but a demonstration of empirical evidence, such as similar DRC [dose-response curve] shapes, is not required."* Thus RPFs can be applied for chemicals with dissimilar dose-response curves, as the establishment of a known or suspected common mode of action (MOA) shared by members of the class of compounds is considered more fundamental. It is common practice to estimate RPFs closer to the low-dose range of the dose-response function. This practice is intended to reduce possible high-dose influences on estimated RPFs that may arise due to saturation of certain kinetic processes (*e.g.*, receptor binding, metabolic elimination). However, this approach also carries an implicit assumption that dose-response curve shapes will be similar below the selected response level (U.S. EPA, 2023).

   For parallel dose-response curves, the RPF is constant regardless of the response level (that is, 5%, 10%, or 40%). As discussed earlier in Section 2.4.1.3 of the CRA TSD, candidate RPFs calculated using BMD_5, BMD_{10}, and BMD_{40} estimates derived using Metafor Version 4.6.0 were nearly identical across response levels for DEHP (RPFs ranged from 0.82–0.84), DCHP (RPFs ranged from 1.66–1.71), and DINP (RPFs ranged from 0.19–0.21), providing evidence of parallel dose-response curves with the index chemical DBP. For DIBP, an RPF of 0.53 was calculated at both the 10 and 40 percent response levels, providing evidence of parallel dose-response curves with the index chemical; however, no RPF could be calculated at the 5 percent response level because a BMD_5 could not be estimated for DIBP. For BBP, an RPF of 0.52 was calculated using the BMD_{40} estimate. RPFs could not be estimated for BBP at the 5 or 10 percent response levels because BMD_5 and BMD_{10} values could not be estimated for BBP.

   For use in the CRA, EPA selected RPFs based on BMD_{40} estimates calculated using Metafor Version 4.6.0, since this was the only the only response level at which a full set of RPFs could be derived for all phthalates included in the CRA. Because candidate RPFs could not be derived for BBP or DBP at the 5 percent response level, or for BBP at the 10 percent response level, there is some uncertainty regarding constant proportionality for these two phthalates in the low-end range of the dose-response curve. However, this uncertainty was addressed by calculating candidate RPFs using BMD estimates derived via Metafor Version 2.0.0, which allowed BMD estimates to be calculated for all phthalates at all response levels. As discussed earlier in Section 2.4 of the CRA TSD, there was little variability in candidate

RPFs calculated using BMD_5, BMD_{10}, and BMD_{40} estimates derived using Metafor Version 2.0.0, providing evidence of parallel dose-response curves for DEHP, DBP, BBP, DCHP, DIBP, and DINP. Further, candidate RPFs calculated using BMD_5 estimates derived using Metafor Version 2.0.0, were similar to the selected RPFs calculated using BMD_{40} estimates derived using Metafor Version 4.6.0. This indicates that the selected RPFs derived from the 40 percent response level are expected to provide a reasonable estimates of potency at the 5 and 10 percent response levels, and provides evidence of parallel dose-response curves for all the phthalates included in the CRA.

4. *Use of a new Bayesian Hierarchical Modeling approach for BMD modeling*. During the August 2025 phthalate peer-review meeting, a public commentor (EPA-HQ-OPPT-2024-0551-0155) described a new method for estimation of RPFs that has recently been applied to dioxin-like compounds (Ring et al. 2023). A key concern addressed by the new RPF method is the possibility of a lack of parallelism in the dose-response curves between the compound for which the RPF is being calculated and the index chemical.

   The new RPF integration method (Ring et al. 2023) was developed to address a large body of knowledge about dioxin-like compounds comprising 604 RPFs of varying quality (Haws et al. 2006). To allow the new RPF method to be used, a machine learning model was developed and trained to assign study quality predictions to each RPF (Wikoff et al. 2023). The underlying dose-response dataset were available for approximately half the RPFs. Where the underlying dose-response datasets were available, the new method re-estimated the RPF as a function of response level. A Bayesian statistical framework allowed for weighting of each RPF based on the machine learning estimate of study quality and the uncertainty in the RPF estimate where available. The implementation of the new RPF method, while described in a peer-reviewed scientific publication, is not yet available as open-source software. A machine learning model is not available to determine the study quality of phthalate RPFs.

   EPA recognizes that although the Bayesian Hierarchical Modeling approach may represent an alternative method to estimate BMD values and RPFs, the new method is not yet available as open-source software and is not reasonably available to EPA at this time. Under TSCA, reasonably available information means "*information that EPA possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations,* ***considering the deadlines specified in TSCA section 6(b)(4)(G) for completing such evaluation*** *[emphasis added]...*" (40 CFR § 702.33).

   Importantly, EPA considers its current analysis using Metafor to be scientifically valid and appropriate for deriving BMD estimates and RPFs. This is because EPA's current analysis demonstrates that for reduced fetal testicular testosterone, RPFs do not vary across a range of BMRs (*i.e.,* BMRs of 5, 10, and 40%). Further, similar BMD estimates across a range of response levels were derived using two BMD modeling approaches (*i.e.,* Metafor analysis of combined data and BMD analysis of individual data sets using EPA's BMD Software). The similarity in BMD estimates between the two modeling approaches indicates that the linear-quadratic model in Metafor provides reasonable BMD/BMDL estimates. All these reasons provide confidence that the current analysis with Metafor remains appropriate.

2.5.6.2 SACC Minor or Editorial Comments and EPA Response (Charge Question 5.f)

Draft Meta-analysis and Benchmark Dose Modeling of Fetal Testicular Testosterone for DEHP, DBP, BBP, DIBP, and DCHP (U.S. EPA, 2024):

1. **SACC Comment:** Figures in Appendix A.3 need legends explaining what the numbers are. For example, what is the "Estimate"? Is this a response, benchmark dose, or percent change?

   EPA Response: EPA has added legends to all figures in Appendix A defining what is meant by "estimate." That is 'Estimate [95% CI]' indicates the estimated effect of DIBP on free testes testosterone expressed as the log transformed ratio of means.

2. **SACC Comment:** Tables such as Table 4.2 need legends. What do Tau and I^2 represent?

   EPA Response: EPA has added notes to Table 4.2 and all other relevant tables in the meta-analysis TSD to define Tau (estimated standard deviation of the true underlying effect sizes across studies in the random-effects model meta-analysis) and I2 (describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error), as well as all other acronyms used in each table.

2.5.7 Charge Question 5.g

In Section 4.3 of the *Draft Non-cancer Human Health Hazard Assessment for DBP*, EPA has preliminarily selected an HED of 2.1 mg/kg/day ($BMDL_5$ of 9 mg/kg/day) based on decreased fetal testicular testosterone for assessing risks from acute, intermediate, and chronic duration exposure to DBP. The $BMDL_5$ that serves as the basis of the HED was derived through meta-analysis and benchmark dose modeling of fetal testicular testosterone data from eight studies of DBP with rats (Gray *et al*. 2021; Furr *et al*. 2014; Johnson *et al*. 2011; Struve *et al*. 2009; Howdeshell *et al*. 2008; Martino-Andrade *et al*. 2008; Johnson *et al*. 2007; Kuhl *et al*. 2007). Please comment on the strengths and uncertainties in the selected acute/intermediate/chronic HED for DBP.

2.5.7.1 SACC Recommendations and EPA Response (Charge Question 5.g)

1. **SACC Recommendation:** EPA should clarify differences in the dose responses obtained from studies measuring testosterone content in the testes compared to those studies in which testosterone production rate was determined. It is important to distinguish potential differences in quantitative response and determine if the slope and intensity of responses are similar. This is needed because these methods measure different aspects of testicular function and reflect either static testicular content or the ability of testicular Leydig cells to produce and release testosterone.
2. **SACC Recommendation:** EPA should clarify differences in dose response obtained from studies measuring testosterone content and those that measured testosterone production rate to distinguish potential differences in quantitative responses and to determine if the slope and intensity of responses are similar.

   EPA Response to Recommendations 1-2: EPA notes that the first and second listed recommendations from SACC are nearly identical, and the second bullet appears to be an editorial issue. Therefore, this response is to the first listed recommendation.

   EPA acknowledges that testosterone content and testosterone production rate are two related, although different outcomes measured and reported for DBP. Data for both outcomes are pooled as part of the meta-analysis and BMD analysis of decreased fetal testicular testosterone data,

which is the basis of the selected POD. To determine if pooling of the data was appropriate, EPA conducted BMD modeling of testosterone data from 7 of the 8 individual studies included in the meta-analysis using EPA's BMD Software (BMDS Online Version 25.1). This includes fetal testicular testosterone content data from 4 studies (Martino-Andrade et al. 2008; Kuhl et al. 2007; Struve et al. 2009; Johnson et al. 2007) and *ex vivo* fetal testicular testosterone production data from 3 studies (Howdeshell et al. 2008; Furr et al. 2014; Gray et al. 2021). EPA did not conduct BMD modeling of testosterone content data from Johnson et al. (2011) because this study only evaluated one dose group. This additional analysis is included in the final *Non-cancer Human Health Hazard TSD for DBP*.

Adequate BMD model fits were obtained for data from 4 of the 7 publications. BMD modeling supports BMD_5 and $BMDL_5$ values of 24 and 16 mg/kg-day for reduced fetal testis testosterone content based on the best-fitting Exponential 3 model (Martino-Andrade et al. 2008); BMD_5 and $BMDL_5$ values of 22 and 14 mg/kg-day for reduced fetal testis testosterone content based on the best-fitting exponential 3 model (Kuhl et al. 2007, 1321665); BMD_5 and $BMDL_5$ values of 30 and 28 mg/kg-day for reduced fetal testis testosterone content based on the best-fitting linear model (Struve et al., 2009); and BMD_5 and $BMDL_5$ values of 49 and 39 mg/kg-day for reduced *ex vivo* testis testosterone production based on the best-fitting polynomial degree 3 model (Howdeshell et al., 2008). Overall, this BMD analysis of fetal testicular testosterone data from individual studies provides BMD_5 and $BMDL_5$ estimates similar to the BMD_5 and $BMDL_5$ estimates from the updated meta-analysis (*i.e.,* BMD_5/$BMDL_5$ values of 11/9 mg/kg-day). This demonstrates that the linear-quadratic model in the meta-analysis provided a reasonable fit compared to the wider array of models included in EPA's BMD Software, and suggests that there are not major differences in dose-response for either fetal testicular testosterone content or *ex vivo* fetal testicular testosterone production data. However, the meta-analysis of fetal testicular testosterone content and *ex vivo* fetal testicular testosterone production data reflects data from eight studies and is expected to provide a more precise estimate and therefore is preferred over the BMD analysis of individual studies, which support slightly higher $BMDL_5$ estimates

3. **SACC Recommendation:** Fetal testicular testosterone concentration and fetal testicular testosterone production are very different terms. The EPA should verify that these terms reflect the science cited throughout the *Draft Non-cancer Human Health Hazard Assessment for DBP* document.

   EPA Response: EPA has reviewed and revised the *Non-cancer Human Health Hazard TSD for DBP* and updated the use of the terms "Fetal testicular testosterone concentration" and "fetal testicular testosterone production" to more accurately reflect the measured outcome for each cited study.

2.5.7.2 SACC Minor or Editorial Comments and EPA Response (Charge Question 5.g)

The following corrections are recommended:

1. **SACC Comment:** Page 19, lines 567, 570 and 573: the acronym should be LOAEL (not LAOEL)

   EPA Response: EPA has fixed the acronym to be "LOAEL," as suggested by SACC.

2. **SACC Comment:** Appendix D, page 123, line 3053: In the example calculation of HEC unit conversion, the HEC is given as 13 mg/m^3, it should be 12 mg/m^3.

EPA Response: EPA has revised the human equivalent concentration (HEC) to 12 mg/m^3 in Appendix D, as suggested by SACC.

3. **SACC Comment:** Line 1560: Is there an extra F in the sentence beginning "F Fetal rat…"?

   EPA Response: EPA has deleted the extra 'F' in the sentence indicated by SACC.

2.5.8 Charge Question 5.h

As described in Section 4.2 of the *Draft Non-cancer Human Health Hazard Assessment for DIBP*, EPA considered three options for deriving an acute/intermediate/chronic HED for DIBP, including use of a NOAEL (Option 1, Section 4.2.2.1), use of a data-derived adjustment factor (Option 2, Section 4.2.2.2), and use of benchmark dose modeling of individual fetal testicular testosterone studies (Option 3, Section 4.2.2.3). As described in Section 4.3 of the non-cancer hazard assessment for DIBP, EPA has preliminarily selected a HED of 5.7 mg/kg/day ($BMDL_5$ of 24 mg/kg/day) based on benchmark dose modeling of decreased *ex vivo* fetal testicular testosterone production data from Gray *et al*. (2021) for assessing risks from acute, intermediate, and chronic duration exposure to DIBP (Option 3). Please comment on the strengths and uncertainties in the selected acute/intermediate/chronic HED for DIBP.

2.5.8.1 SACC Recommendations and EPA Response (Charge Question 5.h)

1. **SACC Recommendation:** The Committee recommends that EPA proceed with the BMD analysis approach (option 3) as the basis for the POD.
2. **SACC Recommendation:** The Committee considers the Gray, Lambright *et al*. (2021) data to be of high quality, and the BMDS analysis of this dataset to be suitable for determination of a POD. However, The Committee recommends that EPA evaluate BMD modeling tools other than Metafor, with the capability of performing meta-regression and BMD, including but not limited to Bayesian BMD analysis, which would enable incorporation of all appropriate datasets, including the data from Howdeshell, Wilson *et al*. (2008) and Hannas, Lambright *et al*. (2011) into the assessment. A meta-analysis and BMD analysis of these three high-quality datasets would produce the most rigorous BMD estimate for POD determination.
3. **SACC Recommendation:** The Committee recommends that EPA consider metabolism following dermal and inhalation exposure to improve their extrapolation of oral toxicity data to the dermal and inhalation exposure routes.

   EPA Response to Recommendations 1–3: Consistent with the committee's recommendation, EPA has retained used of the $BMDL_5$ of 24 mg/kg-day (HED of 5.7 mg/kg-day) based on reduced *ex vivo* fetal testicular testosterone production in the study by Gray et al. (2021) as the acute/intermediate/chronic POD for characterizing risk from exposure to DIBP in the final DIBP risk evaluation.

   As discussed in the DIBP Non-cancer human health hazard assessment, EPA utilized a meta-analysis (Metafor Versions 2.0.0 and 4.2.0) approach for BMD modeling of decreased fetal testicular testosterone. This approach allowed data from 3 studies to be integrated as part of the dose-response assessment (Hannas et al. 2011; Howdeshell et al. 2008; Gray et al. 2021). However, no $BMDL_5$ could be derived using this meta-analysis approach and therefore, EPA attempted BMD modeling of individual fetal testicular testosterone datasets from each study using EPA's BMD Software (Version 3.3.2), which has the added benefit of including additional models not included within Metafor. For example EPA's BMD Software includes Exponential,

Hill, Polynomial, Power, and Linear models, while Metafor only includes linear and linear-quadratic models. The BMD analysis of individual datasets supports the selected POD (the $BMDL_5$ of 24 mg/kg-day, equivalent to HED of 5.7 mg/kg-day).

SACC recommended that EPA evaluate BMD modeling tools other than Metafor, with the capability of performing meta-regression and BMD, including but not limited to Bayesian BMD analysis, which would enable incorporation of all appropriate datasets, as a meta-analysis and BMD analysis of the three high-quality DIBP datasets would produce the most rigorous BMD estimate for POD determination. However, SACC did not recommend any specific tools for EPA to use to accomplish this, other than the Bayesian hierarchical model approach recommended by one public commenter (EPA-HQ-OPPT-2024-0551-0155). The new Bayesian method (Ring et al, 2023) was developed to address a large body of knowledge about dioxin-like compounds comprising 604 RPFs of varying quality (Haws e tal 2006). To allow the new RPF method to be used, a machine learning model was developed and trained to assign study quality predictions to each RPF (Wikoff et al, 2023). The underlying dose-response dataset were available for approximately half the RPFs. Where the underlying dose-response datasets were available, the new method re-estimated the RPF as a function of response level. A Bayesian statistical framework allowed for weighting of each RPF based on the machine learning estimate of study quality and the uncertainty in the RPF estimate where available. The implementation of the new RPF method, while described in a peer-reviewed scientific publication, is not yet available as open-source software. A machine learning model is not available to determine the study quality of phthalate RPFs.

EPA recognizes that although the Bayesian Hierarchical Modeling approach may represent an alternative method to estimate BMD values, the new method is not yet available as open-source software and is not reasonably available to EPA at this time. Under TSCA, reasonably available information means "*information that EPA possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations, considering the deadlines specified in TSCA section 6(b)(4)(G) for completing such evaluation...*" (40 CFR § 702.33). Therefore, EPA was unable to derive BMDL estimates using this tool. EPA did not identify any other reasonably available tools to support combining and BMD modeling data from the three studies of DIBP. Additionally, it is important to note the Bayesian modeling averaging approaches for continuous models have not yet been integrated into EPA's BMD Software, so Bayesian BMD modeling of fetal testicular testosterone data cannot be accomplished using EPA's current BMD Software. Bayesian model averaging is only available for dichotomous models within EPA's BMD Software.

In response to feedback from the SACC, EPA added a new section (Section 4.4 Route-to-Route Extrapolation) to the Non-cancer Human Health Hazard Assessment for DIBP. This section describes the strengths, limitations, and uncertainties of extrapolation of oral toxicity data to the dermal and inhalation exposure routes. This includes discussion of available absorption and metabolism data for DIBP for each route of exposure.

2.5.8.2 SACC Minor or Editorial Comments and EPA Response (Charge Question 5.h)

SACC Comments:

- To support the BMR selection, please provide a reference in *the Draft Non-cancer Human Health Hazard Assessment for DIBP* to Appendix B of the *Cumulative Risk Assessment* document, which provides justification for use of $BMDL_5$ as the POD.

- The title of section 4.2.2, "Options Considered by EPA for Deriving the Acute Non-Cancer POD," should be changed to include the intermediate and chronic POD.
- Page 40, lines 1206–1209: These sentences can be clarified/simplified. The authors of the current document did not need to conduct BMD modeling because it already had been done and published in 2020. Suggest deleting "EPA considered BMD modeling of data from Saillenfait *et al.* (2008).
- Page 40, lines 1209–1211: This sentence describing the BMD modeling from the Bessinger *et al*. (2020) publication is odd as it reports that the results of modeling a BMR 5% falls outside the range of measured tested doses. That is expected. Please clarify the concern or point of discussion in this sentence.
- Page 41, line 119: "Each of these studies gavaged…" and lines 1232–1233, "Results from these studies did not observe…" have awkward subject/verb pairings.
- Page 42, line 1260: mg/mg/day should read mg/kg/day.
- Page 42 lines 1271–1279. Recommend deleting the details of the ECHA approach. It is confusing and results in a very different POD than that in EPA's Option 2. It is enough to say that ECHA also considered a potency-informed approach to derive their POD.
- There is a typo on line 1249: "No $BMDL_5$ could not be derived…"
- Line 1264 should read, "potent as DBP *at* reducing fetal testicular testosterone."
- Line 1328 should read, "*four* xenograft studies," rather than two.
- There is a sentence fragment at the beginning of the paragraph at line 1351.

EPA Response: The Agency addressed all the editorial and syntax errors identified in the DIBP Non-Cancer Human Health Hazard Assessment. Likewise, the Agency made sure to provide a reference to Appendix B of the *Cumulative Risk Assessment* document to justify the use of $BMDL_5$ as the POD. Further, the agency clarified the concern of the Blessinger et al. (2020) publication having BMR 5 percent modeling results from being outside of the range of measured tested doses by referencing the EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012), which states that the lack of data to inform the low-end of the dose-response curve reduces EPA's confidence in the derived BMD_5 and $BMDL_5$ values (found in Table 4-4) stated in the human health hazard assessment.

