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Comments from Scientists, Academics, and Clinicians on the Draft Risk Evaluation for Dibutyl Phthalate (DBP) Under TSCA

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These comments are submitted on behalf of the undersigned scientists, academics, and clinicians. We declare that we have no direct or indirect financial or fiduciary interests in the subjects of these comments. The co-signers' institutional affiliations are included for identification purposes only and do not imply institutional endorsement or support, unless indicated otherwise by an asterisk.

We appreciate the opportunity to provide written comments on EPA's Draft Risk Evaluation for Dibutyl Phthalate (DBP), (hereafter referred to as the *DBP Draft Risk Evaluation*) conducted under the Toxic Substances Control Act (TSCA), which requires EPA to evaluate chemical risks based on the "best available science."[1] DBP is a plasticizer and stabilizing agent used to make adhesives, paints and coatings, plastic products and rubber products.[2] EPA has identified male reproductive effects associated with phthalate syndrome as the main health hazards of DBP exposure from which a point of departure (POD) was derived.[3]

In the DBP Draft Risk Evaluation, EPA has **failed to incorporate the best available science and makes a number of scientifically-unsupported assumptions that, if adopted, will result in acceptance of serious risks to human health**. For certain occupational conditions of use, there are serious inconsistencies between EPA's risk estimates and EPA's conclusions regarding unreasonable risk. EPA repeatedly downplayed or disregarded the high risks it calculated using high-end exposure estimates. EPA used only central tendency estimates of DBP exposure and risk for workers in most conditions of use in its unreasonable risk determination and did not use high-end estimates, without adequate scientific justification. EPA is therefore disregarding unreasonable risks of non-cancer effects that may be faced by workers with exposures that are greater than median exposure levels, leaving 50% of the worker population unaddressed and at risk. In doing so, EPA sets a dangerous precedent that risks to more highly exposed individuals can be dismissed or downplayed without scientific support.

In addition, EPA has failed to adequately consider the scientific evidence and continued to rely on a systematic review methodology that is not consistent with best practices, violating TSCA's "best available science" requirement.[4] For example, EPA improperly excluded all human epidemiological studies from dose-response assessment, relied on outdated systematic review methods that lacked transparency, inappropriately excluded at least 446 PECO-relevant health-effects studies from the hazard assessment, and dismissed *all* health-effects studies not related to male reproductive harm from dose-response consideration without scientific justification. EPA's Science Advisory Committee on Chemicals (SACC) recently criticized EPA's decision to

[1] 15 U.S.C. § 2625(h).
[2] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 10.
[3] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 128.
[4] 15 U.S.C. § 2625(h).

disregard epidemiology studies in the dose-response assessment in the DINP Draft Risk Evaluation.[5] In addition, EPA has not conducted a comprehensive literature search for DBP since 2019, and as a result, is missing reasonably available scientific information. The National Academies of Sciences, Engineering, and Medicine (NASEM) recommended the use of existing systematic review methods and improved approaches for TSCA risk evaluations in 2021, and EPA has still not implemented most of these recommendations.[6] The SACC also provided over 200 recommendations to EPA on improving its systematic review methods in 2022,[7] and EPA has still not responded to the SACC report except in piecemeal fashion. EPA should prepare a new TSCA systematic review methodology that is aligned with the best available scientific methods, including NASEM and SACC recommendations, and issue updated draft systematic review protocols for all risk evaluations currently in development, including DBP.

The DBP Draft Risk Evaluation also relies on dose-response and risk characterization methods that violate TSCA's "best available science" requirement. Although EPA ultimately selected a point of departure (POD) based on benchmark dose (BMD) modeling, it failed to apply BMD analysis to dose-response data from 11 relevant toxicology studies on male reproductive toxicity. Instead, EPA dismissed these studies because their reported no-observed-adverse-effect levels (NOAELs) and/or lowest-observed-adverse-effect levels (LOAELs) fell within range of the selected POD. Without conducting BMD modeling for these studies, EPA cannot know whether its selected POD of 9 mg/kg-day is the most sensitive. EPA then applied the scientifically deficient margin of exposure approach for risk characterization. We applied methods developed by the World Health Organization (WHO) to quantify the risk of male reproductive effects from chronic DBP exposure, and found that EPA's current approach results in acceptance of exposures producing an unacceptable upper bound risk of 1-in-36, a level 28,000 times higher than the 1-in-1,000,000 target risk level EPA typically applies for protection of carcinogenic effects.