2.6 Charge Question 6

In Section 4.3.1.1.6 of the *Draft Cancer Human Health Hazard Assessment for DEHP, DBP, BBP, DIBP, and DCHP*, EPA has preliminarily concluded that the weight of the scientific evidence indicates that the tumor triad (*i.e.*, liver tumors, pancreatic acinar cell tumors, Leydig cell tumors) in rats is related to PPARα activation following chronic exposure to DEHP. This preliminary conclusion is supported by inferences from hypolipidemic drugs that lower lipid-levels in humans by activating PPARα, and also induce the tumor triad in rats, but not humans (Section 4.3.1.1.4). Additionally, EPA has also preliminarily concluded that DEHP is Not Likely to be Carcinogenic to Humans at doses below levels that do not result in PPARα activation and that the non-cancer POD based on effects on the developing male reproductive system consistent with phthalate syndrome that was selected to characterize risk is expected to adequately account for all chronic toxicity, including carcinogenicity (assuming a threshold MOA), which could potentially result from exposure to DEHP (Section 4.3.1.4).

2.6.1 Charge Question 6.a

Please comment on the strengths and uncertainties of EPA's preliminary conclusion that the tumor triad in rats is related to PPARα activation following chronic exposure to DEHP. 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 assessment.

2.6.1.1 SACC Recommendations and EPA Responses (Charge Question 6a)

1. **SACC Recommendation:** Adopt the use of a non-linear threshold approach for cancer risk assessment of tumors induced by DEHP based on lack of genotoxicity and associated data.

   EPA Response: EPA agrees with the committee that use of a non-linear threshold approach for cancer risk assessment of tumors induced by DEHP is appropriate. As discussed further in response to SACC recommendations for Charge Question (CQ) 6b, EPA has revised the cancer classification for DEHP to be *Not likely to be carcinogenic to humans*, consistent with SACC recommendations. Consistent with EPA's *Guidelines for Carcinogen Risk Assessment*, EPA did not conduct a cancer dose-response assessment or evaluate DEHP for cancer risk.

2. **SACC Recommendation:** Incorporate additional relevant information that describes the dose response and relevance of other mechanistic considerations that may be involved in DEHP's effects relevant to humans, including fatty acid metabolism, cell proliferation and apoptosis, oxidative stress and ROS production, and signaling pathways related to endocrine effects. These biological effects, if they are relevant, should be characterized in a dose-response manner and associated with modes of action as appropriate.

   EPA Response: EPA has integrated further discussion of cytotoxicity and regenerative proliferation into Sections 4.3.1.1.1 (liver tumors), 4.3.1.1.2 (pancreatic tumors), and 4.3.1.1.3 (Leydig cell tumors) of the phthalate cancer human health hazard assessment. Other potential modes of carcinogenic action, including through other cell signaling pathways are discussed in Section 4.3.1.1.1 of the phthalate cancer human health hazard assessment.

3. **SACC Recommendation:** Incorporate a discussion of epidemiological evidence on DEHP carcinogenesis into the weight-of- evidence.

   EPA Response: In section 4.1.3, EPA concluded that the epidemiologic evidence is insufficient to identify an association between DEHP exposure and subsequent cancer outcomes in humans. This conclusion and epidemiologic data have been integrated briefly into Sections 4.3.1.2.1 and 4.3.1.4 of the phthalate cancer TSD.

2.6.2 Charge Question 6.b

Please comment on the strengths and uncertainties of EPA's preliminary cancer classification for DEHP.

2.6.2.1 SACC Recommendations and EPA Responses (Charge Question 6b)

1. **SACC Recommendation:** The EPA should revise its cancer classification of DEHP to eliminate the "PPARα activation" caveat in light of data on MOA, receptor activation differences, and receptor-related sequellae in humans versus rodents.

   EPA Response: In the draft DEHP human health hazard cancer assessment of DEHP, EPA concluded that DEHP is *Not likely to be carcinogenic to humans* at doses below levels that do

not result in PPARα activation. Per SACC recommendations, EPA has revised the cancer classification for DEHP and removed the "at doses below levels that do not result in PPARα activation" caveat considering data on MOA, receptor activation differences between species, receptor-related sequellae in humans versus rodents, and the fact that exposure concentrations that result in any of the triad tumors are higher in rodents (>100 mg/kg-day) than humans might be exposed to under environmentally relevant conditions. The revised cancer classification for DEHP is *Not likely to be carcinogenic to humans.*

2. **SACC Recommendation:** The EPA should investigate associations of DEHP exposure with tumors in endocrine-active organs such as breast and prostate given the ability of DEHP to interfere with endocrine-related cellular signaling pathways.

   EPA Response: EPA considered the associations of DEHP exposure with tumors in endocrine-active organs such as breast and prostate. As discussed in Section 4.1.2.1, several epidemiologic studies have evaluated the link between DEHP and breast cancer outcomes. Available studies either found no link between DEHP exposure and breast cancer outcomes or found an inverse relationship between increased urinary DEHP metabolite levels and decreased breast cancer. Similarly, in some of the available rodent cancer bioassays, chronic DEHP exposure was linked with reduced incidence of mammary tumors. However, as discussed in Section 4.3.1.2.1 of the phthalate cancer TSD, this effect on mammary tumor incidence in rodents is likely linked with reduced body weight and dietary restriction caused by testing of doses that exceeded the maximum tolerable dose. Studies have demonstrated simple dietary restriction in female rats is linked with reduced mammary tumor incidence, likely due to lower sustained levels of prolactin in aging rats (Harleman et al. 2012). EPA did not identify any evidence of prostate tumors linked to DEHP exposure, and this is not further discussed in the phthalate cancer TSD.

3. **SACC Recommendation:** The Agency is advised to revise or refine its classification to align with the U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment.*

   EPA Response: EPA has added discussion of Harleman et al. (2012) to Section 4.3.1.2.1 (conclusions for uterine tumors) of the phthalate cancer TSD. This includes discussion of the potential role for caloric restriction and body weight loss on increased incidence of uterine tumors in female rats.

4. **SACC Recommendation:** The Agency should re-examine the MOA in humans relative to rodents.

   EPA Response: EPA has further considered the cytotoxicity and regenerative proliferation MOA for tumors in the tumor triad. As further discussed in Sections 4.3.1.1.1, (liver tumors), 4.3.1.1.2 (pancreatic tumors), and 4.3.1.1.3 (Leydig cell tumors), evidence of cytotoxicity has inconsistently or has not been observed in these tissues, indicating that a cytotoxic MOA is unlikely. Mention of cytotoxicity and regenerative proliferation as an uncertainty in Section 4.3.1.1.5 has been removed.

2.7 Charge Question 7

In the *Draft Cancer Human Health Hazard Assessment for DEHP, DBP, BBP, DIBP, and DCHP*, EPA preliminarily concluded that there is Suggestive Evidence of Carcinogenic Potential for BBP (Section 4.3.2.4) and DBP (Section 4.3.3.3) in rodents based on evidence of pancreatic acinar cell tumors in rats.

EPA has further preliminarily concluded that pancreatic acinar cell tumors observed in rats are not appropriate for conducting dose-response assessment for human health risk assessment.

2.7.1 Charge Question 7.a

Please comment on the strengths and uncertainties of EPA's preliminary cancer classification and rationale for not carrying forward pancreatic acinar cell tumors in rats into dose response assessment for BBP.

2.7.1.1 SACC Recommendations and EPA Responses (Charge Question 7.a)

1. **SACC Recommendation:** A minority of the Committee agreed with EPA's classification of BBP as "Suggestive Evidence of Carcinogenic Potential." A majority of the Committee recommend that a classification of *Not likely carcinogenic* is more appropriate based on the text of the EPA (2005) cancer guidelines.

   EPA Response: Consistent with the SACC majority opinion, EPA has revised its cancer classification for BBP to *Not Likely to be Carcinogenic to Humans*.

2. **SACC Recommendation:** Table 4-14 lists the carcinogenicity studies evaluated for BBP. The Committee recommends that EPA expand this table to include the incidence of the tumor type for each dose.

   EPA Response: Tumor incidence data is summarized in other tables throughout the phthalate cancer TSD. EPA has added table references to summary Table 4-14 indicating where the tumor incidence data for each tumor type can be found.

3. **SACC Recommendation:** The Committee requests clarification from EPA regarding the value of reporting the positive association between a urinary marker of BBP exposure and cancer mortality. Phthalates are used in medical devices and saline/drug/blood bags; therefore, this association might be associated with treatment for cancer instead of associated with an exposure prior to the observation of cancer.

   EPA Response: EPA agrees with the committee that phthalates are used in medical devices and saline/drug/blood bags; therefore, this association might be associated with treatment for cancer instead of associated with an exposure prior to the observation of cancer. This confounder is one of the primary uncertainties associated with the phthalate epidemiologic evidence. This is discussed in Section 4.1.3 of the phthalate cancer TSD.

4. **SACC Recommendation:** In section 4.3.1.1.5, regarding uncertainties etc , page 62 line 1793,, EPA notes: "Regardless, the possibility remains that mechanisms other than PPARα may play a role in the observed PACTs and Leydig cell tumors in rats, such as activation of other nuclear receptors or cytotoxicity and regenerative proliferation." If cytotoxicity and regenerative proliferation did occur, it would have been obvious in the shorter-term studies in the testicle and pancreas. Also, for cytotoxicity and regenerative proliferation response, if it did occur, would be a high-dose effect with doses greater than what is typically necessary for PPARα activation in rats.

   EPA Response: EPA has added discussion of cytotoxicity and regenerative proliferation to Section 4.3.2.2.1 (Conclusions on pancreatic tumors for BBP) of the phthalate cancer TSD.

Cytotoxicity (e.g., necrosis) in the pancreas has not been observed in rats chronically exposed to BBP, providing evidence that a cytotoxic MOA for pancreatic tumors is unlikely.

5. **SACC Recommendation:** L1235: "Given the limitations and uncertainties, EPA concludes that there is indeterminant evidence of an association between phthalate exposure and subsequent cancer outcomes." This is indecisive or noncommittal language; the Committee recommends EPA be more specific and state that an association cannot be identified, much less a cause and effect.

   EPA Response: EPA has revised the text to be more explicit. The updated text reads "EPA concludes that the epidemiologic evidence is insufficient to identify an association between phthalate exposure and subsequent cancer outcomes."

2.7.1.2 SACC Minor or Editorial Comments and EPA Response (Charge Question 7.a)

SACC Comments: In *Draft Cancer Human Health Hazard Assessment for DEHP, DBP, BBP, DIBP, and DCHP* 78) line 2352: change "deceased" to "decreased."

EPA Response: EPA has changed "Deceased" to "Decreased" as suggested by the committee.

2.7.2 Charge Question 7.b

Please comment on the strengths and uncertainties of EPA's preliminary cancer classification and rationale for not carrying forward pancreatic acinar cell tumors in rats into dose response assessment for DBP.

2.7.2.1 SACC Recommendations and EPA Response (Charge Question 7.b)

1. **SACC Recommendation:** Any tumor response would be most likely to occur at higher doses and there would be no tumor response at doses below where there is not a PPAR□ agonist response in the rodent. Based on a threshold response, this seems consistent with the determination of "*Not Likely to be Carcinogenic.*"

   EPA Response: Consistent with the SACC majority opinion, EPA has revised its cancer classification for DBP to *Not Likely to be Carcinogenic to Humans*.

2. **SACC Recommendation:** Clarify the presence or absence of data regarding the uncertainties described in 4.3.1.1.5. Describe any data to suggest other MOA, such as cytotoxicity and regenerative proliferation. If these studies are not reported in the relevant short-term studies, then so state.

   EPA Response: EPA has added discussion of cytotoxicity and regenerative proliferation to Section 4.3.3.1.1 (Conclusions on pancreatic tumors for DBP) of the phthalate cancer TSD. Cytotoxicity (*e.g.*, necrosis) in the pancreas has not been observed in rats chronically exposed to DBP, providing evidence that a cytotoxic MOA for pancreatic tumors is unlikely.

2.8 Charge Question 8

As discussed in Section 5 of the *Draft Cancer Human Health Hazard Assessment for DEHP, DBP, BBP, DIBP, and DCHP*, no chronic toxicity or cancer bioassays of experimental animal models are

reasonably available for DIBP or DCHP. Therefore, EPA used elements of the Rethinking Chronic Toxicity and Carcinogenicity Assessment for Agrochemicals Project (ReCAAP) weight of evidence framework (Hilton *et al*. 2022; OECD 2024) as an organizational tool to evaluate the extent to which the lack of carcinogenicity studies imparts significant uncertainty on the human health risk assessments for DIBP and DCHP. Human health hazards and toxicokinetic properties of DIBP and DCHP were evaluated and compared to DEHP, BBP, DBP, DINP, and DIDP (also referred to as "read-across phthalates").

2.8.1 Charge Question 8.a

Please comment on the strengths and uncertainties of EPA's application of the ReCAAP framework.

2.8.1.1 SACC Identified Uncertainties and EPA Responses (Charge Question 8a)

1. **SACC Comment:** In Table 5-7 of *Draft Cancer Human Health Hazard Assessment for DEHP, DBP, BBP, DIBP, and DCHP*, add species to the Effect column, as some are not labeled.

   EPA Response: EPA has added the species to the effect column in Table 5-7 as requested by the SACC.

2. **SACC Comment:** Because EPA is applying a new framework for this TSCA assessment adapted from ReCAAP for this read- across weight of evidence analysis, a rationale for selecting this framework is necessary. What advantages does this framework offer over others?
   In the last SACC review of risk evaluation documents that included an application of read across (1,1-dichloroethane), a different read-across approach/framework was referenced (Lizarraga *et al*. 2019) and the SACC recommended incorporating the work of Lizarraga *et al*. (2023) (US EPA, 2024b). Please explain the selection of the adapted ReCAAP framework, including its advantages and disadvantages compared with the Lizarraga *et al*. (2023) read-across framework.

   EPA Response: See EPA response to SACC recommendation 2 below.

3. **SACC Comment:** In the *Draft Cancer Human Health Hazard Assessment for DEHP, DBP, BBP, DIBP, and DCHP*, page 96 lines 2914–2926, the Agency outlines the elements of the ReCAAP framework that were used. Please explain which elements were not used and why.

   EPA Response: EPA has added clarification to Section 5 of the phthalate Cancer TSD that most elements of the ReCAAP framework were considered. The one exception to this is that use patterns and exposure scenarios were not considered in the phthalate cancer TSD. This information is however provided and discussed in the individual risk evaluations for DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP.

4. **SACC Comment:** Another example of the application of the ReCAAP and OECD IATA framework has been published and might be a useful additional reference for page 96, line 2912, Goetz *et al*. (2024) presents additional examples of the application of the framework.

   EPA Response: EPA has reviewed and added the Goetz et al. (2024) reference to the Section 5 of the phthalate Cancer TSD.

5. **SACC Comment:** In section 5.6 "Evidence of Immune System Perturbation," with regard to the relationship of the immune system (aside from lymphocytic tumors), it is specifically immune

suppression that is considered procarcinogenic in humans where there is a loss of immune surveillance of transformed cells (Cohen *et al*. 2019).

EPA Response: EPA agrees with the committee that immune system suppression is the specific effect relevant to carcinogenesis. As noted in Section 5.6, immune system suppression has not been identified as a hazard of concern for DIBP, DCHP, DEHP, DBP, BBP, DINP, or DIDP.

6. **SACC Comment:** On page 106 line 3141–3142 reads, "As discussed in Section 3.3, DBP was positive for mutagenic activity in several *in vitro* mouse lymphoma assays; however, DBP showed no mutagenic activity in other *in vitro* bacterial reverse mutation assays. This evaluation needs further scrutiny. Were the assays positive at high concentrations only, and would they be concentrations that are cytotoxic and cause oxidative stress in the mouse lymphoma assay system?

   EPA Response: EPA has further reviewed the *in vitro* mouse lymphoma assays of DBP, as suggested by the committee. In the draft assessment, EPA cites three mouse lymphoma assays (Hazelton, 1986; NTP 1995; Barber et al. 2000), however, the Hazleton and Barber references report data from the same study and are duplicate. Therefore, there are only 2 *in vitro* mouse lymphoma studies of DBP. In the first study, NTP (1995) found a significant increase in mutagenic activity in the absence of metabolic activation, but only at concentrations that caused marked decreases in cell survival. Similarly, in the second study (Barber et al. 2000; Hazleton 1986), a significant increase in mutagenic activity was noted in the presence of rat liver S9 at high concentrations that were above the solubility limit and coincided with a marked decrease in cell survival. This additional detail has been added to Section 3.3 of the phthalate cancer TSD.

7. **SACC Comment:** A summary of the structural similarity measures (e.g., Tanimoto scores, Dice similarity index) should also be included with a description of the chemical functional groups and/or structural alerts.

   EPA Response: EPA has added Tanimoto scores to Section 5.1 of the phthalate cancer TSD as recommended by the SACC.

8. **SACC Comment:** The title is misleading since this TSD summarizes the genotoxicity and cancer hazards associated with DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP – as opposed to title listing of DEHP, BBP, DBP, DIBP, & DCHP.

   EPA Response: The phthalate cancer TSD summarizes information primarily for DEHP, DBP, BBP, DIBP, and DCHP. Information for DIDP and DINP were previously summarized in separate non-cancer and cancer human health hazard TSDs and reviewed separately by the SACC in 2024. Information on DIDP and DINP is included in the current phthalate Cancer TSD to support read-across. Since separate documents are the primary sources of genotoxicity and carcinogenicity information for DIDP and DINP, EPA does not believe DINP and DIDP warrant being included in the title of the document, and the document title was not updated.

9. **SACC Comment:** Use of the term "read across" is repeatedly used as an "adjective" and not in the correct manner. Read across is a method and read across is conducted. Chemicals used to predict DIBP and DCHP effects can be called DIBP or DCHP analogs or surrogates.

   EPA Response: EPA has updated the phthalate Cancer TSD such that the term 'read-across' is no longer used as an adjective.

2.8.1.2 SACC Recommendations and EPA Responses (Charge Question 8a)

1. **SACC Recommendation:** EPA should consider presenting the findings using the RISK21 (RISK21, 2025) framework approach, as it is a very useful decision support and communication tool.

   EPA Response: EPA acknowledges that the Risk21 framework approach can be a useful decision support and communication tool. EPA did not integrate the suggested framework into the phthalate Cancer TSD because it would not significantly change the results or conclusions of the assessment. EPA may consider integrating the Risk21 framework in future risk evaluations.

2. **SACC Recommendation:** EPA should explain the selection of the adapted ReCAAP framework, including its advantages and disadvantages compared to the Lizarraga *et al*. (2023) read-across framework.

   EPA Response: EPA has added clarification to Section 5 of the phthalate Cancer TSD that the ReCAAP framework was selected over other read-across frameworks such as the one presented by Lizarraga et al (2019, 2023) because the ReCAAP frameworks purpose is to specifically determine the need for rodent cancer bioassays for chemicals, such as DIBP and DCHP, lacking the rodent cancer bioassays. In contrast, Lizarraga et al. (2019, 2023) presents a more general read-across framework.

2.8.2 Charge Question 8.b

Please comment on EPA's preliminary conclusion that the lack of chronic toxicity and carcinogenicity studies are not a significant source of remaining scientific uncertainty in the qualitative and quantitative risk characterization for DIBP and DCHP.

2.8.2.1 SACC Recommendations and EPA Responses (Charge Question 8b)

SACC Recommendation: The Committee found the Agency's approach to characterizing uncertainty for DIBP and DCHP appropriate and had no further recommendations.

EPA Response: EPA thanks the committee for their feedback.

2.9 Charge Question 9

In Section 2.3 of the *Revised Draft Technical Support Document for the Cumulative Risk Analysis of DEHP, DBP, BBP, DIBP, DCHP, and DINP Under the Toxic Substances Control Act (TSCA)*, EPA preliminarily selected DBP to serve as the index chemical because it: has a high quality toxicological database demonstrating effects on the developing male reproductive system consistent with a disruption of androgen action and phthalate syndrome; is well characterized for the MOA associated with phthalate syndrome; and has the most fetal testicular testosterone dose-response data in the low-end range of the dose-response curve where the BMD and BMDL estimates at the 5 and 10 percent response level are derived. Please comment on the strengths and uncertainties of the selection of DBP as the index chemical.

2.9.1 SACC General Comments and EPA Responses (Charge Question 9)

1. **SACC Comment:** EPA may wish to consider recent publications on cumulative risk assessment (Moretto *et al*. 2016; Solomon *et al*. 2016).

2. **SACC Comment:** Section 2.1 "Relative Potency Factor Approach": The Agency may wish to use the approach in Moretto *et al*. (2016) to represent the RPF in a clear way for improved communication of the individual and combined risk.

3. **SACC Comment:** In Section 5.1 "Estimation of Cumulative Risk," the Agency should plot the options using the approach described in Moretto *et al*. (2016) for a simple way to compare the different options and select the best approach.

   EPA Response (General Comments 1–3): The intention of the framework presented in Moretto *et al*. (2016) is to determine whether it is appropriate to conduct a cumulative risk assessment for a group of chemicals. EPA's approach for determining cumulative risk under TSCA is uniquely specific to individual COUs. The approach for selecting the group of phthalates for consideration in a CRA and conducting the CRA for the phthalates was peer reviewed and received support by the SACC in 2023. The Moretto et al (2016) publication encourages the use of the RISK21 approach developed by Health and Environmental Sciences Institute (HESI). EPA notes that the HESI RISK21 approach involves "problem formulation-based, exposure-driven, tiered acquisition approach that leads to an informed decision" and advocates the use of "Enough precision to make the decision". EPA's 1992 *Guidelines for Exposure Assessment* recommends a tiered approach to exposure assessment which involves various iterations where the level of detail or degree of confidence is evaluated at each iteration; this evaluation considers the extent to which the assessment achieves its the purpose. Successive iterations continue until the answer is affirmative, new input data are generated, or as is the case for many assessments, the available data, time, or resources are depleted. EPA's cumulative risk assessment of phthalates follows the exposure guidelines and is such consistent with the HESI RISK21 approach.

4. **SACC Comment:** On page 15, line 599, fetal testicular testosterone as acute effect. Is the idea then to select a POD based on the acute response with the conclusion that if there is no acute response then there would be no response from repeated exposure either?

   EPA Response: EPA considers decreased fetal testicular testosterone an acute effect because studies have demonstrated that a single exposure to DBP during the critical window of development is sufficient to decrease fetal testicular testosterone content and cause later life reproductive tract malformations in adult male rats. This is discussed in Appendix C of the DBP non-cancer human health hazard TSD (note: similar appendices are included in the non-cancer human health hazard TSDs for DEHP, DCHP, BBP, and DIBP). Since effects on the developing male reproductive system consistent with phthalate syndrome are the most sensitive effect following oral exposure to DBP, DEHP, DCHP, BBP, and DIBP, the acute POD is also used to assess risk from intermediate and chronic exposures. Since acute exposures are higher than intermediate and chronic exposures for each assessed exposure scenario, and since a single POD is used to assess risk for all durations, protecting for acute effects will also be protective of intermediate and chronic duration risk.

5. **SACC Comment:** On page 16, line 609, protecting for acute exposure will protect from longer exposure. This approach makes sense and is a good use of resources with an ability to achieve protection goals.

   EPA Response: EPA acknowledges this feedback from the SACC.

6. **SACC Comment:** Section 1.1 "Risk Cup Concept in Cumulative Risk Assessment": This is a useful approach that is consistent with the approach used for crop protection products, and it is a good way to determine when the risk level is getting too great or if there is still a good amount of space in the risk cup so that it would take a lot to increase the risk to a level of concern.

   EPA Response: EPA acknowledges this feedback from the SACC.

7. **SACC Comment:** There is a typo on page 25, line 880: "Resource" should be "Research."

   EPA Response: EPA has changed "Resource" to "Research" as recommended by SACC.

8. **SACC Comment:** Regarding the uncertainty factor (UF) of 30, (see page 26, line 929): this seems a well-reasoned decision that provides an opportunity to address the interspecies UF of 3 through clearly articulated additional experimental approaches, should that be desired by registrants and other stakeholders.

   EPA Response: EPA acknowledges this feedback from the SACC.

9. **SACC Comment:** Regarding Section 4, "Phthalate Exposure and Risk for The US Population Using NHANES Urinary Biomonitoring Data," EPA might find Cuvelier, Avanasi *et al*. (2024) of interest in addressing the use of NHANES data more quantitatively for exposure evaluation.

   EPA Response: Generally, the proposed approach in Cuvelier, Avanasi *et al*. (2024) integrates modeled population exposure with human biomonitoring data to predict urinary concentrations based on ingestion from dietary recall. The modeled results rely on the use of EPA's DEEM model, dietary recall, crop residue data, and a pharmacokinetic model, all of which are available for lambda-cyhalothrin but not for phthalates. First, the exposure to lambda-cyhalothrin is understood to be primarily through diet based on its use as a pesticide. Therefore, the proposed approach relies heavily on pesticide residue data that is available for lambda-cyhalothrin. No food residue data as robust as the pesticide data program, a national pesticide residue monitoring program through the USDA, exists for phthalates. Exposure to phthalates occurs not only through diet but through many other exposure pathways as well. Through its systematic review, EPA has not found a robust data source effectively characterizing the total exposure profile of an exposed individual to phthalates to be used for direct comparison to human biomonitoring data as was done in Cuvelier, Avanasi *et al*. (2024). Additionally, no robust ADME model is available for phthalates for such a comparison. Because of the disperse sources of exposure for phthalates that is not well-characterized, EPA believes that the National Health and Nutrition Examination Survey (NHANES) urinary biomonitoring data is the best available data to characterize non-attributable exposure to phthalates quantitatively.

2.9.2 SACC Recommendations and EPA Responses (Charge Question 9)

1. **SACC Recommendation:** EPA should clarify any differences in PODs between studies on testosterone content as compared to testosterone production.

   EPA Response: EPA has responded to SACC's recommendation "EPA should clarify any differences in PODs between studies on testosterone content as compared to testosterone production." As part of the response to Charge Question 5g.

2. **SACC Recommendation:** EPA should provide their rationale for not using the standard deviation in its benchmark dose analysis.

   EPA Response: EPA acknowledges that EPA's BMD Technical Guidance (U.S. EPA, 2012) recommends always reporting BMD model results for a BMR of 1 control SD for continuous datasets for comparison purposes. However, BMD technical guidance also clearly states that "The ideal is to have a biological basis for the BMR for continuous data." Since EPA has determined that a BMR of 5% is the most appropriate BMR for evaluating decreased fetal testicular testosterone, there is little value added by reporting the results of a BMR of 1 control SD (although EPA did report results for a BMR of 1 control SD for comparison purposes for BMD modeling of individual fetal testicular testosterone datasets of BBP and DIBP). It is also important to note that BMD modeling of decreased fetal testosterone data was not used just for determining the POD, but also for deriving RPFs. RPFs must be derived at a constant response level so that they are comparable. Since a BMR of 1 control SD does not represent a constant response level (the magnitude of the standard deviation of the control will vary across studies and across phthalates), a BMR of 1 control SD cannot be used to calculate RPFs.

2.10 Charge Question 10

As described in Section 2.4 of the *Revised Draft Technical Support Document for the Cumulative Risk Analysis of DEHP, DBP, BBP, DIBP, DCHP, and DINP Under the Toxic Substances Control Act (TSCA)*, for input into the draft CRA of phthalates under TSCA, EPA has preliminarily selected *relative potency factors (RPFs)* calculated using BMD_{40} estimates based on reduced fetal testicular testosterone content and/or production. Please comment on the strengths and uncertainties of the derived RPFs.

2.10.1 SACC Recommendations and EPA Responses (Charge Question 10)

1. **SACC Recommendation:** The Committee recommends that EPA must first evaluate whether it would be possible to use alternative tools for meta-analysis and BMD modeling to provide additional support for the RPF calculation or to ensure that there is not a better way to estimate the RPFs. Specifically, EPA should determine whether another analysis tool would provide a greater number of possible BMD models that could provide better fits for the data being analyzed, and whether another tool could be used to determine BMD_5 and BMD_{10} estimates for all of the chemicals under consideration. This would enable calculation of RPFs based on the low end of the dose-response curve, consistent with the Agency's stated preference.
2. **SACC Recommendation:** Given the importance of similarity in the shape of the low end of the dose-response curves for determination of RPFs, the Committee recommended that the Agency should provide additional supporting information to compare the shapes of the dose-response curves in Table 2-4 If it is possible, EPA could report the slope parameter from the definitive BMD model or a sigmoid dose-response curve, as in Furr, Lambright *et al*. (2014). The Agency could also provide the BMD_{1SD} for comparison across chemicals, consistent with the BMD Technical Guidance (U.S. EPA 2012).
3. **SACC Recommendation:** The Agency should consider reporting the DIBP $BMDL_5$ from the *Draft Non-Cancer Hazard Assessment for DIBP*), based on *ex vivo* testosterone production in Gray, Lambright *et al*. (2021); or other BMD estimates as available from EPA's single-chemical BMDS analyses.
4. **SACC Recommendation:** The above recommendations should be considered before reverting to the RPFs as currently calculated. However, in principle, the Committee agreed that the calculation

of RPFs for DEHP, DCHP, DINP, DIBP, and BBP based on the ratio of BMD_{40} for testosterone production to the corresponding BMD_{40} of the index chemical, DBP, can be justified.

5. **SACC Recommendation:** The Agency should justify its choice of values for calculating RPFs, whether BMD_5, BMD_{10}, or BMD_{40}, on the basis of the Agency's scientific priorities, not on the basis of availability of data in an incomplete dataset.
6. **SACC Recommendation:** The Agency should clarify whether *ex vivo* testosterone production and testicular testosterone concentration data were analyzed separately to determine whether it was statistically appropriate to combine them in the testosterone meta-analysis and BMD analysis in Table 2-1. This analysis could be based on nonlinear regression analysis to test the null hypothesis that the regression lines are the same; or on a two-way analysis of variance (ANOVA), in cases where the same discrete doses are present in both datasets. This analysis could be done with either the DEHP or DBP dataset as proof of concept.

   EPA Response to Recommendations 1–6: See Response to Charge Question 5d (addresses BMR of 1 control SD comment) and 5f (addresses other SACC recommendations).

7. **SACC Recommendation:** If the RPFs will be used to calculate hazard for other life stages such as adult males or women above reproductive age, the Agency should clarify, and provide evidence, that they were calculated based on data from the most sensitive life stage.

   EPA Response: The RPFs derived by EPA are intended to be used to calculate hazard for females of reproductive age/pregnant women, male infants, and male children. Use of the RPFs for other lifestages such as adult males or women above reproductive age may be overly conservative and is not intended. EPA has added this clarification to Section 2.6 of the CRA TSD.

2.10.2 SACC Minor or Editorial Comments and EPA Responses (Charge Question 10)

1. **SACC Comment:** The BMD_{40} estimate of 279 mg/kg/day in Table 2-2, BMD Modeling Results of Fetal Testicular Testosterone for DEHP, DBP, DIBP, BBP, DCHP, and DINP in the *Revised Draft Technical Support Document for the Cumulative Risk Analysis of DEHP, DBP, BBP, DIBP, DCHP, and DINP Under the Toxic Substances Control Act*, should be revised to be 270 mg/kg/day based on Table 4-12, Comparison of Benchmark Dose Estimates for DIBP and Fetal Testosterone, and the Metafor version 4.6.0 results in the Cross Phthalate Modeling Files.

   EPA Response: EPA has updated the BMD_{40} estimate in Table 4-12 to be 270 mg/kg-day, as suggested by the committee.

2. **SACC Comment:** Line 249 of the Draft Meta-analysis and Benchmark Dose Modeling of Fetal Testicular Testosterone refers the reader to "Section 0" rather than (Section 4.2) for DEHP results.

   EPA Response: EPA has revised "Section 0" to "Section 4.2" as suggested by the committee.

2.11 Charge Question 11

In Section 5 of the *Revised Draft Technical Support Document for the Cumulative Risk Analysis of DEHP, DBP, BBP, DIBP, DCHP, and DINP Under the Toxic Substances Control Act (TSCA)*, EPA

describes two options for characterizing cumulative risk from exposure to phthalates under TSCA. Option 1 involves scaling each individual exposure by relative potency using RPFs to express all phthalate exposures in terms of index chemical (DBP) equivalents and then combining exposures from individual consumer or worker COUs/OES with non-attributable cumulative exposures estimated from NHANES biomonitoring data to estimate cumulative risk (Section 5.1). For Option 2, phthalate exposures from individual consumer and occupational COUs are not scaled by relative potency using RPFs but instead use the individual phthalate POD to estimate risk, which is then combined with non-attributable cumulative exposure and risk estimated using NHANES (Section 5.2).

- Part A: Please comment on the strengths and uncertainties of Option 1.
- Part B: Please comment on the strengths and uncertainties of Option 2

2.11.1 SACC Recommendations and EPA Responses (Charge Question 11)

1. **SACC Recommendation:** Given the limitations and uncertainties associated with both Options 1 and 2, the SACC recommends that EPA address the key issues discussed in Charge Questions 2, 3, 5f, and 10 before relying on either option. Resolving these questions and/or updating the metrics involved may lead to changes in the calculations underlying both options. The EPA is encouraged to make a concerted effort to resolve the discrepancies between the two options to ensure a more consistent and scientifically sound approach.

   EPA Response: See EPA responses to Charge Questions 2, 3, 5f, and 10.

2. **SACC Recommendation:** Regardless of whether the EPA is able to fully reconcile the tension between Options 1 and 2, the SACC recommends that the EPA consider using both options in parallel. Since each is based on different data sources, emphasizes different protective goals, and offers distinct strengths, their combined use may help fill gaps in data availability, data quality, and sensitivity, thereby providing a more comprehensive risk assessment.

   EPA Response: EPA considered both CRA risk characterization approaches for each of the phthalates and selected a single approach, supported by the strengths and limitations of each option, to present in the individual risk evaluations. As discussed in Section 5.4 of the CRA TSD, to determine which approach is most scientifically defensible for use in the final risk characterization and decision making for each individual phthalate, EPA considered the strengths, limitations, and uncertainties of underlying dose-response data supporting both approaches for each phthalate included in the CRA. To support transparent and consistent decision making, EPA developed a framework that outlines key considerations used by EPA to determine the most scientifically defensible approach for the contribution of cumulative risk to the individual risk characterization for each phthalate.

3. **SACC Recommendation:** The SACC recommends that the EPA apply BMD modeling consistently across all phthalates in Option 2, as BMD modeling is generally considered more scientifically rigorous and reliable than the NOAEL approach. In addition, for consistency, when scaling "non-attributable" exposures back calculated from NHANES data under Option 2, the EPA should use the POD ratios for scaling, rather than relying on RPFs as is currently done for both options.

   EPA Response: As suggested by the SACC, for Option 2, EPA considered using the individual phthalate PODs for calculating the margin of exposure (MOE) from the "non-attributable" exposure component from NHANES, instead of using RPFs to scale each individual phthalate

exposure. However, using each individual phthalate POD did not have a meaningful impact on the non-attributable cumulative MOE. For example, the 95th percentile cumulative MOE for black non-hispanic females of reproductive age is 407 when RPFs are used and would be 222 if each individual phthalate POD was used. A cumulative MOE of 407 indicates the risk cup is 7.4% full, while a cumulative MOE of 222 indicates the risk cup is 13% full, assuming a benchmark MOE of 30. Similarly small differences are apparent for other NHANES age groups and populations. For example, using RPFs and the index chemical POD the cumulative MOE is 194 (indicates risk cup is 15.5% full), while the cumulative MOE is 128 (indicates risk cup is 23.4% full) for male children 3-5 years of age based on 95th percentile NHANES exposure estimates. Given that both approaches contribute a similarly small fraction to the overall risk cup, EPA did not revise how it calculated non-attributable cumulative risk for Option 2.

4. **SACC Recommendation:** A significant expansion of exposure scenarios is necessary across all of the life cycle elements specified in TSCA. Detailed discussion and recommendations on this issue are offered in CQ 12.

   EPA Response: See EPA response to Charge Question 12.

5. **SACC Recommendation:** The Committee strongly recommends that the EPA leadership provide the resources and support that their scientists need to create or adopt methods and models which provide competent, person-oriented probabilistic aggregate and cumulative exposure assessments with comprehensive analysis options to assess the relevance and effectiveness of relative contribution and risk mitigation options. This should be complemented with the resources and support that their scientists need for comprehensive data collection and contemporary data analysis, and to use all of the models in the many relevant sciences that contribute to these important chemical review dossiers. The Committee recommends that the EPA leadership accomplish these actions—highlighted by SACC over the past several years—without further delay.

   EPA Response: EPA thanks for the SACC for this feedback.

6. **SACC Recommendation:** EPA's final Risk Determination should note the limitations of the deterministic additive approach regarding capacity to calculate aggregate—and certainly cumulative—exposure and its departure from EPA's own principles for aggregate and cumulative exposure and risk assessment. Probabilistic modeling, as previously developed by EPA, would provide a far more realistic distribution of potential exposure and risk across the population and quantify relative contributions by individual COUs, probable effects of risk mitigation for key factors and COUs, and other enlightening information for the regulatory decision-makers, public, and stakeholders. Details on these points are provided in the written report.

   EPA Response: EPA has added discussion of the use of deterministic exposure estimates to Sections 3.1 and 3.2 of the CRA TSD. Due to the wide range of cumulative exposure scenarios that may exist in phthalate-containing workplaces, it was not possible to provide a robust quantitative assessment of cumulative risk for workers who may be exposed to multiple phthalates based on reasonably available data. EPA did not have data on specific use patterns, facility campaigns, or quantitative estimates of co-exposure in an occupational setting necessary for development of probabilistic exposure models. Individual occupational exposure scenarios provided estimates of worker exposure using reasonably available data, but the development of

cumulative occupational exposure scenarios that involve combining these deterministic exposure estimates across multiple COUs for multiple phthalates without data to support a coherent exposure profile of a worker may lead to unrealistic cumulative exposure estimates that may yield both large overestimation and underestimation of exposure scenarios according to the SACC.

Additionally EPA did not estimate co-exposure of phthalates from the direct use of multiple consumer products beyond the estimation of non-attributable exposure. To do so would require additional data, which was not reasonably available, on consumer data to support evidence of co-use and use patterns of products for the development of probabilistic exposure models. Individual exposure scenarios provided estimates of consumer exposure using reasonably available data, but the development of cumulative consumer exposure scenarios that involve combining these deterministic exposure estimates across multiple COUs for multiple phthalates without data to support a coherent exposure profile of a consumer may lead to unrealistic cumulative exposure estimates that may yield both large overestimation and underestimation of exposure scenarios according to the SACC.

7. **SACC Recommendation:** These issues should be fully addressed, or if time does not permit the additional work, their absence and concerns about the issues should be prominently noted in the report. Details are, again, provided in our written response. References to SACC recommendations should carefully and faithfully relay the full intent and context of the Committee review comments. Corrections throughout the current EPA documents are necessary. SACC reviews must be properly acknowledged, accurately characterized, and reflected within the content of the final EPA scientific documents.

   EPA Response: See Responses to SACC recommendations 1 through 6 above. EPA has added additional nuanced discussion to the CRA TSD to better reflect certain conclusions and recommendations from the 2023 SACC meeting.

8. **SACC Recommendation:** EPA should explore the implications for production and use of the NHANES findings on DINP and MCOP identified in the issues section above.