Another critical concern with the DBP Draft Risk Evaluation is EPA's failure to evaluate real world exposures and risks. For example, EPA fails to consider exposures from "non-TSCA" uses of DBP, including exposures through food and food packaging. Given that food is the primary route of exposure to many phthalates in children and adults,[8] likely as a result of leaching from plastic food packaging materials, EPA will understate the risk to the general population from the TSCA uses of these chemicals if it does not take into account the background exposures from these and other non-TSCA uses. The SACC recently criticized EPA's decision to disregard exposures outside of the jurisdiction of TSCA.[9]

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[5] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," pp. 91-92.

[6] National Academies of Sciences, Engineering, and Medicine (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations.

[7] U.S. EPA (2022). Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2022-2. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0044.

[8] U.S. Consumer Product Safety Commission, *Report by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives* 102–03 (2014), pp. 3, 52–53, and 59.

[9] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 16.

EPA also failed to adequately identify potentially exposed or susceptible subpopulations (PESS) and calculate risks posed to these groups, as required under TSCA.[10] In the DBP Draft Risk Evaluation, EPA failed to adequately account for the increased susceptibility of individuals with pre-existing disease, genetic factors, lifestyle factors, nutrition, socio-demographic factors, geographic factors, or exposures to other chemical and non-chemical stressors that may exacerbate harm from DBP exposure. A failure to evaluate risk to these groups violates TSCA and results in risk characterization that is not representative of the human population.

Accordingly, EPA must make extensive revisions to the DBP Draft Risk Evaluation to more accurately characterize real-world exposures and risks, including to potentially exposed or susceptible subpopulations. This includes conducting an updated literature search, adopting best available scientific methods including upgraded systematic review methods and dose-response assessment methods, revising the risk characterization to incorporate quantitative non-cancer risk estimates, using high-end exposure and risk estimates for the unreasonable risk determination for all conditions of use, and removing the use of any scientifically-unsupported justifications that downplay or disregard risk.

Our detailed comments on the Dibutyl Phthalate (DBP) Draft Risk Evaluation address the following issues:

1. **EPA did not apply the best available science to identify and evaluate relevant and useful health effects studies for DBP.**
    a. **EPA did not conduct a comprehensive and up-to-date literature search.**
    b. **EPA relied on an assessment conducted by Health Canada to exclude studies, without supporting justification and inconsistent with the best available science.**
    c. **EPA used deficient inclusion and exclusion criteria for health effects evidence that inappropriately excluded important toxicity endpoints.**
    d. **EPA inappropriately excluded at least 446 PECO-relevant health effects studies of DBP from evidence integration without valid scientific justification.**
    e. **EPA's methods for evaluation of study quality need to incorporate further improvements recommended by the National Academies.**
    f. **EPA continues to use unclear terminology regarding evidence synthesis and integration.**
    g. **EPA released an incomplete draft systematic review protocol for DBP that was not made publicly available in advance of the draft risk evaluation.**
    h. **EPA should prepare a new TSCA systematic review handbook that is aligned with the best available scientific methods and issue updated draft systematic review protocols for all risk evaluations currently in development.**

2. **EPA's non-cancer hazard identification and dose-response assessment for DBP is not consistent with the best available science.**
    a. **EPA did not adequately consider all reasonably available evidence for multiple potential non-cancer hazards of DBP.**

[10] 15 U.S.C. § 2602(12).

i. **EPA inappropriately excluded all epidemiology studies from dose-response assessment.**
ii. **EPA inappropriately excluded animal toxicology studies from dose-response assessment.**

b. **EPA failed to make appropriate use of benchmark dose modeling to specify a non-cancer point of departure for risk characterization.**
c. **EPA should apply best available methods to generate quantitative estimates of non-cancer risks for varying levels of exposure to DBP.**