   EPA Response: EPA considered the implication of production values (PV) of the phthalates on the NHANES urinary biomonitoring data in the Technical Support Document for the Cumulative Risk Analysis of Di(2-ethylhexyl) Phthalate (DEHP), Dibutyl Phthalate (DBP), Butyl Benzyl Phthalate (BBP), Diisobutyl Phthalate (DIBP), Dicyclohexyl Phthalate (DCHP), and Diisononyl Phthalate (DINP) Under the Toxic Substances Control Act (TSCA). EPA considered whether temporal trends in national aggregate production volume data mirror those observed in NHANES urinary biomonitoring data. To do this, EPA extracted national aggregate production volume (PV) data for DEHP, DBP, DIBP, BBP, DCHP, and DINP from the 2016 and 2020 Chemical Data Reporting (CDR). In CDR, national aggregate PV data is reported as a range to protect PV data claimed as confidential business information (CBI). Given the large ranges in reported PV data for each phthalate, EPA was unable to conclude whether or not there are any trends in PV for any phthalate over this time period.

9. **SACC Recommendation:** In several places in the description of NHANES data, EPA uses the phrase “decreases with age.” EPA’s characterization of findings across age groups implies a conclusion that is not supported by data; that is, that an individual’s exposure decreases over

time. Please adjust the language to reflect that the age-related decrease observed in the data pertains to population age groups, and not an individual's time course of exposure.

EPA Response: EPA has clarified throughout the CRA TSD that trends in NHANES exposure observed over time for various age groups pertain to population level trends, not an individual's time course of exposure.

10. **SACC Recommendation:** The Committee agrees with EPA that, as published, the Bayesian approach to reverse dosimetry from Stanfield *et al*. (2024) (discussed at the *Revised Draft Technical Support Document for the Cumulative Risk Analysis of DEHP, DBP, BBP, DIBP, DCHP, and DINP Under the Toxic Substances Control Act (TSCA)* document, line 1675) is not appropriate for the current application. However, the Committee urges EPA to consider similar approaches in the future to incorporate more probabilistic data analysis methods in TSCA risk evaluations. Stanfield *et al*. is an example of high-quality, probabilistic approaches to exposure that have been developed in other sections of EPA but not leveraged by the TSCA program. *Cumulative Risk Analysis of DEHP, DBP, BBP, DIBP, DCHP, and DINP Under the Toxic Substances Control Act (TSCA)* document, line 1675) is not appropriate for the current application. However, the Committee urges EPA to consider similar approaches in the future to incorporate more probabilistic data analysis methods in TSCA risk evaluations. Stanfield *et al*. is an example of high-quality, probabilistic approaches to exposure that have been developed in other sections of EPA but not leveraged by the TSCA program.

    EPA Response: EPA thanks for the SACC for this feedback. EPA will consider the probabilistic method presented by Stanfield et al., as well as similar approaches, for use in future risk evaluations.

2.11.2 SACC Minor or Editorial Comments and EPA Responses (Charge Question 11)

Cumulative Risk Analysis of DEHP, DBP, BBP, DIBP, DCHP, and DINP Under the Toxic Substances Control Act (TSCA) document, line 1675) is not appropriate for the current application. However, the Committee urges EPA to consider similar approaches in the future to incorporate more probabilistic data analysis methods in TSCA risk evaluations. Stanfield *et al*. is an example of high-quality, probabilistic approaches to exposure that have been developed in other sections of EPA but not leveraged by the TSCA program.

1. **SACC Comment:** EPA also noted that potency scaling (i.e., Option 1) resulted in a more "sensitive" risk assessment than Option 2 for some of the phthalates. The *Revised Draft Technical Support Document for the Cumulative Risk Analysis of DEHP, DBP, BBP, DIBP, DCHP, and DINP Under the Toxic Substances Control Act (TSCA),* page 62, lines 1834–1836). The term "more sensitive" is used in two different ways in this section. It is used to describe differences between the DEHP and DBP individual PODs and then also to describe differences in the cumulative risk estimates calculated by Options 1 and 2. Please clarify what "more sensitive" means in both contexts. Also, is the "cumulative risk estimate" the cumulative MOE? Recommend being as clear as possible with terms and specifying the comparison, *i.e.*, "more sensitive" compared to what? The need for clarification on the meaning of "more sensitive" also applies to Table 5-3, page 80, line 2322.

    EPA Response: EPA added clarification to the use of the term "more sensitive" to the CRA TSD. This includes clarifying language that the individual DEHP POD of 1.1 mg/kg-day is lower (i.e., more sensitive) than the index chemical (DBP) POD of 2.1 mg/kg-day. Similarly, EPA has

clarified that for approach 2, cumulative MOEs are approximately 1.1-1.2x lower than aggregate MOEs from the individual phthalate assessment (*i.e.,* more sensitive). These clarifications have been made throughout Section 5 of the phthalate CRA TSD.

2. **SACC Comment:** The MOE should not be described as a "risk estimate"; it is not a probability. It is a tool that facilitates a comparison of exposures for characterization of the potential for increased health risk. The Agency may wish to review a new publication on MOE from EFSA (Bennekou *et al*. 2025).

   EPA Response: EPA has reviewed the EFSA reference (EFSA 2025) provide by SACC. EPA agrees that the MOE is a tool that facilitates a comparison of exposures for characterization of the potential for increased health risk.

2.12 Charge Question 12

The *Draft Risk Evaluations* of DBP, DCHP, and DEHP contain three examples of the application of the phthalates cumulative risk assessment (CRA) within an individual chemical risk evaluation. Please comment on the integration of the CRA approaches within the single chemical evaluations.

Editorial Note: Key issues and recommendations for this charge question were organized into two groups by the SACC. Group 1 includes recommendations on presentation, structure, and order of cumulative risk content in the individual chemical risk evaluation documents, including issues related to the clarity and scientific soundness of the approach to integrating the results presented in the Draft Revised Phthalates Cumulative Risk Analysis (US EPA, 2023a, 2023b). Group 2 includes comments and recommendations related to interpretation and treatment of aggregate and cumulative risk concepts more broadly in the context of TSCA risk evaluation.

2.12.1 SACC Group 1 Recommendations and EPA Responses (Charge Question 12)

1. **SACC Recommendation:** The Committee recommends that EPA more completely address in each risk evaluation where there are discrepancies between the PODs derived in the individual *Draft Non-cancer Human Health Hazard Evaluation* documents for male developmental reproductive toxicity and the PODs developed in the CRA. Presenting both kinds of POD estimates with equally "robust confidence" creates problematic interpretation. Enhanced discussion of the sources of differences in the most sensitive PODs derived individually and via the cumulative risk analysis and RPF approach would help here. To some extent the issue of when and whether to use the PODs developed for the individual chemicals is addressed in more detail under CQ 11. The recommendation here pertains to the need to develop a clear discussion and rationale in the individual risk evaluations, especially in the cases where the risk evaluation no longer reflects the conclusions of the non-cancer hazard evaluation.

   EPA Response: EPA has added further discussion of the strengths, uncertainties, and limitations of CRA Approaches 1 and 2 to Section 5.4 of the CRA TSD. To determine which approach is most scientifically defensible for use in the final risk characterization and decision making for each individual phthalate, EPA considered the strengths, limitations, and uncertainties of underlying dose-response data supporting both approaches for each phthalate included in the CRA. To support transparent and consistent decision making, EPA developed a framework that outlines key considerations used by EPA to determine the most scientifically defensible approach for the contribution of cumulative risk to the individual risk characterization for each phthalate. This framework and its application for each individual phthalate is provided in Sections 5.4.1

through 5.4.7 of the CRA TSD. Phthalate specific narrative pertaining to the application of the developed framework has also been integrated into each individual phthalate risk evaluation.

2. **SACC Recommendation:** Section 4.1.3, General Population Exposures, needs to reflect more completely the release of phthalates to the environment during use and degradation of plastic articles.

   EPA Response: Section 3.2 of the Environmental Media and General Population Exposure technical support document for each phthalate discusses landfills where phthalates may be deposited into landfills through various waste streams including plastic articles, consumer waste, residential waste, industrial waste, and municipal waste. Section 3.1 in each phthalate risk evaluation discusses consumer disposal down the drain and landfills.

   EPA also considered aggregate exposure to phthalates using NHANES urinary biomonitoring data. NHANES provides an estimate of non-attributable (*i.e.,* cannot be attributed to specific TSCA or non-TSCA sources) aggregate exposure to phthalates.

3. **SACC Recommendation:** Section 6 in each of the individual phthalate risk evaluations, the Unreasonable Risk Determinations:
   - Must clearly state when and why unreasonable risk determinations rely on individual PODs or the DBP POD scaled by RPF and include an overall statement of whether the addition of risk from non-attributable exposures had an influence on EPA's final determination. For example, at line 5333 of DEHP Risk Evaluation, some additional explanation is required about the computational basis for the unreasonable risk determinations.
   - Should have a clearer tabular presentation of risks using individual vs. cumulative approaches that are easier for readers to compare and understand EPA's decisions.

   EPA Response: EPA acknowledges these recommendations from the SACC. In the final risk evaluations of DEHP, DBP, BBP, DCHP, and DIBP, EPA has revised the Section 6 unreasonable risk determinations to clearly state that the risk determinations are based solely on risks identified from exposures to the individual phthalates. In other words, the addition of non-attributable cumulative phthalate exposure from NHANES did not contribute to the unreasonable risk determination for DEHP, DBP, BBP, DCHP, or DIBP.

4. **SACC Recommendation:** Overall, EPA should edit all risk evaluations to harmonize integration after the questions of how to use the cumulative risk analysis are resolved (e.g., the choice of Option 1 or Option 2), such that all are explicit about where the individual chemical assessments or elements of the CRA were used for decision making concerning unreasonable risks.

   EPA Response: See response to SACC recommendation 1 for charge question 12 above. EPA has developed a framework to support consistent and transparent decision making and to support the selection of Approach 1 or Approach 2 for each individual phthalate. This framework has been integrated into each individual phtalate risk evaluation.

2.12.2 SACC Group 2 Recommendations and EPA Responses (Charge Question 12)

The SACC identified several recommendations related to the broader application of the exposure assessment and reverse dosimetry that provide a foundation for application of cumulative risk analysis:

1. **SACC Recommendation:** EPA should develop and model selected aggregate exposure scenarios for the individual phthalates.
2. **SACC Recommendation:** The Committee recommends the *inclusion of high exposure scenarios,* i.e., medical exposures, including exposures to healthcare workers of reproductive age in hospital settings. The PESS identified by EPA such as pregnant women and infants may be especially affected by medical exposures to phthalates, particularly DEHP and DINP which have multiple uses in medical plastics, some of which were mentioned above. Further, vinyl furnishings, disposable goods, and packaging are prevalent in healthcare facilities. EPA should include this scenario, at a minimum, considering both the aggregate exposure to DEHP and DINP, and cumulative exposure derived from other phthalates from articles present in healthcare facilities. A new section 3.5 should be added to the Cumulative Risk Assessment, to follow Section 3.4 on non-TSCA exposure to health care, and a cumulative exposure exercise undertaken for hospital workers.
    - Exposure and risk from products containing phthalates and *used in healthcare facilities* and by healthcare workers in other environments should be included in the Cumulative exposure/risk assessment and for the assessment for each phthalate (unless EPA can point specifically to the law and Agency review undertaken for those products) in terms relevant to the exposure and risk objectives of TSCA.
    - The EPA risk assessments should include
        - the full array of exposure scenarios from *chemical production, industrial stages* for simple and complex product creation and associated processes, transportation, distribution and disposal.
        - processes of recycling and disposal practices which inadequately confine plastics; this includes contemporary market dynamics—massive scale transportation centers, distribution centers, exposure to those workers, and contamination of nearby air and water.
    - For each phthalate, a comprehensive aggregate exposure assessment should be conducted which includes all possible exposure opportunities for the general population, highly exposed populations, and workers at all levels. The aggregation should include exposures that arise from different stages of the life cycle of phthalate use in manufactured articles, including degradation in indoor and outdoor environments. Probabilistic methods are preferred relative to deterministic additive exposure methods, as probabilistic methods avoid overestimation of exposure that includes high-centile values needed in deterministic models to capture the high exposures (see discussions in CQ 11).
    - Exposure scenarios discussed in this response to CQ 12 should be included in the exposure assessments for each of the individual phthalates (and cumulative assessment for phthalates) utilizing data available in the scientific literature, and in EPA's databases and computational tools that have been developed for consumer products exposure.
    - *Exposure via the diet for the general population* and PESS communities (not addressed by NHANES surveys) should be considered, recognizing use of phthalate-containing products in agriculture, food processing, packaging (including retail/restaurants/fast food), serving and disposal to be considered in this TSCA review in terms relevant to the exposure and risk objectives of TSCA—discussed by this SACC and previous SACC reviews.
    - Exposure and risk from products containing phthalates and used in *healthcare facilities and by healthcare workers in other environments* should be included in the Cumulative exposure/risk assessment and for the assessment for each phthalate (unless EPA can point specifically to the law and Agency review undertaken for those products) in terms relevant to the exposure and risk objectives of TSCA.

3. **SACC Recommendation:** The Committee recommends that EPA provide a qualitative discussion of microplastics as a pathway of phthalate exposure as part of the uncertainties and limitations to the cumulative risk analysis. Exclusion of microplastic routes of exposure may underestimate the estimates of risk to the general population that result from phthalates released to environmental media via plastic particles during both expected use of articles (such as tires), disposal of articles, as well as recycling and re-use of some plastic and rubber articles.
4. **SACC Recommendation:** As many exposure scenarios should include the off gassing of phthalates from the plastic or rubber, the rate of off-gassing over time and under different conditions (heat, type of plastic or rubber, condition of use) should be studied by the industry for EPA use in these assessments. During consideration of exposure from products, phthalate escape from matrices under stress (heat, wearing, sunlight, etc.) should be included in the assessment.
5. **SACC Recommendation:** All potential *exposure scenarios should be acknowledged* by EPA in these reviews, even if EPA cannot compute the resulting exposures that populations or PESS may experience. EPA may not be able to include quantitative assessment for all of these, but they can be recognized in the schema with acknowledgement that these are new venues for EPA to consider and the underlying information and computational tools necessary for an exposure/risk assessment have not yet been collected and organized for exposure assessment. EPA should not infer that these unquantified exposures—individually or in some combination—do not pose risks. Future risk assessment should consider these scenarios. Relevant data should be available from industries.

   EPA Response to Recommendations 1–5: EPA believes that the risk evaluations for all five phthalates are protective of human health and the environment. EPA's assessments include various steps along the lifecycle including manufacturing across multiple sections, processing, disposal, and consumer exposure. Consistent with statutory authorities, EPA assessments include multiple lifestages including potentially exposed or susceptible subpopulations (PESS), the PODs are derived for the most sensitive hazard associated with the well-established mode of action for phthalate syndrome. As noted by the SACC, EPA's exposure assessments across numerous scenarios utilize conservative deterministic approaches thereby compounding assumptions leading to protective risk assessments. EPA recognizes that the risk evaluations did not explicitly consider tire crumbs or microplastics. However, the risk evaluations did evaluate exposure to phthalate containing consumer products including, but not limited to, children's clothing, textiles (*e.g.*, furniture), and legacy toys. Children's exposure through these scenarios is expected to be significantly higher than to tire crumbs or microplastics. EPA has assessed inhalation, ingestion (via mouthing, settled dust, and suspended dust) and dermal exposure to phthalates from air mattresses in young (infants to teenagers, birth to 20 years of age) children, and therefore the vinyl bedding in hospitals scenario suggested by SACC is implicitly addressed in EPA's risk assessments. Healthcare workers are expected to have lower phthalate exposures compared to workers involved in manufacturing and processing because healthcare workers are expected to be exposed to phthalates through their handling of products containing phthalates vs. handling of neat chemical or raw materials.

6. **SACC Recommendation:** While the Committee agrees that it is appropriate to focus the risk evaluations on the hazard endpoints that are the basis of the cumulative risk analysis, EPA should incorporate other toxicological endpoints from the non-cancer assessments into Risk Evaluation Sections 4.2 Summary of Human Health Hazard, including findings from epidemiological studies, into the weight of evidence and confirm that the final risk conclusions would be protective. The TSCA team should be resourced to have full access to support and

consultation from scientists in ORD, OPP, and other parts of EPA who have experience with exposure modeling and cumulative risk assessment.

EPA Response: EPA has developed detailed non-cancer human health hazard assessments for DEHP, DBP, DIBP, BBP, and DCHP. These assessments considered all reasonably available information, including information from human epidemiologic studies, studies of experimental animal models, and mechanistic studies. EPA integrated information across these three lines of evidence and developed weight of scientific evidence narratives based on modified Bradford-Hill criteria to reach conclusions for each assessed human health hazard for each phthalate. This detailed information can be found in the non-cancer human health hazard assessment for each phthalate. Notably, in developing its weight of evidence narratives, OPPT consulted with OPP and ORD subject matter experts, as well as subject matter experts at other U.S. government agencies, such as NIEHS and the Division of Translational Toxicology.

2.12.3 SACC Minor or Editorial Comments and EPA Responses (Charge Question 12)

1. **SACC Comment:** In the Executive Summary paragraphs of the three risk evaluations, EPA integrated content to reflect the use of CRA results in the respective evaluation. For example, the DEHP risk evaluation reads:

> This non-attributable cumulative exposure and risk, representing the national population, was taken into consideration by EPA in its draft risk evaluation for DEHP. By taking into account cumulative exposure and risk as other authoritative bodies have done, EPA is confident that it is not underestimating the risk of DEHP and is reflecting the best available science. (*Draft Risk Evaluation for Diethylhexyl Phthalate,* p.12 Lines 483-486).

The Committee recommends EPA develop alternative, more accurate, executive summary language to replace "taking into consideration" and "taking into account." Further, whether risks are underestimated or overestimated is an issue beyond the integration of cumulative estimates. It is preferable to say that integrating a component of general population cumulative exposure into the risk evaluation increases EPA's confidence in the overall risk determinations.

EPA Response: Consistent with SACC recommendations, EPA has revised the language to "Integrating a component of national population cumulative exposure into the risk evaluation increases EPA's confidence in the overall risk conclusions."

2. **SACC Comment:** EPA should aim for consistency in how cumulative risk information is presented in each risk evaluation, but at the same time tailor the presentation to make sense for each phthalate. For example, DBP has content in Section 4.4.3 that can be simplified: edit text at lines 4471–4475 to indicate no conversion of exposure is required and delete equation (see EPA Year, page). Additionally, for Step 3 at line 4529, there is extraneous information that is not relevant to the index chemical.
3. **SACC Comment:** EPA should assess and reduce the level of repetition of text in the risk evaluation documents related to RPF derivation and reverse dosimetry. This could be tightened perhaps with a summary table, which will improve the readability of the lengthy and dense dockets for these phthalates. While not a subject of the charge, the same could be said for

checking redundant explanations of these cross- phthalates elements in the non-cancer human health hazard assessments, as well.

EPA Response to SACC Comments 2 and 3: EPA has updated each individual phthalate risk evaluation to make presentation of the cumulative risk assessment as consistent as possible. Consistent with SACC recommendations, EPA has also removed repetitive text, tables, and example calculations from the CRA section of each phthalate risk evaluation to help streamline the assessment. For example, EPA has removed repetitive text from Section 4.4.2 in each risk evaluation pertaining to calculation of non-attributable cumulative exposure from NHANES, and has condensed several tables into a single table in Section 4.4.2 of each risk evaluation to show only the cumulative phthalate daily intake values used in subsequent cumulative risk characterization. EPA has also removed cumulative risk example calculations from each individual phthalate risk evaluation. Removed information was repetitive with information presented in the CRA TSD, and is now retained only in the CRA TSD.

4. **SACC Comment:** The draft documents make it difficult to compare the individual chemical MOEs to the MOEs with the RPF approached (for example, DEHP Table 4-17 vs. Table 4-22). A few changes to the drafts will improve this: first, the cumulative MOE tables could be formatted such that the COUs appear in the same order and with the same OES name. This is not the case at present. In fact, it would be good practice to present COUs in the same order in all documents and all sections. Second, in the text for the cumulative risk section that refers to these tables, please provide reference back to the preceding table, and a more detailed discussion of differences. This is particularly important where the MOEs are close to benchmark.

   EPA Response: EPA had revised occupational and consumer cumulative risk tables for each phthalate such that COUs and occupational exposure scenarios (OESs) appear in the same order as presented in the occupational and consumer cumulative risk tables from the individual chemical assessment. EPA has also added additional citations to risk summary tables and excel-based risk calculators throughout the cumulative risk assessment section of the risk evaluation for each phthalate.

5. **SACC Comment:** Several typos were noted:

   - In the DCHP Risk Evaluation, line 2990 is missing the word “testosterone.”
   - In the DCHP Risk Evaluation, line 3039, “monoester metabolites” should be re-written to include some of the secondary metabolites that are also measured in NHANES.
   - In the DCHP Risk Evaluation, line 3242, “for each individual phthalate exposures were scaled by relative potency per chemical, expressed…” should be replaced by “DCHP exposures were scaled by relative potency expressed….”
   - In the DEHP Risk Evaluation, page 15, line 539: DEHP should replace DBP.

   EPA Response: EPA has fixed all of the typos noted by the SACC.

2.13 Charge Question 13

Because phthalates have very low vapor pressure and absorb relatively slowly, a “flux-based” approach was followed in estimating dermal exposures. The flux-limited dermal absorption approaches for liquid and solid products and articles assume a constant rate of absorption of the phthalate, independent of the concentration of phthalate in the products and articles. EPA used the chemical absorptive flux

(determined through empirical data from literature or modeling) in conjunction with surface area of contact and absorption time to determine potential dermal exposure. Please comment on the use of a flux-based approach for estimating dermal exposure to materials with low volatility and low rates of absorption. See Appendix D of the *Draft Environmental Release and Occupational Exposure Assessment for DCHP*, Appendix C of the *Draft Environmental Release and Occupational Exposure Assessment for DBP*, and Section 2.3 of the *Draft Consumer and Indoor Dust Exposure Assessments for DBP, DCHP, and DEHP*.

2.13.1 SACC Recommendations and EPA Responses (Charge Question 13)

1. **SACC Recommendation:** Review the findings of Hopf *et al*. (2024) and evaluate whether those data may be preferable to those of Doan *et al*. (2010) for estimating dermal absorption in the flux-based approach.

   EPA Response: EPA has conducted an updated review of dermal absorption data available for DBP and DEHP, including the work of Hopf *et al*. (2024) that reports fluxes of DBP and DEHP *in vitro* using human skin and *in vivo* with human subjects. Though the study of Hopf *et al.* (2024) provides *in vitro* dermal absorption data for DBP and DEHP through human skin, the study does not verify metabolic activity and only measures the metabolite rather than the parent compound. Therefore, it is possible that the *in vitro* data presented in Hopf *et al.* (2024) slightly underestimate dermal absorption in human skin. The risk evaluation of DEHP integrated absorption data from an earlier study by the same author (Hopf et al. 2014) which does verify metabolic activity of human skin, and therefore, these data were determined to be preferrable. *In vivo* experiments from Hopf *et al*. (2024) result in similar levels of estimated dermal uptake of DEHP (approximately 0.010 µg/cm^2/hour) compared to *in vitro* results (0.025 µg/cm^2/hour) reported in metabolically active skin in the earlier study by Hopf *et al*. (2014); thereby adding to the weight of evidence supporting the selection of the dermal absorption rate from the earlier *in vitro* study using metabolically active human skin (Hopf et al. 2014). EPA considered the *in vitro* data from Hopf *et al.* (2014) to have higher confidence than the value estimated from the *in vivo* study by Hopf *et al.* (2024) because the estimation from the *in vivo* study relies exclusively on the excreted DEHP and does not account for any DEHP that was absorbed but not excreted or DEHP that was excreted but was from other sources (*e.g.*, dietary exposure). Regarding absorption data for DBP, Hopf *et al.* (2024) also cites the work of Beydon *et al.* (2010). The study of Beydon *et al.* (2010) used metabolically active human skin and measured for both DBP metabolites and parent compound during testing. Consequently, EPA has selected Beydon *et al.* (2010) as the most representative study for estimating dermal absorption of DBP.

2. **SACC Recommendation:** Review the written public comments by John Kissel and update the Appendix D section 2 appropriately, which will include distinguishing differences in fugacity between pure powder, liquid phthalates, and solids or articles. Recognize that the permeability coefficient may be reduced due to mass transfer resistance.

   EPA Response: EPA agrees that the permeability coefficient of a compound is affected by the physical-chemical properties of the material under investigation. However, EPA utilized a bounding approach to estimate the upper limit of absorption a phthalate chemical from a solid matrix. Specifically, it was assumed that absorption from a solid matrix would be less than absorption from a saturated aqueous material. Because estimation at the bounding level showed low levels of dermal uptake in comparison to PODs and benchmark MOEs, EPA did not apply more advanced methodologies to account for variations in chemical concentration below the saturation limit.

3. **SACC Recommendation:** EPA should provide a transparent basis for assuming 7% emulsion for the calculations and how 7% compares to actual formulations and product use scenarios.

   EPA Response: After further review of dermal absorption data of DBP, EPA is no longer using data presented in Doan *et al.* (2010) for dermal exposure assessment. The work of Doan *et al.* (2010) used an oil-in-water emulsion for *in vivo* dermal absorption testing using guinea pig species, and EPA has identified data that are more representative of dermal absorption in humans.

4. **SACC Recommendation:** Add clarification and detail as outlined above.

   EPA Response: EPA has added clarification and details to the risk evaluations of DBP and DEHP based on the SACC recommendations.

2.13.2 SACC Minor or Editorial Comments and EPA Responses (Charge Question 13)

1. **SACC Comment:** Lines 1128–1130. Do all the liquid products under consideration contain polymers?

   EPA Response: Liquid products containing phthalates are not necessarily polymeric materials. For instance, liquid laboratory chemicals containing phthalates generally do not contain polymers. The function of the phthalate in the liquid product will determine whether polymers exist in the final product.

2. **SACC Comment:** Line 1171. Describe the oil-in-water emulsion. Was the DBP in water or was there another oil? The vehicle can affect dermal absorption. For example, an oily vehicle may reduce absorption of a hydrophobic penetrant, such as DBP.

   EPA Response: The work of Doan *et al.* (2010) was considered for the *Draft Risk Evaluation for Dibutyl Phthalate (DBP)*. However, after further review of existing data related to dermal absorption of DBP in human skin, EPA is no longer using data from Doan *et al.* (2010) for dermal exposure estimation for DBP. The oil-in-water emulsion was specific to the study parameters of Doan *et al.* (2010).

3. **SACC Comment:** Lines 1190–1192. Was the rate of absorption constant over 24h?

   EPA Response: The rate of dermal absorption is known to vary over time and eventually reaching a steady-state rate. However, data were not available for timepoints below the 24-hour duration for the phthalate chemicals under investigation.

4. **SACC Comment:** Lines 1202–1204. How did the flux from the Elsisi *et al*. and other studies compare to Doan *et al*., (2010)? Did the methods in the newer Doan study differ from the previous studies?

   EPA Response: The work of Elsisi *et al.* (1989) evaluated *in vivo* absorption in rats over a 7-day period, whereas Doan *et al.* (2010) evaluated absorption in guinea pig species over a 24-hour period. Therefore, the comparison of these two studies is not necessarily useful. However, as mentioned above, the work of Doan *et al.* (2010) was considered only for the *Draft Risk*

Evaluation for Dibutyl Phthalate (DBP). After further review of existing data related to dermal absorption of DBP in human skin, EPA is no longer using data from Doan *et al.* (2010) for dermal exposure estimation for DBP.

5. **SACC Comment:** Equation 2-1. The lack of a concentration term is problematic. Please explain what the "effect of stratum corneum" (FA) means.

   EPA Response: Equation 2-1 from the *Environmental Release and Occupational Exposure Assessment for DBP* and the *Environmental Release and Occupational Exposure Assessment for DCHP*, which is based on Equation 3.2 from the *Risk Assessment Guidance for Superfund (RAGS), Volume I: Human Health Evaluation Manual, (Part E: Supplemental Guidance for Dermal Risk Assessment)* (U.S. EPA, 2004), is used to estimate dermal uptake from aqueous media. Therefore, the concentration term in the equation is the aqueous solubility of the chemical which is given by the term S_w in the equation. Though the term *FA* is described in detail in the *Risk Assessment Guidance for Superfund (RAGS), Volume I: Human Health Evaluation Manual, (Part E: Supplemental Guidance for Dermal Risk Assessment)* (U.S. EPA, 2004), EPA has included a more detailed description of the term in the *Environmental Release and Occupational Exposure Assessment for DBP* and the *Environmental Release and Occupational Exposure Assessment for DCHP*.

6. **SACC Comment:** Lines 1345–1347. The methods matter more than the publication date.

   EPA Response: EPA agrees that methods of measuring dermal absorption may be more important than recency of the data, and EPA has updated the dermal absorption data considered in its risk evaluations based on SACC feedback and public comments.

7. **SACC Comment:** Lines 1351–1354. Split thickness skin is used because the penetrant needs to reach the upper papillary dermis to be absorbed.

   EPA Response: There are several factors that need to be considered in dermal absorption testing, including but not limited to dose, vehicle of absorption, duration, and skin thickness. Further, the use of metabolically active skin provides a more realistic evaluation of absorption in live human tissue, and these data were preferred over data from non-viable skin samples.

8. **SACC Comment:** Section 2.4.3.3. Did EPA consider using studies of vinyl films containing phthalates such as Deisinger *et al*. (1998) or Kawakami *et al*. (2020). It was noted that EPA used the Chemical Manufacturers Association (1991) study report, which was published as Deisinger *et al*. (1998).

   EPA Response: EPA has reviewed studies measuring absorption of phthalates from solid materials and considered the utility of such studies as surrogate for estimating dermal uptake of phthalates without solid absorption data. However, the absorption profile of each phthalate is unique, and there were no solid matrix absorption data for several phthalates under investigation. Because of the differences in structure and physical-chemical properties between the phthalates without solid matrix absorption data (*i.e.*, DBP, DIBP, and DCHP) and the phthalates with solid matrix absorption data (*i.e.*, DEHP and BBP), EPA has chosen to model dermal uptake from solid matrices for phthalates without absorption data rather than using surrogate data.

2.14 Charge Question 14

For DBP (liquid products) and DEHP (liquid products and solid articles), empirical dermal flux absorption data were available (Sections 2.3.1 and 2.3.2 in the *Draft Consumer and Indoor Dust Exposure Assessment for DBP, Memo for DBP Dermal Absorption Data*, and Section 2.3.1 in the *Draft Consumer and Indoor Dust Exposure Assessment for DEHP*). Please comment on EPA's evidence integration and examination of the weight of scientific evidence (including strengths, limitations, and uncertainties) and resulting study selection for determination of dermal flux from contact with different forms and formulations of the phthalate (e.g., solid, liquid, neat, aqueous dilution, etc.). See Sections 2.1.2 of the *Draft Non-cancer Human Health Hazard Assessment for DEHP*, Section 2.4.4 of the *Draft Environmental Release and Occupational Exposure Assessment for DCHP* and Section 2.4.3 of the *Draft Environmental Release and Occupational Exposure Assessment for DBP, Memo for DBP Dermal Absorption Data*, and Section 2.3 of the *Draft Consumer and Indoor Dust Exposure Assessments for DBP, DCHP, and DEHP*.

2.14.1 SACC Recommendations and EPA Response (Charge Question 14)

1. **SACC Recommendation:** EPA should use consistent values across assessments, even if experimental data are not prioritized, particularly when such data seem to be implausible or unreliable.

   EPA Response: EPA agrees that it is important to maintain consistency in dermal exposure assessments across chemicals and disciplines. Based on feedback from the SACC and public comments, EPA has revised the dermal exposure assessments of DBP and DIBP to utilize data derived from metabolically active human skin samples (Beydon et al 2010). EPA has also revised the dermal absorption approach for BBP to utilize data dervied from metabolically active human skin (Sugino et al. 2017). This is consistent with the data used in the analogous dermal exposure assessments of DEHP (Hopf et al. 2014). Further, EPA has utilized the same dermal absorption modeling approach for chemicals without dermal absorption data from solid matrices (*i.e.*, DCHP, DBP, and DIBP) to provide consistent assessment of the exposure scenario.

2. **SACC Recommendation:** EPA should review new study by Hopf *et al*. (2024) that also evaluated diffusion, absorption, and excretion in humans following dermal exposure to DBP and DEHP. Given the criteria the Agency set for acceptability of studies, the data from Hopf *et al*. may be more appropriate than those from Doan *et al*. (2010), who used the hairless Guinea pig, for estimating dermal absorption using the flux-based approach.

   EPA Response: EPA has conducted an updated review of dermal absorption data available for DBP and DEHP, including the work of Hopf *et al.* (2024). Though the study of Hopf *et al.* (2024) provides dermal absorption data for DBP and DEHP through human skin, the study does not verify metabolic activity and only measures the metabolite rather than the parent compound. Therefore, it is possible that the data presented in Hopf *et al.* (2024) slightly underestimate dermal absorption in human skin. The risk evaluation of DEHP integrated absorption data from Hopf *et al.* (2014) which does verify metabolic activity of human skin, and therefore, these data were determined to be preferrable. Regarding absorption data for DBP, Hopf *et al.* (2024) also cites the work of Beydon *et al.* (2010). The study of Beydon *et al.* (2010) used metabolically active human skin and measured for both DBP metabolites and parent compound during testing. Consequently, EPA has selected Beydon *et al.* (2010) as the most representative study for estimating dermal absorption of DBP.

3. **SACC Recommendation:** EPA should review the various references by Weschler *et al*. given above, which contains empirical evidence of direct dermal absorption of DBP from vapor.

   EPA Response: EPA reviewed the vapor to skin modeling methodology of Weschler *et al.* (2014), as well as the empirical studies of vapor to skin exposure presented in Weschler *et al.* (2015) and Morrison *et al.* (2016). The study of Weschler *et al.* (2015) measured exposure to participants wearing only shorts, and results showed levels of dermal uptake similar to levels of inhalation exposure. However, Weschler *et al.* (2015) noted that "[a]lthough these experiments indicate substantial dermal uptake directly from air for both DEP and DnBP, the measured values for the contribution of the dermal pathway directly from air are lower than those predicted in recent studies (Weschler and Nazaroff 2012, 2014)." Therefore, the vapor to skin modeling approach of Weschler *et al.* (2014), which is based on steady-state dermal uptake from vapors, is shown to overpredict dermal exposure to DBP vapor. Further, Weschler *et al.* (2015) states that "higher-molecular-weight phthalates such as butyl benzyl phthalate (BBzP), di(2-ethylhexyl) phthalate (DEHP), and di(isononyl) phthalate (DiNP) tend to have low gas-phase concentrations. This results in kinetic constraints on the flux from air to skin; it is too small for dermal uptake from air to be an important pathway for compounds such as DEHP and DiNP." The study of Morrison *et al.* (2016) investigates the effect of clothing, both clean and contaminated, on dermal uptake of phthalates. Morrison *et al.* (2016) showed that clean clothes have a significant protective effect on dermal uptake of DBP vapor, while contaminated clothing led to increased levels of dermal exposure. Since it is assumed that workers will wear clean clothing to work, rather than clothing that has been saturated with phthalate chemicals, the results based on the use of clean clothing from Morrison *et al.* (2016) are most relevant to the dermal exposure assessment. EPA included discussion of vapor to skin exposures in the risk evaluations of DBP and DIBP.

2.14.2 Charge Question 15

EPA used the dermal flux values along with dermal surface area and exposure duration to determine dermal exposure. For each phthalate, empirical dermal flux absorption data specific to liquid or solid products were used if available. If empirical data were not available, for example in the case of DBP (solid articles) and DCHP (solid articles and liquid products), dermal uptake was modelled using the Consumer Exposure Model (CEM) permeability coefficient (Kp) approach. See Section 2.3.3 in the D*raft Consumer and Indoor Dust Exposure Assessment for DBP*, Section 2.3.1 in the *Draft Consumer and Indoor Dust Exposure Assessment for DCHP*, Section 2.4.4.1 in the *Draft Environmental Release and Occupational Exposure Assessment for DCHP*, and Section 2.4.3.3 in the *Draft Environmental Release and Occupational Exposure Assessment for DBP* for more details.

2.14.2.1 Charge Question 15.a

Comment on the use of aqueous absorption modeling to estimate dermal uptake from solid materials.

2.14.2.1.1 SACC Recommendation and EPA Response (Charge Question 15.a)

1. **SACC Recommendation:** Continue to use aqueous permeability coefficients to estimate dermal absorption from solids if partition coefficients are available (to convert aqueous phase driving force to solid phase driving force).

   EPA Response: EPA will continue to utilize the best available models for estimating permeability coefficients based on the dermal exposure scenario and will work to incorporate solid phase partition coefficients when available. EPA agrees that partition coefficients from solids to water will affect dermal uptake of phthalates from solid matrices. However, for the

current evaluations EPA utilized a bounding approach to estimate the upper limit of absorption a phthalate chemical from a solid matrix. Specifically, it was assumed that absorption from a solid matrix would be less than absorption from a saturated aqueous material. Because estimation at the bounding level showed low levels of dermal uptake in comparison to PODs and benchmark MOEs, EPA did not apply more advanced methodologies to account for variations in solid to water partition coefficients; however, it is recognized that the approach lively overestimates exposure from solid materials.

2. **SACC Recommendation:** Develop and maintain a database (or MSDS requirement) describing vapor pressures of SVOCs above solid products.

   EPA Response: EPA agrees that further investigation regarding vapor pressures of semi-volatile organic compounds (SVOCs) above solid products would be a useful tool in TSCA risk evaluations, and such work will be considered for future development.

2.14.2.2 Charge Question 15.b

Comment on the use of the Consumer Exposure Model to approximate the aqueous permeability coefficient (Kp) and the use the Superfund Guidance for Dermal Risk Assessment to estimate the dermally absorbed dose.

2.14.2.2.1 SACC Recommendation and EPA Response (Charge Question 15.b)

SACC Recommendation: Review, correct and provide a transparent documentation of the calculated fluxes since currently uptakes are somehow being averaged and declared "steady state" fluxes.

EPA Response: EPA reviewed and corrected any instances where the modeled absorption rate was incorrectly declared as "steady-state" rather than "average". The modeling approach utilized for estimating dermal uptake takes into account the variation in absorption rate over time. Therefore, EPA calculated the average absorption rate for each modeled scenario based on the absorption duration of the scenario under investigation.

2.14.2.3 Charge Question 15.c

Suggest alternative approaches for estimating dermal absorption in the absence of data.

2.14.2.3.1 SACC Recommendations and EPA Response (Charge Question 15.c)

1. **SACC Recommendation:** Review and consider the data on dermal absorption from solid articles (Deisinger *et al*. 1998 and Kawakami *et al*. 2020) as an alternative approach.

   EPA Response: EPA reviewed studies measuring absorption of phthalates from solid materials and considered the utility of such studies as surrogate for estimating dermal uptake of phthalates without solid absorption data. However, the absorption profile of each phthalate is unique, and there were no solid matrix absorption data for several phthalates under investigation. Because of the differences in structure and physical-chemical properties between the phthalates without solid matrix absorption data (*i.e.*, DBP, DIBP, and DCHP) and the phthalates with solid matrix absorption data (*i.e.*, DEHP and BBP), EPA chose to model dermal uptake from solid matrices for phthalates without absorption data rather than using surrogate data.

2. **SACC Recommendation:** During the process of preparing the Draft Risk Evaluation, when EPA recognizes data gaps, the Agency's stakeholders should be approached to run these studies prior to the draft being finalized in order to have sufficiently robust and appropriate data to address risk.

   EPA Response: EPA strives to foster partnerships with stakeholders to better understand the scenarios of exposure and typical workplace practices where the chemicals are being handled. Such questions will be considered and revisited as EPA continues risk evaluation of high-priority substances under TSCA.