3. **EPA's approach systematically underestimates real-world DBP exposures and risks.**
   a. **EPA considered aggregate exposure to only a limited extent.**
   b. **EPA failed to conduct a background exposure assessment, underestimating risk to potentially exposed or susceptible subpopulations.**

4. **EPA failed to adequately identify and quantify risks to potentially exposed or susceptible subpopulations (PESS), as required by TSCA.**

5. **EPA's determination of unreasonable risk inappropriately discounts and disregards high-end exposures without justification and violates TSCA's requirement to assess risks to groups with greater exposures.**
   a. **EPA's failure to use high-end risk estimates resulted in incorrect determinations of no unreasonable risk for 10 occupational conditions of use.**
   b. **EPA improperly disregarded high-intensity exposure and risk estimates in its unreasonable risk determination for consumer exposures to DBP in paints and toys.**

We appreciate the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these comments.

Sincerely,

Daniel Axelrad, MPP
Independent Consultant
Washington, DC

Rashmi Joglekar
Associate Director, Science and Policy
Program on Reproductive Health and the Environment
University of California, San Francisco

Abena BakenRa, MPH
Science Associate, Science and Policy
Program on Reproductive Health and the Environment
University of California, San Francisco

Jessica Trowbridge, PhD, MPH

Associate Research Scientist, Science and Policy
Program on Reproductive Health and the Environment
University of California, San Francisco

Emily Lasher, MSPH
Science Associate, Science and Policy
Program on Reproductive Health and the Environment
University of California, San Francisco

Tracey Woodruff, PhD, MPH
Director
Program on Reproductive Health and the Environment
University of California, San Francisco

Nicholas Chartres, PhD
Senior Research Fellow
School of Pharmacy, Faculty of Medicine & Health, The University of Sydney

Ronald H White, MST
Principal
RHWhite Environmental Health Consulting

Patrice Sutton, MPH
Research Collaborator
UCSF Program on Reproductive Health and the Environment

Sharyle Patton
Director
Health and Environment Program - Commonweal

Daniel Ruiz, PhD
Postdoctoral Fellow
Emory University School of Medicine, Department of Human Genetics

Courtney Carignan, PhD
Associate Professor
Michigan State University

Robert M. Gould, MD
Adjunct Assistant Professor
Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
UCSF

Robert M. Gould, MD*

President
San Francisco Bay Physicians for Social Responsibility

Donna M. Staton, MD, MPH
Pediatrician, retired
Pediatrician Member, P-SNAP, Physician & Scientist Network Addressing Plastics & Health

Linda S. Birnbaum, PhD
Scientist Emeritus
NIEHS

Ted Schettler MD, MPH*
Science Director
Science and Environmental Health Network

Phil Brown, PhD
University Distinguished Professor of Sociology and Health Sciences
Northeastern University

Christopher LeBoa, PhD
Post-doctoral scholar
UC Berkeley

Bridget Lee, MD
Doctor
BlueWater Health

Sydney Engel, MSN, FNP-BC
Pediatric Nurse Practitioner
Atrius Health

Robert Feder, MD
Executive Counsel
Medical Society Consortium on Climate and Health

James Seward, MD, MPP
Clinical Professor of Medicine
UCSF

Susanne Brander, Ph.D.
Associate Professor, Ecotoxicologist
Oregon State University

Sarah Evans, PhD, MPH
Assistant Professor
Icahn School of Medicine at Mount Sinai

Timothy H. Ciesielski, ScD, MD, MPH
Research Scientist
Case Western Reserve University School of Medicine

Sara Carpenter, MD, MSPH, DCM
Retired

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1. **EPA did not apply the best available science to identify and evaluate relevant and useful health effects studies for DBP.**

    a. **EPA did not conduct a comprehensive and up-to-date literature search.**

The need for transparent, consistent and comprehensive approaches to identifying health effects literature has been a key driver for increased adoption of systematic review methods in environmental health assessments over the past 15 years.[11,12,13] EPA's recent draft risk evaluations of DBP and other phthalates are a concerning step backward in this area, as the approach to identifying evidence is not clear, consistent, or comprehensive. Based on the inconsistent procedures applied, it is unlikely that EPA has identified and included all relevant health effects studies. This indicates critical deficiencies in the EPA systematic review protocol and the DBP Draft Risk Evaluation.