3. **SACC Recommendation:** EPA refers to Deisinger *et al*. as Chemical Manufacturers Association (1991), which is a technical report. Deisinger *et al*. is a peer-reviewed publication. EPA might want to note this is in a footnote.

   EPA Response: In the DEHP Risk Evaluation and its accompanying TSDs (human health hazard, consumer exposure, and occupational exposure), EPA linked the two associated dermal absorption publications relevant to solids in the narrative as follows "EPA used the study by Chemical Manufacturers Association (1991), subsequently summarized in a peer-reviewed publication by Deisinger et al. (1998). Additionally, in the consumer exposure TSD, the relationship between these two publications was noted in relevant tables using a footnote."

2.15 Charge Question 16

Because phthalates are semi-volatile and exhibit low rates of absorption, EPA assumed the material may remain on the skin until washed. Also, EPA assumed that a worker may contact the material multiple times per day. Therefore, it is possible that material exists on the skin surface for the duration of the work shift (or until the material on the skin surface is depleted), although the worker is not necessarily handling the material directly for the entirety of the work shift. Please comment on the possibility and likelihood that a non-volatile chemical with low absorption may be contacted multiple times during a work shift (i.e., the worker is handling the chemical intermittently throughout the work shift) and may exist on the skin surface for a total of 8 hours (or until the material on the skin surface is depleted), including the representativeness of this exposure scenario to the COUs.

2.15.1 SACC Recommendations and EPA Response (Charge Question 16)

1. **SACC Recommendation:** Based on the available evidence, phthalates are semi-volatile rather than non-volatile compounds, and assumptions about exposure should be made accordingly.

   EPA Response: EPA incorrectly stated that phthalates are "non-volatile" rather than "semi-volatile" in the initial charge question, but EPA agrees that phthalates are semi-volatile chemicals and have assessed them as such.

2. **SACC Recommendation:** The limited available data that have measured dermal loading of phthalates on the skin surface indicate that these measurements are very consistent with the weight of evidence in the literature for quantitative dermal loading across the majority of compounds tested. The Agency could consider an upper bound loading value for phthalates on human skin of 1 mg/cm^2.

   EPA Response: In absence of chemical-specific data on dermal loading, EPA has utilized surrogate dermal loading data from occupational studies that measure dermal loading of various

substances during common worker activities. Though dermal loading of 1 mg/cm^2 is a plausible level for occupational tasks, EPA prefers to use a more robust statistical analysis of measured data, when such data are available.

3. **SACC Recommendation:** The nature and frequency of skin contact with phthalates of interest (whether semi-volatile or non-volatile) will depend entirely on the scenario in which they are being manufactured, processed, or used. As a result, developing an assumption related to any single duration of contact with the skin does not appear to be scientifically supportable or reliable. An assumption of 8 hours could certainly represent a reasonable scenario, but that assumption may also overestimate or underestimate the potential for exposure, possibly significantly, as evidenced in the research of Elsisi *et al*. (1989).

   EPA Response: Though EPA has used an absorption duration of 8-hours for occupational dermal exposure scenarios in the current assessments of phthalates based on information provided in the U.S. EPA Chemical Engineering Branch manual (CEB, 1991), EPA plans to conduct more robust analyses in future assessments that include potential variability in absorption duration as well as variability in other parameters that affect dermal exposure such as surface area. EPA recognizes, however, that this assumption likely overestimates exposure in many situations.

4. **SACC Recommendation:** If the Agency decides to maintain an assumption of 8 hours, EPA should provide a transparent explanation for the selection of that value and how it might cover or omit a variety of scenarios.

   EPA Response: EPA chose the duration of an 8-hour absorption time based on information provided in the U.S. EPA Chemical Engineering Branch manual (CEB, 1991), which indicates that dermal exposure from multiple contacts may extend up to 8 hours per workday. Therefore, the value of 8 hours was chosen for the occupational dermal exposure assessment to provide a protective assessment of worker dermal exposure. This is explained within the occupational exposure technical support document for each phthalate. However, as mentioned above, EPA plans to conduct more robust analyses in future assessments that include potential variability in absorption duration as well as variability in other parameters that affect dermal exposure such as surface area.

5. **SACC Recommendation:** EPA should examine the range of risk estimates that result for the relevant COUs when assuming a uniform distribution of between 0 and 24 hours of exposure duration on the skin surface and performing a probabilistic analysis to understand at what duration of contact time the risk would become unreasonable.

   EPA Response: As mentioned above, EPA plans to conduct more robust analyses in future assessments that include potential variability in absorption duration as well as variability in other parameters that affect dermal exposure such as surface area.

2.16 Charge Question 17

In Section 2.3.2 and Appendix B of the *Draft Consumer and Indoor Dust Exposure Assessment for DEHP*, EPA described the rationale, approach, and studies used to refine dermal exposure from air beds. In section 5.1, EPA discussed the limitations and strengths of the refined dermal exposure assessment approach for air beds. Briefly, EPA moved from the flux-limited dermal absorption approach to an

approach which models dermal absorption using the specific phthalate concentration in the solid article. In this refined approach, material- and chemical-specific partition coefficients, and a barrier bedsheet between the air bed and the skin are incorporated. Please comment on the input data used in the calculations, the strengths and limitations of the dermal absorption refined approach for air beds. Specially comment on the equations used to calculate the dermal flux from air beds to skin for DEHP.

2.16.1 SACC Recommendations and EPA Response (Charge Question 17)

1. **SACC Recommendation:** EPA should clarify the distinctions among low-, medium-, and high-intensity use scenarios. Please make clear if these all refer to contact duration alone, or also include DEHP content, (which differs widely), or a combination of contact time and content of plasticizer.

   EPA Response: Regarding the comment about distinctions among low-, medium-, and high-intensity use exposure scenarios, EPA added text to clarify, the scenarios consider the range of air bed DEHP concentrations (see Table 2-10 in DEHP consumer TSD), and the subsequent calculated parameters that result in low-, medium-, and high-intensity use exposure inputs and outputs from the air bed DEHP concentrations.

2. **SACC Recommendation:** EPA should perform a separate review or "reality check" of this exposure model and results to increase confidence that model is constructed in a scientifically sound manner.

   EPA Response: Regarding a separate review or "reality check" of the air beds dermal exposure refined approach, EPA agrees that an independent review of the approach would likely increase the confidence in the model and the results. However, at this moment there is no experimental equivalent or modeling tools that could independently corroborate each of the inputs used in this approach.

3. **SACC Recommendation:** EPA should consider the skin permeation study by Hopf *et al*. (2024), which was an *in vivo* study in humans.

   EPA Response: In regard to the comment to consider Hopf et al. (2024), EPA reviewed Hopf et al., 2024 and concluded that the *in vitro* experiments of Hopf *et al.* (2024) study slightly underestimate phthalate absorption. Interpretation of chemical excretion data from *in vivo* human testing requires a more thorough understanding of compound metabolism. Further, the *in vitro* experiments of the Hopf *et al.* (2024) study only measured for metabolites of the phthalates but did not verify that the previously frozen skin samples were metabolically active. Therefore, EPA selected other dermal studies for estimating dermal uptake.

2.16.2 Other SACC Comments and EPA Response (Charge Question 17)

Narrative in SACC report addressed multiple other topics. EPA feedback on other topics noted by SACC is addressed here.

EPA Response: On differences between text values and values in table 2-10. There was an error in transcription for the text values. Table 2-10 values were correct. Values used in the calculations were those from Table 2-10, there is no need to recalculate.

On skin permeability coefficient for air-phase transfer (K_{Air}) also known as K_P. EPA agrees that there are differences between CEM K_P calculations and those obtained from Li et al., 2019 (taken from Gong

et al., 2014) which used the Stimulating Peripheral Activity to Relieve Conditions (SPARC) model to obtain K_P. The SPARC model mainly uses physical and chemical properties like CEM. EPA disagrees in having to recalculate K_P values for DEHP dermal exposures to air beds refinement using CEM. The range of possible K_P values is an acceptable source of variability specially since MOE values were one order of magnitude larger than the benchmark and changes to physical chemical properties for calculating K_P values would not impact the MOE enough to change the risk determination for this scenario.

Several requests for additional clarifying text were added in various locations of the DEHP consumer TSD in the air beds dermal exposure refined approach section for the following questions:

- What makes this a refined approach?
- What is the difference between lowercase "*k*" and uppercase "*K*"?
- What are the units for C_{Skin}?
- What is a "risk estimate"? Is it the same as margin of exposure (MOE)?

2.17 Charge Question 18

In Section 2.1.1 and 2.2.3.1 of the *Draft Consumer and Indoor Dust Exposure Assessments* for DBP, and DEHP, EPA assessed exposures to each of these phthalates due to use of adult toys. Both ingestion exposure due to mouthing of the articles and dermal exposure due to skin contact were quantified. Exposures due to expected direct contact with mucus membranes during the product's intended use were not evaluated due to a lack of modeling tools available to assess these exposure routes. Please suggest approaches for evaluation of exposure due to direct contact with mucus membranes.

2.17.1 SACC Recommendations and EPA Response (Charge Question 18)

1. **SACC Recommendation:** Make every effort to assess risks from direct contact of sex toys with mucosa.
2. **SACC Recommendation:** Consider using absorption data from skin as a surrogate for mucosa.
3. **SACC Recommendation:** A better option is to use data on absorption of pharmaceuticals through mucosa along with read-across methods to develop a model that can be used for phthalates. For example, EPA could compare progesterone mucosal and skin permeabilities/uptake and using that ratio as the basis to extrapolate phthalate skin permeability to a mucosal permeability/uptake.
4. **SACC Recommendation:** Consider the migration data in Nillson *et al*. (2006).
5. **SACC Recommendation:** Consider data that describe chemicals in tampons and other personal care as a surrogate for sex toys (Gao *et al*. 2020; Marcelis *et al*. 2025).
6. **SACC Recommendation:** Consider exposures from tampons and other personal care products as a direct route of phthalate exposure.

EPA Response to Recommendations 1–6: EPA is grateful for the committee's suggestions and shared references. In summary, EPA tried to quantitatively assess direct contact of adult toys with mucosa (*e.g.,* vaginal and anal exposures), however, it was concluded that there were significant uncertainties due to lack of adult toys specific information. The committee suggested various paths:

> To use absorption of pharmaceuticals through mucosa along with read-across methods to develop a model that can be used for phthalates. For this effort the committee provided

Corbo et al., 1989; Gafitanu et al., 2017; Falavigna et al., 2020; and Levy et al., 1999. In general, these studies support arguments about mucosal cavities and membranes enhanced absorption, however the chemicals used are not easily comparable to phthalates nor adult toys are comparable to drug delivery devices. Drug delivery devices are intentionally supposed to release the drug so the drug can be absorbed at certain rate while adult toys are not built to intentionally release phthalates. Also, drugs are larger and have different physical and chemical properties in comparison to phthalates. Thus, the concentrations of the drugs and the duration of exposures used in the studies is unlikely to be representative of phthalate absorption from adult toys for mucosal membranes.

To use hygiene and personal use products like sanitary pads, tampons, and menstrual cups data as a surrogate for sex toys. For this approach the committee provided Gao *et al*. 2020; and Marcelis *et al*. 2025 studies. Gao et al., 2020 used dermal absorption as a proxy for feminine hygiene products exposure assessment. The study considered the high transdermal absorption of chemicals by vulvar skin and vaginal mucosa. Marcelis *et al*. 2025 study discussed extractable and leachable phthalates from menstrual and intimate care products. While the leachable data can be used as a proxy for adult toys, the study does not provide absorption data.

To use buccal mucosa and dermal as a proxy for vaginal exposures the committee provided Galey et al., 1976; Van der Bijl and van Eyk, 2004; and Nilsson et al., 2006 for buccal exposures. EPA performed a quantitative mouthing and dermal exposure assessment of adult toys, however in agreement with the studies provided by the committee, vaginal and anal exposure are expected to be higher than mouthing and dermal. While a factor can be applied to the mouthing and dermal exposure doses, EPA is uncertain the magnitude of the factor to multiply adult toys mouthing and dermal doses.

To use hydrocortisone absorption through forearm and vulvar skin the committee provided Britz et al., 1980. The study provided a comparison of absorption of hydrocortisone in the forearm compared to the vulvar skin (labia majora) of 5 women. However, the study results showed high inter-individual variability of absorption. In addition, the shortest exposure duration experiment in the study was for 0 to 6 hours, which is much higher than the exposure duration used for adult toys in this assessment (15, 30, and 60 minutes). All of these factors make the study inappropriate for use in an extrapolation to absorption of phthalates due to contact with vaginal and anal mucosa. This study was used in DEHP, DBP, and BBP consumer technical support documents to discuss adult toys mucosal membranes exposures.

The committee provided Williams et al., 2025; Collar et al., 2022; and Herbenik et al., 2023 for adult toys use patterns. Of the studies provided Herbenik et al., 2023 contained duration of use information. The study provides a summary of past surveys and their own survey about partnered sex duration. While the study collected information on use of adult toys among age groups and genders, the study was not clear about the duration of use of the adult toys. However, the durations of partnered sexual activity reported by the study were similar to the duration of use for adult toys used in the modelling. The mean duration of partnered sexual activity reported for all age groups and genders was approximately 30 minutes. The study reported on past surveys that reported partnered sex durations ranging from 15 to 57 minutes. EPA used 15, 30, and 60 minutes for duration of use for the low, medium, and high intensity use exposure scenarios for adult toys, respectively.

2.18 Charge Question 19

As described in Section 2.3.3 of the *Draft Environmental Release and Occupational Exposure Assessment for DBP*, EPA assessed releases of DBP to the environment using data reported to the EPA when available. However, when programmatic reporting data such as Toxic Release Inventory (TRI), Discharge Monitoring Reporting (DMR), or National Emissions Inventory (NEI) were unavailable, EPA estimated releases using standard EPA models and equations, as described in Section 2.3.4 of the *Draft Environmental Release and Occupational Exposure Assessment for DBP*. For some OES estimated using standard models and equations, environmental releases could not be attributed to a specific media type. As an example, releases from the Manufacturing OES, as discussed in Section 3.1.3.2 of the *Draft Environmental Release and Occupational Exposure Assessment for DBP*, are categorized as being part of "Water, Incineration, or Landfill"

2.18.1 Charge Question 19.a

In Section 3.2.2 of the *Draft Environmental Release and Occupational Exposure Assessment for DBP*, EPA states that there is moderate confidence in the releases modeled for the Manufacturing OES. Please comment on the strengths and uncertainties of using standard EPA models and equations for estimating releases in the absence of programmatic data and the confidence in these model estimates.

In Section 3.3 of the *Draft Risk Evaluation for DBP*, EPA estimates surface water concentrations for Manufacturing OES for its general population and environmental exposure assessment. EPA was unable to attribute a specific portion of the total release to just water. Therefore, for the screening level assessment for general population and environmental exposure, EPA conservatively assumed 100 percent of the release was attributed to water. Please comment on potential sources of existing information and approaches that may reduce the uncertainty of EPA's assessment of releases to multimedia categories when using standard models when programmatic reporting data (TRI, NEI, DMR) are unavailable.

2.18.1.1 SACC Recommendations and EPA Responses (Charge Question 19.a)

1. **SACC Recommendation:** Improve media-specific attribution. Use literature, analog chemicals, or probabilistic methods to better assign modeled releases to water, air, or land.

   EPA Response: EPA thanks SACC for the recommendation on potential sources of existing information or methods that may reduce the uncertainty of EPA's assessment of releases to multimedia categories when programmatic reporting data (TRI, NEI, DMR) are unavailable. EPA will consider these potential sources of information or methods in the future in the development of the risk evaluation while working with EPA's Office of Water to identify alternate assumptions and other models.

2. **SACC Recommendation:** Refine model inputs. Update assumptions (e.g., throughput, controls, operating days) using more recent data from permits, CDR, or facility-level information.

   EPA Response: EPA is committed to continued improvement in assessment methodologies and includes most recent reasonably available data as model inputs if the data is more appropriate than the ones used previously. EPA will continue to update assumptions in the future as new data become available while working with EPA's Office of Water to identify alternate assumptions and other models.

3. **SACC Recommendation:** Clarify uncertainty. Apply sensitivity or uncertainty analysis to better reflect the range of possible outcomes.

EPA Response: EPA includes weight of scientific evidence conclusion tables in the risk evaluation to discuss uncertainties. EPA will consider more refined analyses in the future to clarify uncertainties related to the range of possible outcomes.

4. **SACC Recommendation:** Use available site-level data. Incorporate permit records or publicly available data to improve realism and confidence in modeled estimates.

   EPA Response: EPA strives to include any reasonably available data appropriate for the assessment including site-level data from publicly available information while working with EPA's Office of Water to identify alternate assumptions and other models if data is unavailable.

5. **SACC Recommendation:** Avoid unrealistic assumptions about emissions sources. Reevaluate assumptions such as open liquid surfaces where not supported by data that describe industrial practices.

   EPA Response: EPA is committed to continued improvement in assessment methodologies and use the data which are most appropriate for an assessment from reasonably available information. EPA will continue to update assumptions in the future if there are data available which better represent an emission scenario.

6. **SACC Recommendation:** Address data gaps transparently. Avoid defaulting to zero when data are missing; clearly explain how gaps are handled.

   EPA Response: EPA attempts to be transparent about data gaps and provides explanation of the gaps in the risk evaluations. EPA will aim to provide a more thorough analysis on how the data gaps may impact aspects of the risk evaluation and ultimately exposure estimates. EPA continues to foster partnerships with stakeholders to obtain data relevant and appropriate for risk evaluation, and any data received from stakeholders to fill data gaps will be considered.

7. **SACC Recommendation:** Reassess analog facility use. Justify or revise the use of data from non-DBP manufacturing facilities if physical operations or emissions are meaningfully different.

   EPA Response: EPA strives to use the data which are most appropriate from reasonably available information. Data from an analog facility are only used when there are no data for the COU and releases are expected to be similar from both the processes.

8. **SACC Recommendation:** Engage directly with reporting facilities. Contact known manufacturers, such as Dystar LP, to validate key assumptions like production volume and operating days.

   EPA Response: EPA strives to foster partnerships with stakeholders to obtain data for risk evaluation assessment and any reliable and relevant data received from stakeholders (e.g. production volume or operating days) will be considered in the future development of risk evaluations.

9. **SACC Recommendation:** Attempt to refine model outputs before drafting the risk evaluation by corresponding with stakeholders to obtain data.

EPA Response: EPA will continue to work with stakeholders to obtain critical data for use in the risk evaluations.

2.18.2 Charge Question 19.b

In Section 3.3 of the *Draft Risk Evaluation for DBP*, EPA estimates surface water concentrations for Manufacturing OES for its general population and environmental exposure assessment. EPA was unable to attribute a specific portion of the total release to just water. Therefore, for the screening level assessment for general population and environmental exposure, EPA conservatively assumed 100% of the release was attributed to water. Please comment on potential sources of existing information and approaches that may reduce the uncertainty of EPA's assessment of releases to multimedia categories when using standard models when programmatic reporting data (TRI, NEI, DMR) are unavailable.

2.18.2.1 SACC Recommendations and EPA Response (Charge Question 19.b)

1. **SACC Recommendation:** *Leverage regulatory datasets.* Use RCRA, NPDES, or other permit-based sources to better estimate how DBP waste is distributed across media.

   EPA Response: EPA thanks SACC for the recommendation. EPA strives to use information from any reasonably available source for the assessment. EPA will consider Resource Conservation and Recovery Act (RCRA), National Pollutant Discharge Elimination System (NPDES), and other permit-based sources in the future to estimate how waste is distributed across media.

2. **SACC Recommendation:** *Engage with industry*. Encourage submissions or stakeholder input to improve understanding of release practices where data gaps exist.

   EPA Response: EPA continues to foster partnerships with stakeholders to obtain data for risk evaluation assessment and any data received from stakeholders will be considered in the future development of risk evaluations.