To identify epidemiology studies of DBP, EPA relied on a Health Canada assessment completed in 2020,[14,15] and a literature search that was conducted in 2019 and has not been updated since. As stated in EPA's systematic review protocol for DBP:

> The search for peer-reviewed and gray literature relevant references was completed in September and May 2019, respectively.[16]

EPA has not conducted a search for studies relevant to the DBP Draft Risk Evaluation in the five-plus years prior to its release for public comment, and therefore the literature compiled for use in evaluating DBP is not up to date.

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[11] National Research Council (2011). Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.
[12] Woodruff TJ, Sutton P; Navigation Guide Work Group. An evidence-based medicine methodology to bridge the gap between clinical and environmental health sciences. Health Affairs 2011 May; 30(5):931-7.
[13] Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122:711–718.
[14] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 23.
[15] Health Canada (2020). Screening assessment - Phthalate substance grouping.
[16] U.S. EPA (2024). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 9.

Further, EPA did not conduct study quality evaluation or data extraction for any epidemiology study published before 2018:

> Previous phthalates risk assessments have been conducted by authoritative sources including Health Canada and the EPA IRIS program. OPPT used these previous assessments to facilitate efficient and scientific risk evaluation. Therefore, data quality evaluation and extraction were conducted only for references published after the literature search end date of the most recent authoritative assessment.
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> The most recent authoritative assessment was published by Health Canada in 2020 and included literature published up to 2018 (Health Canada, 2020). Therefore, data quality evaluation and extraction were conducted for references published from the beginning of 2018 through the end date of the OPPT literature search, as well as for references that were published from the beginning of 2018 through the end of 2023 that were sent with public comments in phthalates dockets. Data quality evaluation and extraction was not conducted for any references published before 2018.[17]

EPA's procedures therefore resulted in dividing the set of epidemiology studies into three inconsistent subsets based on the date of publication:

- Studies published prior to 2018 – are included in EPA's assessment only if they were included in the assessment conducted by Health Canada. The Health Canada document is not a systematic review or and it does not appear to have been peer reviewed. EPA did not assess the quality of the studies identified by Health Canada or extract their data. The DBP draft protocol indicates that 212 PECO-relevant pre-2018 epidemiology studies were excluded from the risk evaluation;[18] it is unclear why EPA did not include these studies. Additionally, EPA did not consider any studies published before 2018 if they were not discovered by or not included in the Health Canada assessment for any reason.
- Studies published from 2018 to September 2019 – EPA conducted its own search of the literature and applied its own inclusion/exclusion criteria.
- Studies published from September 2019 through 2023 – are included in EPA's assessment only if they were submitted by public commenters to the EPA docket.

Thus, only those epidemiology studies published in a span of 21 months were identified and evaluated through a comprehensive process following an EPA protocol. For earlier studies (before 2018), EPA excluded hundreds of relevant studies, relied entirely on the Health Canada assessment and did not apply its own search, inclusion/exclusion and study evaluation procedures. For later studies (after September 2019), EPA did not conduct a search but included only those studies that were submitted by the public to EPA. This is not a clear, comprehensive or consistent approach to identifying the epidemiological evidence relevant to assessing the health effects of DBP. A further concern is that these inconsistent procedures for identifying

[17] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 23.
[18] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 24.

epidemiological evidence were ultimately relevant only to the identification of DBP hazards, since EPA subsequently excluded **all** epidemiological studies from consideration for dose-response assessment, without consideration of the merits of individual studies (see comment 2a above).

For identifying toxicology studies, EPA applied a similar process:

> Previous phthalates risk assessments have been conducted by authoritative sources including Health Canada (EC/HC) (2015a) and (2020). OPPT used these previous assessments to facilitate an efficient and scientific risk evaluation. Based on these existing assessments, a total of 21 key studies for point of departure (POD) refinement...moved directly to the data evaluation and extraction step under TSCA.[19]
>
> The literature search conducted by OPPT for the DBP risk evaluation…covered the years 2014 – 2019…and another reference was added by assessors to aide in meta-analysis during POD refinement (Gray et al., 2021).[20]