3. **SACC Recommendation:** *Use probabilistic methods to estimate media distribution.* When measured data are not available, apply information from published studies or expert engineering assumptions to estimate how releases are likely divided among water, air, and land.

   EPA Response: EPA thanks SACC for the recommendation on sources of information that may be used to potentially estimate releases going to each media. EPA will consider these potential sources of information in the future in the development of the risk evaluations.

4. **SACC Recommendation:** *Include relevant criteria and monitoring data.* Reference EPA's Water Quality Criteria for DBP and explore state-level permit or monitoring data to help validate or refine surface water concentration estimates.

   EPA Response: EPA has included references to the Water Quality Criteria and Effluent Limitation Guidelines for DBP, DEHP, and BBP to help contextualize the modeled results.

5. **SACC Recommendation:** *Address data aggregation conservatively.* When releases cannot be allocated to specific media, consider evaluating total release for each relevant medium, particularly water, in the absence of better information.

EPA Response: In the risk evaluation, EPA has considered evaluating total release for each relevant medium, particularly water, in the absence of better information. EPA acknowledges the input and has assumed 100% to each media type when releases are modeled to multimedia categories as a starting point for the screening analysis.

6. **SACC Recommendation:** *Clarify data inconsistencies.* Ensure internal consistency between (1) exposure assumptions and existing EPA documents such as Water Quality Criteria; and (2) bioaccumulation potential.

   EPA Response: With regard to the difference in bioaccumulation potential between this risk evaluation and the 2015 AWQC, EPA notes that the conclusion in the 2015 AWQC was based on a framework specific to the AWQC, and that the updated data available for this risk evaluation indicate that a finding of low bioaccumulation potential is best supported by the weight of scientific evidence (not solely the estimated BAF value). EPA has included an explanation of its determination of low bioaccumulation potential for DBP, which is based on a combination of biomonitoring studies showing low to moderate bioaccumulation in individual aquatic organisms and negative biomagnification *(i.e.,* biodilution) across trophic levels, and on metabolic studies showing rapid metabolism of DBP.

7. **SACC Recommendation:** *Improve transparency on reported data.* Clearly state when and how production volume and release data were derived or imputed across facilities.

   EPA Response: EPA has included explanations of how production volume and release data were derived or inputed across facilities in the Environmental Release and Occupational Exposure Assessment document for the phthalates.

2.18.3 Charge Question 19.c

In Section 3.3.1.1 of the *Draft Risk Evaluation for DBP*, EPA determined that there is slight confidence in the precision of the estimated surface water concentrations, and subsequent risk associated with exposure to those concentrations, for the Manufacturing OES because of the combination of conservative assumptions of all releases going to surface water and pairing high-end modeled releases with lower flow receiving waterbodies (P50). The SACC has previously commented on DIDP's risk evaluation, which paired high-end modeled releases with P50 flows, that the EPA should revisit the modeling of DIDP concentrations of water and sediment by reconsidering the rates of environmental releases or the scale of the receiving environment in the modeling while maintaining conservatism in the assessment. EPA now estimates surface water concentrations based on multiple flows (P50, P75, and P90). EPA has moderate to robust confidence that the estimates using P50 flow values represent theoretical upper bounds of potential release concentrations appropriate for screening level assessments. Please comment on potential information sources and approaches to support use of a single flow value to refine the surface water concentration estimates.

2.18.3.1 SACC Recommendations and EPA Response (Charge Question 19.c)

1. **SACC Recommendation:** *Incorporate protective low-flow metrics.* Use 7Q10 or P50 of 7Q10, rather than 30Q5, as a default for surface water exposure estimates.

   EPA Response: Per EPA's Water Quality Standards Handbook (https://www.epa.gov/sites/default/files/2014-09/documents/handbook-chapter5.pdf), EPA's Office of Water (OW) recommends the harmonic mean flow for implementing human health

criteria and 7Q10 for aquatic life. In the handbook, EPA also recommends critical low-flow values that differ from the recommendation of harmonic mean for specific pollutants such as 30Q5 for implementing chronic criteria for ammonia. There are no specific recommendations for phthalates, but generally for estimating exposure to the general population under TSCA, EPA utilizes the harmonic mean flow for assessing chronic exposure, in line with OW's Water Quality Standards Handbook, which is less conservative than the 7Q10 but more predictive for human health. For assessing acute exposure under TSCA, EPA utilizes the 30Q5, which yields a more conservative surface water estimate than the harmonic mean and has been recommended for other pollutants. There are no EPA recommendations for using 7Q10 for implementing human health criteria in EPA's Water Quality Standards Handbook.

2. **SACC Recommendation:** *Correct non-standard values.* Review and revise Table 3-4 to address implausible or duplicated release estimates, including any zero values without justification.

   EPA Response: Methods to estimate releases is explained in the Environmental Release and Occupational Exposure Assessment document for the phthalates. The zero values represent situations where the reported facilities did not report any releases.

3. **SACC Recommendation:** *Clarify basis for flow assumptions.* Ensure that the origin and rationale for P50–P90 flow percentiles are clearly described within the main *Risk Evaluation for DBP* document.

   EPA Response: EPA has added text to Section 3.3 of each risk evaluation briefly describing where the flow statistics are drawn from and adding clear citation to Appendix B of the Environmental Media and General Population and Environmental Exposure Technical Support Documents of each phthalate for more details.

4. **SACC Recommendation:** *Contextualize modeled outputs.* Compare modeled surface water concentrations to EPA water quality criteria (U.S. EPA, 2025) to gauge plausibility and regulatory relevance.

   EPA Response: EPA has included the ambient water quality criteria (AWQC) and the federal effluent limitation guidelines (ELGs) into the technical support documents and risk evaluations when applicable. DEHP, DBP, and BBP have ELGs and AWQCs but DCHP and DIBP do not. Although the ELGs and AWQC may not directly represent releases associated with all COUs assessed under TSCA, EPA generally compared modeled results to the ELGs and AWQC.

5. **SACC Recommendation:** *Avoid compounding conservatism.* Assess whether overlapping conservative assumptions (*e.g.*, worst-case releases + P50 flow + no dilution) are justified in screening-level contexts.

   EPA Response: For OES with no reported releases and no facility-specific data, EPA often does not have data on wastewater treatment, location of release, nor flows of receiving waterbodies. EPA recognizes that concurrent use of many conservative assumptions, in the absence of data, such as assuming 100% of releases to a single media type when modeled results report to multiple media, no wastewater treatment, release to low flow receiving waterbodies, and exposure at the site of release with no assumptions of dilution, can lead to compounding conservatism and a likely and unintended departure from the statutory authority risk standard. EPA uses the environmental concentrations modeled using many conservative assumptions as a

starting point for its screening-level assessment to represent an upper-bound of exposure. If no MOEs are below the benchmark using the conservative exposure values, then EPA has robust confidence that no other exposure scenarios would yield MOEs below the benchmark. However, if the conservative exposure values result in MOEs below the benchmark, EPA considers additional information as available, such as physical and chemical properties, environmental monitoring, or similar release data to refine modeled estimates to represent realistic exposure scenarios and to be consistent with statutory authority.

6. **SACC Recommendation: Develop a flow percentile framework.** Provide a tiered approach to flow percentile selection that considers site-, sector-, or region-specific information and maintains screening-level protectiveness.

   EPA Response: In the absence of reported release data and location of releasing facilities, EPA has limited information to assess environmental concentrations of chemicals in the environment resulting from releases. However, EPA continues to utilize reasonably available data to develop methods to estimate environmental media concentrations including surface water concentration. EPA strives to foster partnerships with stakeholders to understand if and where chemicals are being released into the environment to better characterize concentrations of chemicals in the environment resulting from releases using site-, sector-, or region-specific information.

2.18.4 Charge Question 20

Within Section 3 of the *Draft Environmental Release and Occupational Exposure Assessments for DBP, DEHP, and DCHP* EPA has used the *Generic Model for Central Tendency and High-End Inhalation Exposure to Total and Respirable Particulates Not Otherwise Regulated (PNOR)* (US EPA, 2021) to estimate worker inhalation exposure to solid particulates for several occupational exposure scenarios (OES). The primary strength of this approach is the use of monitoring data from Occupational Safety and Health Administration (OSHA) Chemical Exposure Health Data (CEHD) datasets. The primary limitation for this method is that the OSHA CEHD dataset used in the PNOR model is not chemical specific but instead specific to a North American Industry Classification System (NAICS) code. Please suggest additional methods for estimating occupational inhalation exposures to solid particulates which are more chemical specific.

2.18.4.1 SACC Recommendations and EPA Response (Charge Question 20)

1. **SACC Recommendation:** As early as possible during the process of preparing any Draft Risk Evaluation, when EPA recognizes data gaps, the Agency's stakeholders should be approached to provide data prior to the draft being finalized in order to have appropriate data to evaluate risks.

   EPA Response: EPA thanks SACC for the recommendation to approach stakeholders as early as possible during the process of preparing the draft risk evaluation to obtain appropriate data to evaluate risks. EPA strives to foster partnerships with stakeholders to obtain data for risk evaluation, and any data received from stakeholders will be considered in the future development of risk evaluations.

2. **SACC Recommendation:** The EPA's inhalation exposure assessment should consider the potential for vapor exposure to semi-volatiles in addition to solids.

   EPA Response: EPA considers inhalation exposure to both dust and vapor in the occupational exposure assessment depending on the occupation exposure scenario. For an occupational

exposure scenario where either vapor or solid particulate exposure is expected, EPA considers exposure to either vapor or solid particulates for that occupational exposure scenario. However, for occupational exposure scenarios where both vapor and solid particulate exposures are expected, EPA includes inhalation exposure estimates from both vapor and solid particulates in the assessment.

REFERENCES

Abdul-Ghani, S, Yanai, J, Abdul-Ghani, R, Pinkas, A, Abdeen, Z. (2012). The teratogenicity and behavioral teratogenicity of di(2-ethylhexyl) phthalate (DEHP) and di-butyl phthalate (DBP) in a chick model. Neurotoxicol Teratol 34(1):56-62. doi: 10.1016/j.ntt.2011.10.001. Epub 2011 Oct 13. PMID: 22019469.

Ahmad R, Gautam AK, Verma Y, Sedha S, Kumar S. (2014). Effects of in utero di-butyl phthalate and butyl benzyl phthalate exposure on offspring development and male reproduction of rat. Environ Sci Pollut Res Int 21: 3156-3165. http://dx.doi.org/10.1007/s11356-013-2281-x.

Alam, MS, Maowa, Z, Hasan, MN. (2024). Phthalates toxicity in vivo to rats, mice, birds, and fish: A thematic scoping review. Heliyon 11(1):e41277. doi: 10.1016/j.heliyon.2024.e41277. PMID: 39811286; PMCID: PMC11731458.

Aso, S; Ehara, H; Miyata, K; Hosyuyama, S; Shiraishi, K; Umano, T; Minobe, Y. (2005). A two generation reproductive toxicity study of butyl benzyl phthalate in rats. J Toxicol Sci 30: S39-S58. http://dx.doi.org/10.2131/jts.30.S39.

ATSDR (2022). Toxicological Profile for di(2-ethylhexyl) phthalate (DEHP) [ATSDR Tox Profile]. (CS274127- A). Atlanta, GA. https://www.atsdr.cdc.gov/ToxProfiles/tp9.pdf.

Bencic, D, Flick, R, Bell, M, *et al*. (2024). A multiomics study following acute exposures to phthalates in larval fathead minnows (Pimephales promelas) – The potential application of omics data in risk evaluations under TSCA (internal use only). (EPA/600/X-24/098). U.S. Environmental Protection Agency. Cincinnati, OH, U.S. Environmental Protection Agency,

Bennekou SH, Allende A, Bearth A, Casacuberta J, *et al*., (2025). Statement on the use and interpretation of the margin of exposure approach. EFSA J 23:e9606

Blessinger, T., Davis, A., Chiu, W. A., Stanek, J., Woodall, G. M., Gift, J., Thayer, K. A., Bussard, D. (2020). Application of a unified probabilistic framework to the dose-response assessment of acrolein. Environ Int, 143,105953. https://doi.org/10.1016/j.envint.2020.105953.

Blystone CR, Kissling GE, Bishop JB, Chapin RE, Wolfe GW, Foster PM (2010). Determination of the di-(2- ethylhexyl) phthalate NOAEL for reproductive development in the rat: importance of the retention of extra animals to adulthood. Toxicological Sciences: 640-6.

Brehm E, Flaws JA (2021). Prenatal exposure to a mixture of phthalates accelerates the age-related decline in reproductive capacity but may not affect direct biomarkers of ovarian aging in the F1 generation of female mice. Environ Epigenet 7: dvab010. https://doi.org/10.1093/eep/dvab010 .

Britz MB, Maibach HI, Anjo DM. (1980). Human percutaneous penetration of hydrocortisone: the vulva Arch Dermatol Res. 267(3):313-6. doi: 10.1007/BF00403852 . PMID: 7406539.

Chen TC, Clark J, Riddles MK, Mohadjer LK, Fakhouri THI. (2020). National Health and Nutrition Examination Survey, 2015-2018: Sample Design and Estimation Procedures. Vital Health Stat 2. (184):1-35. PMID: 33663649. https://pubmed.ncbi.nlm.nih.gov/33663649/

Chikae, M, Hatano, Y, Ikeda, R, Morita, Y, Hasan, Q, Tamiya, E. (2004a). Effects of bis(2-ethylhexyl) phthalate and benzo[a]pyrene on the embryos of Japanese medaka (Oryzias latipes). Environ Toxicol Pharmacol 16: 141-145. http://dx.doi.org/10.1016/j.etap.2003.11.007 822

Chikae, M, Ikeda, R, Hatano, Y; Hasan, Q; Morita, Y, Tamiya, E. (2004b). Effects of bis(2-ethylhexyl) phthalate, γ-hexachlorocyclohexane, and 17β-estradiol on the fry stage of medaka (Oryzias latipes). Environ Toxicol Pharmacol 18: 9-12. http://dx.doi.org/10.1016/j.etap.2004.04.004

Cohen, SM, Boobis, AR, Dellarco, VL, Doe, JE, Fenner-Crisp, PA, Moretto, A, Pastoor, TP, Schoeny, RS, Seed, JG, Wolf, DC. (2019). Chemical carcinogenicity revisited 3: Risk assessment of carcinogenic potential based on the current state of knowledge of carcinogenesis in humans, Regulatory Toxicology and Pharmacology, Volume 103, Pages 100-105. https://doi.org/10.1016/j.yrtph.2019.01.017

Collar, AL, Fuentes, JE, Rishel Brakey, H, *et al*. (2022). Sexual Enrichment Aids: A Mixed Methods Study Evaluating Use, Hygiene, and Risk Perception among Women. J Sex Res 59:1153-1162. https://doi.org/10.1080/00224499.2021.2015568.

Corbo DC, Liu JC, Chien YW (1989). Drug absorption through mucosal membranes: effect of mucosal route and penetrant hydrophilicity. Pharm Res. 6(10):848-52. doi: 10.1023/a:1015952320372. PMID: 2608627.

Corradetti, B, Stronati, A, Tosti, L, Manicardi, G, Carnevali, O, Bizzaro, D. (2013). Bis-(2-ethylexhyl) phthalate impairs spermatogenesis in zebrafish (Danio rerio). Reprod Biol 13: 195-202. http://dx.doi.org/10.1016/j.repbio.2013.07.003

Deisinger PJ, Perry LG, Guest D. (1998). *In vivo* percutaneous absorption of [14C]DEHP from [14C]DEHP- plasticized polyvinyl chloride film in male Fischer 344 rats. Food Chem Toxicol.; 36(6):521-7. doi: 10.1016/s0278-6915(98)00015-5 . Erratum in: Food Chem Toxicol 1998 Dec;36(12):I.

Doan K, Bronaugh R, Yourick JJ (2010). *In vivo* and *in vitro* skin absorption of lipophilic compounds, dibutyl phthalate, farnesol and geraniol in the hairless guinea pig. Food and chemical toxicology Vol. 48, Iss. 1 p.18-23, (Jan 2010): p. 18-23. DOI:19747520; 10.1016/j.fct.2009.09.002

EC/HC (2017). Draft Screening Assessment: Phthalate substance grouping. Ottawa, Ontario, Government of Canada, Environment Canada, Health Canada. https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/draft-screening-assessment-phthalate-substance-grouping.html

EFSA (2021). Outcome of the public consultation on the draft EFSA Opinion on the impact of non-monotonic dose responses on EFSA's human health risk assessments. European Food Safety Authority, EFSA Supporting Publication: EN-6878, https://doi.org/10.2903/sp.efsa.2021.EN-6878

Elsisi AE, Carter DE, Sipes IG. (1989). Dermal absorption of phthalate diesters in rats. Fundam Appl Toxicol.; 12(1):70-7. doi: 10.1016/0272-0590(89)90063-810.1016/0272-0590(89)90063-8.

Fletcher EJ, Stubblefield WS, Huff J, *et al*. (2024). Prenatal exposure to an environmentally relevant phthalate mixture alters serum cytokine levels and inflammatory markers in the F1 mouse ovary. Toxicological Sciences. https://doi.org/10.1093/toxsci/kfae084.

Furr JR, Lambright CS, Wilson VS, Foster PM, Gray LE Jr. (2014). A short-term in vivo screen using fetal testosterone production, a key event in the phthalate adverse outcome pathway, to predict disruption of sexual differentiation. Toxicol Sci.; 140(2):403-24. doi: 10.1093/toxsci/kfu081. Epub 2014 May 5. PMID: 24798384; PMCID: PMC4471440.

Gafitanu, CA, Filip, D, Cernatescu, C, *et al*. (2017). Design, Preparation and Evaluation of HPMC-Based PAA or SA Freeze-Dried Scaffolds for Vaginal Delivery of Fluconazole. Pharm Res 34:2185-2196. https://doi.org/10.1007/s11095-017-2226-z.

Galey WR, Lonsdale HK, Nacht S. (1976) The in vitro permeability of skin and buccal mucosa to selected drugs and tritiated water. J Invest Dermatol. 1976 Dec;67(6):713-7. doi: 10.1111/1523-1747.ep12598596. PMID: 1033956.

Gao CJ, Kannan K. (2020). Phthalates, bisphenols, parabens, and triclocarban in feminine hygiene products from the United States and their implications for human exposure. Environ Int.; 136:105465. doi: 10.1016/j.envint.2020.105465. Epub., PMID: 31945693.

Goetz, A., Ryan, N., Sauve-Ciencewicki, A., Lord CC, Hilton GM., Wolf, DC. (2024). Assessing human carcinogenicity risk of agrochemicals without the rodent cancer bioassay. Front. Toxicol., Sec. Regulatory Toxicology, Vol. 6. https://doi.org/10.3389/ftox.2024.1394361

Gong, M; Zhang, Y; Weschler, CJ. (2014). Measurement of phthalates in skin wipes: Estimating 2592 exposure from dermal absorption. Environ Sci Technol 48: 7428-7435. 2593 http://dx.doi.org/10.1021/es501700u

Gray, LE; Lambright, CS; Conley, JM; Evans, N; Furr, JR; Hannas, BR; Wilson, VS; Sampson, H; Foster, PMD. (2021). Genomic and Hormonal Biomarkers of Phthalate-Induced Male Rat Reproductive Developmental Toxicity Part II: A Targeted RT-qPCR Array Approach That Defines a Unique Adverse Outcome Pathway. Toxicol Sci 182: 195-214. http://dx.doi.org/10.1093/toxsci/kfab053.

Kim J, Cha S, Lee MY, et al. 2018. Chronic low-dose nonylphenol or di-(2-ethylhexyl) phthalate has a different estrogen-like response in mouse uterus. Dev Reprod 22(4):379-391. http://doi.org/10.12717/dr.2018.22.4.379.

Kim J, Cha S, Lee MY, et al. 2019. Chronic and low dose exposure to nonlyphenol or di(2-ethylhexyl) phthalate alters cell proliferation and the localization of steroid hormone receptors in uterine endometria in mice. Dev Reprod 23(3):263-275. http://doi.org/10.12717/dr.2019.23.3.263.

Hannas, BR; Lambright, CS; Furr, J; Howdeshell, KL; Wilson, VS; Gray, LE. (2011). Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following in utero exposure to diethylhexyl phthalate, diisobutyl phthalate, diisoheptyl phthalate, and diisononyl phthalate. Toxicol Sci 123: 206-216. http://dx.doi.org/10.1093/toxsci/kfr146

Hannas, BR, Lambright, CS, Furr, J, *et al*. (2012). Genomic biomarkers of phthalate-induced male reproductive developmental toxicity: a targeted RT-PCR array approach for defining relative potency. Toxicol Sci 125:544-557. https://doi.org/10.1093/toxsci/kfr315.

Hannon PR, Niermann S, Flaws JA. (2016). Acute Exposure to Di(2-Ethylhexyl) Phthalate in Adulthood Causes Adverse Reproductive Outcomes Later in Life and Accelerates Reproductive Aging in Female Mice. Toxicol Sci 150:97-108. https://doi.org/10.1093/toxsci/kfv317.

Harleman, J. H., *et al*., (2012). A review of the incidence and coincidence of uterine and mammary tumors in Wistar and Sprague-Dawley rats based on the RITA database and the role of prolactin. Toxicol Pathol. 40**,** 926-30.

Health Canada. (2018a). Supporting documentation: Evaluation of epidemiologic studies on phthalate compounds and their metabolites for effects on behaviour and neurodevelopment, allergies, cardiovascular function, oxidative stress, breast cancer, obesity, and metabolic disorders. Ottawa, ON.

Health Canada. (2018b). Supporting documentation: Evaluation of epidemiologic studies on phthalate compounds and their metabolites for hormonal effects, growth and development and reproductive parameters. Ottawa, ON

Heindler, FM, Alajmi, F, Huerlimann, R, Zeng, C, Newman, SJ, Vamvounis, G, van Herwerden, L (2017). Toxic effects of polyethylene terephthalate microparticles and Di(2-ethylhexyl) phthalate on the calanoid copepod, Parvocalanus crassirostris. Ecotoxicol Environ Saf 141: 298-305. http://dx.doi.org/10.1016/j.ecoenv.2017.03.029.

Hilton, GM, Adcock, C., Akerman, G., Baldassari, J., Battalora, M., Casey, W., Clippinger, AJ., Cope, R., Goetz, A. Hayes, AW., Papineni, S., Peffer, RC., Ramsingh, D., Williamson Riffle, B., Sanches da Rocha, M., Ryan, N., Scollon, E., Visconti, N., Wolf, DC., Yan, Z., Lowit, A. (2022). Rethinking chronic toxicity and carcinogenicity assessment for agrochemicals project (ReCAAP): A reporting framework to support a weight of evidence safety assessment without long-term rodent bioassays, Regulatory Toxicology and Pharmacology, Vol. 131, 105160, https://doi.org/10.1016/j.yrtph.2022.105160

Hong, Y, Xie, H, Jin, X, Naraginti, S, Xu, D, Guo, C, Feng, C, Wu, F, Giesy, JP (2024). "Prediction of HC5s for phthalate esters by use of the QSAR–ICE model and ecological risk assessment in Chinese surface waters." Journal of Hazardous Materials 467. https://doi.org/10.1016/j.jhazmat.2024.133642

Hopf, NB, Berthet, A, Vernez, D, Langard, E, Spring, P, Gaudin, R (2014). Skin permeation and metabolism of di(2-ethylhexyl) phthalate (DEHP), Toxicology Letters, Vol. 224(1), 47-53. https://doi.org/10.1016/j.toxlet.2013.10.004.

Hopf NB, De Luca HP, Borgatta M, Koch HM, Pälmke C, Benedetti M, Berthet A, Reale E. (2024) Human skin absorption of three phthalates. Toxicology Letters. 398:38-48. doi: 10.1016/j.toxlet.2024.05.016

Howdeshell, KL, Wilson, VS; Furr, J; Lambright, CR; Rider, CV; Blystone, CR; Hotchkiss, AK; Gray, 2478 LE, Jr. (2008). A mixture of five phthalate esters inhibits fetal testicular testosterone production 2479 in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicol Sci 105: 153-165. 2480 http://dx.doi.org/10.1093/toxsci/kfn077 or https://doi.org/kfn077

Huber, S, Warner, NA, Nygård, T, Remberger, M, Harju, M, Uggerud, HT, Kaj, L, Hanssen, L. (2015). A broad cocktail of environmental pollutants found in eggs of three seabird species from remote colonies in Norway. Environ Toxicol Chem 34(6):1296-308. doi: 10.1002/etc.2956. Epub 2015 May 5. PMID: 25728907.

Johnson, KJ; Hensley, JB; Kelso, MD; Wallace, DG; Gaido, KW. (2007). Mapping gene expression changes in the fetal rat testis following acute dibutyl phthalate exposure defines a complex temporal cascade of responding cell types. Biol Reprod. 77: 978-989. 2489 http://dx.doi.org/10.1095/biolreprod.107.062950

Johnson KJ, McDowell EN, Viereck MP, Xia JQ. (2011). Species-specific dibutyl phthalate fetal testis endocrine disruption correlates with inhibition of SREBP2-dependent gene expression pathways. Toxicol Sci.; 120(2):460-74. doi: 10.1093/toxsci/kfr020. Epub 2011 Jan 25. PMID: 21266533; PMCID: PMC3061485

Kawakami T, Isama K, Jinno H. (2020). Skin transferability of phthalic acid ester plasticizers and other plasticizers using model polyvinyl chloride sheets. J Environ Sci Health A Tox Hazard Subst Environ Eng.; 55(10):1163-1172. doi: 10.1080/10934529.2020.1795503.

Kurahashi, N; Kondo, T; Omura, M; Umemura, T; Ma, M; Kishi, R. (2005). The effects of subacute inhalation of di (2-ethylhexyl) phthalate (DEHP) on the testes of prepubertal Wistar rats. J Occup Health 47: 437-444. http://dx.doi.org/10.1539/joh.47.437

Kwak, IS, Lee, W. (2005). Endpoint for DEHP exposure assessment in Chironomus riparius. Bull Environ Contam Toxicol 74: 1179-1185. http://dx.doi.org/10.1007/s00128-005-0705-0.

Levy, T, Gurevitch, S, Bar-Hava, I, *et al*. (1999). Pharmacokinetics of natural progesterone administered in the form of a vaginal tablet. Hum Reprod 14:606-610. https://doi.org/10.1093/humrep/14.3.606.

Li, G, Chen, Y, Wu, M, Chen, K, Zhang, D, Zhang, R, Yang, G, Huang, X. (2023). Di (2-ethyl) hexyl phthalate induces liver injury in chickens by regulating PTEN/PI3K/AKT signaling pathway via reactive oxygen species. Comp Biochem Physiol C Toxicol Pharmacol 270:109639. doi: 10.1016/j.cbpc.2023.109639. Epub 2023 Apr 30. PMID: 37259793.

Li, HL; Ma, WL; Liu, LY; Zhang, Z; Sverko, E; Zhang, ZF; Song, WW; Sun, Y; Li, YF. (2019). 2651 Phthalates in infant cotton clothing: Occurrence and implications for human exposure. Sci Total 2652 Environ 683: 109-115. http://dx.doi.org/10.1016/j.scitotenv.2019.05.132

Li, X, Chen, X, Hu, G, *et al*. (2016). Effects of in Utero Exposure to Dicyclohexyl Phthalate on Rat Fetal Leydig Cells. International Journal of Environmental Research and Public Health 13:246. https://www.mdpi.com/1660-4601/13/3/246.

Li, X, Yin, P, Zhao, L. (2016). Phthalate esters in water and surface sediments of the Pearl River Estuary: distribution, ecological, and human health risks. Environ Sci Pollut Res Int 23(19):19341-9. doi: 10.1007/s11356-016-7143-x. Epub 2016 Jul 1. PMID: 27370535. (note: relative concentration of DEHP)

Li, XN, Li, HX, Yang, TN, Li, XW, Huang, YQ, Zhu, SY, Li, JL. (2020). Di-(2-ethylhexyl) phthalate induced developmental abnormalities of the ovary in quail (Coturnix japonica) via disruption of the hypothalamic-pituitary-ovarian axis. Sci Total Environ 741:140293. doi:10.1016/j.scitotenv.2020.140293. Epub 2020 Jun 18. PMID: 32610232.

Liu, X, Shi, J, Bo, T, Zhang, H, Wu, W, Chen, Q, Zhan, X (2014). Occurrence of phthalic acid esters in source waters: a nationwide survey in China during the period of 2009-2012. Environmental Pollution 184: 262-270. https://doi.org/10.1016/j.envpol.2013.08.035

Lizarraga LE, Dean JL, Kaiser JP, Wesselkamper SC, Lambert JC, Zhao QJ. (2019). A case study on the application of an expert-driven read-across approach in support of quantitative risk assessment of p,p'- dichlorodiphenyldichloroethane. Regul Toxicol Pharmacol.; 103:301-313. doi: 10.1016/j.yrtph.2019.02.010. Epub., PMID: 30794837; PMCID: PMC6854443.

Lizarraga, LE, Suter, GW, Lambert, JC, Patlewicz G, Zhao JQ, Dean JL, Kaiser P. (2023). Advancing the science of a read-across framework for evaluation of data-poor chemicals incorporating systematic and new approach methods. Regulatory Toxicology and Pharmacology 137:105293. https://doi.org/https://doi.org/10.1016/j.yrtph.2022.105293.

Ma, M; Kondo, T; Ban, S; Umemura, T; Kurahashi, N; Takeda, M; Kishi, R. (2006). Exposure of prepubertal female rats to inhaled di(2-ethylhexyl)phthalate affects the onset of puberty and postpubertal reproductive functions. Toxicol Sci 93: 164-171. http://dx.doi.org/10.1093/toxsci/kfl036

Magosso N, de Souza PV, Aquino AM, *et al*. (2025). Maternal Exposure to an Environmentally Relevant Phthalate Mixture Modulates the Steroidogenic Genes in the Adrenal Glands Throughout Postnatal Development of Male Rats. Environ Toxicol. https://doi.org/10.1002/tox.24545.

Marcelis Q, Deconinck E, Rogiers V, Demaegdt H, Mario MD, Vanhaecke T, Desmedt B. (2025). Chemical characterization of menstrual and intimate care products: An extractables & leachables investigation. Environ Int.; 198:109401. doi: 10.1016/j.envint.2025.109401. Epub. PMID: 40239564.

Moretto AS, Ammie Bachman, Alan Boobis, Keith R. Solomon, Timothy P. Pastoor, Martin F. Wilks & Michelle R. Embry (2016) A framework for cumulative risk assessment in the 21st century, Critical Reviews in Toxicology, 47:2, 85-97, DOI: 10.1080/10408444.2016.1211618

Morrison, GC, Weschler, CJ, Beko, G, Koch, HM, Salthammer, T., Schripp, T, Toftum, J, Clausen, G (2016). Role of clothing in both accelerating and impeding dermal absorption of airborne SVOCs. J Expo Sci Environ Epidemiol 26 (1):113-8.

NASEM (2017). Application of systematic review methods in an overall strategy for evaluating low dose toxicity from endocrine active chemicals. In Consensus Study Report. Washington, D.C.: The National Academies Press. http://dx.doi.org/10.17226/24758.

Nilsson, N.H., Malmgren-Hansen, B., Bernth, N., Pedersen, E., Pommer, K., 2006. Survey and health assessment of chemicals substances in sex toys. Survey of Chemical Substances in Consumer Products, no. 77. Danish Technological Institute, Danish Ministry of the Environment. https://www2.mst.dk/udgiv/publications/2006/87-7052-227-8/pdf/87-7052-228-6.pdf

NRC (2008) Phthalates and Cumulative Risk Assessment. The Task Ahead. Committee on the Health Risks of Phthalates, National Research Council, National Academy Press, Washington, DC. https://www.ncbi.nlm.nih.gov/books/NBK215040/

OECD (2024), Case Study on the Use of Integrated Approaches for Testing and Assessment (IATA) for Chronic Toxicity and Carcinogenicity of Agrichemicals with Exemplar Case Studies - Ninth Review Cycle (2023), OECD Series on Testing and Assessment, No. 402, OECD Publishing, Paris, https://doi.org/10.1787/c3b9ac37-en

Pocar, P, Fiandanese, N, Secchi, C, Berrini, A, Fischer, B, Schmidt, JS, Schaedlich, K, Borromeo, V (2012). Exposure to Di(2-ethyl-hexyl) phthalate (DEHP) *in Utero* and during Lactation Causes Long-Term Pituitary- Gonadal Axis Disruption in Male and Female Mouse Offspring, *Endocrinology*, Volume 153, Issue 2, Pages 937–948, https://doi.org/10.1210/en.2011-1450

Pocar P, Fiandanese N, Berrini A, Secchi C, Borromeo V. (2017). Maternal exposure to di(2-ethylhexyl) phthalate (DEHP) promotes the transgenerational inheritance of adult-onset reproductive dysfunctions through the female germline in mice. Toxicol Appl Pharmacol. 1;322:113-121. doi: 10.1016/j.taap.2017.03.008. Epub. PMID: 28286118.

Pogrmic-Majkic K, Samardzija Nenadov D, Tesic B, Fa Nedeljkovic S, Kokai D, Stanic B, Andric N. (2022) Mapping DEHP to the adverse outcome pathway network for human female reproductive toxicity. Arch Toxicol. 96(10):2799-2813. https://doi: 10.1007/s00204-022-03333-y. Epub 2022 Jul 5. PMID: 35790550; PMCID: PMC9352620.

RISK21 (2025). Risk Assessment in the 21st Century (RISK21) Project. Health and Environmental Sciences Institute framework: www.risk21.org

Saillenfait, AM, Sabate, JP, Gallissot, F. (2008). Diisobutyl phthalate impairs the androgen-dependent reproductive development of the male rat. Reprod Toxicol 26:107-115. https://doi.org/10.1016/j.reprotox.2008.07.006.

Schwarz, S, Rackstraw, A, Behnisch, PA, Brouwer, A, Köhler, HR, Kotz, A, Kuballa, T, Malisch, R, Neugebauer, F, Schilling, F, Schmidt, D, Theo von der Trenck, K. (2016). Peregrine falcon egg pollutants: Mirror Stockholm POPs list including methylmercury. Toxicological & Environmental Chemistry, 98(8): 886–923. https://doi.org/10.1080/02772248.2015.1126717

Silva AV, Tarvainen I, Öberg M, *et al*. (2025). Bayesian benchmark dose modeling analysis and derivation of points of departure for female reproductive toxicity following exposure to di(2-ethylhexyl) phthalate (DEHP) - effects on reproductive hormones, folliculogenesis and estrous cyclicity. Toxicol Sci 206:30-45. https://doi.org/10.1093/toxsci/kfaf052 .

Solomon KR, Wilks MF, Bachman A, Boobis A, Moretto A, Pastoor TP, Phillips R, Embry MR. (2016). Problem formulation for risk assessment of combined exposures to chemicals and other stressors in humans. Crit Rev Toxicol. 46(10):835-844 https://doi.org/10.1080/10408444.2016.1211617

Tyl, RW; Myers, CB; Marr, MC; Fail, PA; Seely, JC; Brine, DR; Barter, RA; Butala, JH. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reprod Toxicol 18: 241-264. http://dx.doi.org/10.1016/j.reprotox.2003.10.006http://dx.doi.org/10.1016/j.reprotox.2003.10.006.

US EPA (2004). Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment), EPA/540/R/99/005 OSWER 9285.7-02EP PB99-963312. https://www.epa.gov/sites/default/files/2015-09/documents/part_e_final_revision_10- 03-07.pdf

US EPA (2005). Guidelines for Carcinogen Risk Assessment, EPA/630/P-03/001B, Risk Assessment Forum. Available: https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment

US EPA (2012). Benchmark Dose Technical Guidance. Risk Assessment Forum, U.S. Environmental Protection Agency. EPA Report, EPA/100/R-12/001Washington, DC: https://www.epa.gov/risk/benchmark-dose-technical-guidance.

US EPA (2012). The Stochastic Human Exposure and Dose Simulation Model for Multimedia, Multipathway Chemicals, www.epa.gov › chemical-research › stochastic-human

US EPA (2023a) Meeting Minutes and Final Report for the Science Advisory Committee on Chemicals Public Virtual Meeting "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 Docket # EPA- HQ-OPPT-2022-0918-0067 https://www.regulations.gov/docket/EPA-HQ-OPPT-2022- 0918/document?filter=final%20report

US EPA. (2023b). Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. Washington, DC, U.S., [EPA-HQ- OPPT-2022-0918-0009]. https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0918-0009.

US EPA (2025). EPA Water Quality Criteria. Human Health Ambient Water Quality Criteria. Human Health Criteria available at: https://www.epa.gov/wqc/national-recommended-water-quality-criteria-human-health-criteria-table

van der Bijl P, van Eyk AD. (2004). Human vaginal mucosa as a model of buccal mucosa for *in vitro* permeability studies: an overview. Curr Drug Deliv. 1(2):129-35. doi: 10.2174/1567201043479975.

Wang, H, Li, XN, Li, PC, Liu, W, Du, ZH, Li, JL. (2019). Modulation of heat-shock response is associated with Di (2-ethylhexyl) phthalate (DEHP)-induced cardiotoxicity in quail (Coturnix japonica). Chemosphere 214:812-820. doi: 10.1016/j.chemosphere.2018.10.002. Epub 2018 Oct 2. PMID: 30300839.

Wang, H, Guan, TQ, Sun, JX, Talukder, M, Huang, YQ, Li, YH, Li, JL. (2020). Di-(2-ethylhexyl) phthalate induced nephrotoxicity in quail (Coturnix japonica) by triggering nuclear xenobiotic receptors and modulating the cytochrome P450 system. Environ Pollut 261:114162. doi: 10.1016/j.envpol.2020.114162. Epub 2020 Feb 10. PMID: 32078881.

Weschler, CJ, and Nazaroff, WW. (2012). SVOC exposure indoors: Fresh look at dermal pathways. Indoor Air 22 (5):356-77.

Weschler, CJ, & Nazaroff, WW. (2014). Dermal uptake of organic vapors commonly found in indoor air. Environmental science & technology, 48(2), 1230-1237. https://doi.org/10.1021/es405490a

Weschler, CJ, Bekö, G, Koch, HM, Salthammer, T., Schripp, T., Toftum, J., & Clausen, G. (2015). Transdermal uptake of diethyl phthalate and di (n-butyl) phthalate directly from air: experimental verification. Environmental health perspectives, 123(10), 928-934. https://doi.org/10.1289/ehp.1409151

Williams ME, Lafortune D, Canivet C, Dussault É. (2025). Sex Toy Use in Québec (Canada): Prevalence Across Demographics, Motivations, and Links with Erotophobia and Sexual Satisfaction. J Sex Marital Ther.;51(3):283-297. doi: 10.1080/0092623X.2025.2464092. Epub 2025 Feb 19. PMID: 39970469.

Wood, DL, and Bitman, J (1980). The effect of feeding di-(2-ethylhexyl) phthalate (DEHP) on the lipid metabolism of laying hens. Lipids 15:151-156.

Yang, TN, Li, XN, Li, XW, Li, JY, Huang, YQ, Li, JL. (2022). DEHP triggers a damage severity grade increase in the jejunum in quail (Coturnix japonica) by disturbing nuclear xenobiotic receptors and the Nrf2-mediated defense response. Environ Toxicol Pharmacol 96:104012. doi: 10.1016/j.etap.2022.104012. Epub 2022 Nov 11. PMID: 36372389.

Zhang XF, Zhang T, Han Z, et al. 2015. Transgenerational inheritance of ovarian development deficiency induced by maternal diethylhexyl phthalate exposure. Reprod Fertil Dev 27(8):1213-1221. http://doi.org/10.1071/rd14113.