EPA's procedures therefore resulted in dividing the set of DBP toxicology studies into three inconsistent subsets based on the date of publication:

- Studies published up to 2014 – included only if they were included in the previous assessment by Health Canada. Only 21 studies were included in this subset. The DBP draft protocol indicates that 164 other pre-2014 toxicology studies identified by Health Canada were excluded from the risk evaluation;[21] it is unclear why EPA did not include these studies. Additionally, EPA did not consider any studies published before 2014 if they were not discovered by or not included in the Health Canada assessment for any reason.
- Relevant studies published from 2014 to September 2019 – EPA conducted its own search of the literature and applied its own inclusion/exclusion criteria. This search identified 64 relevant studies but 52 of these studies were excluded from data extraction and study quality evaluation based solely on dose-response data (i.e., value of the LOAEL),[22] and 12 additional studies were excluded from data extraction and study quality evaluation based on consideration of additional study characteristics (e.g. number of animals per dose group; inclusion of only one sex).[23] Therefore not a single toxicology study out of 64 PECO-relevant studies identified by EPA's literature search was considered by EPA for hazard identification and dose-response assessment of DBP.[24]

[19] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), pp. 24-25.
[20] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 25.
[21] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), Figure 4-6.
[22] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 25.
[23] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 27.
[24] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), Figure 4-6, boxes 3a, 4a, 4b, and 6.

- Studies published after September 2019 – were not considered at all, with the exception of a 2021 study by Gray et al. The process by which this study was included is not clearly stated by EPA.

Thus, only those DBP toxicology studies published in a span of approximately 5 years were identified and evaluated through a comprehensive process following an EPA protocol. For earlier toxicology studies (before 2014), EPA relied entirely on the Health Canada assessment and did not apply its own search, inclusion/exclusion and study evaluation procedures. Toxicology studies published between 2014 and 2019 that are relevant to the hazard assessment of DBP were identified by a comprehensive search process but were then excluded from consideration. Toxicology studies published after September 2019 were not included at all, with one exception. This is not a clear, comprehensive or consistent approach to identifying the toxicology evidence relevant to assessing the health effects of DBP.

For both epidemiology and toxicology, studies were treated differently based only on their date of publication. In addition, the procedures for epidemiology differed significantly from those for toxicology; for example, a comprehensive search for epidemiology studies spanned publication dates of only 2018-2019, whereas for toxicology studies it spanned a broader (but still excessively brief) period of 2014-2019. All PECO-relevant toxicology studies identified by the 2014-2019 literature search were excluded from consideration. Post-2019 epidemiology studies were considered if they were submitted to the docket, but EPA makes no mention of whether it considered post-2019 toxicology studies submitted to the docket. It appears that any toxicological findings on DBP published in the past 5 years (with the exception of the study by Gray et al.) were simply not considered by EPA, which is not consistent with the best available science; recent guidance on conducting systematic reviews in environmental health recommends that literature searches should be updated no more than 12 months before publication of a review.[25] Collectively, EPA's practices run a high risk of failing to include all relevant health effects studies and treating relevant studies differently in the DBP Draft Risk Evaluation.

b. EPA relied on an assessment conducted by Health Canada to exclude studies, without supporting justification and inconsistent with the best available science.

EPA reviewed Health Canada assessments of DBP toxicology and epidemiology studies as part of conducting the DBP Draft Risk Evaluation. Epidemiology studies published before 2018 and toxicology studies published before 2014 were included in the TSCA risk evaluation only if they were included in the Health Canada assessments. Studies published before these dates that were not identified in searches conducted by Health Canada or were excluded from these previous assessments for any reason were not considered at all by EPA.

In principle, the use of previous assessments can be a useful part of conducting a TSCA risk evaluation, but the previous assessments must be carefully evaluated against pre-specified

[25] P. Whaley, et al. Recommendations for the conduct of systematic reviews in toxicology and environmental health research (COSTER). Environment International 143 (2020), 105926. https://doi.org/10.1016/j.envint.2020.105926.

criteria to determine whether they are of sufficient quality. The resulting risk evaluation must still employ procedures that are transparent, comprehensive, consistent and unbiased, and must meet the TSCA section 26(h) scientific standards which direct that the Agency:

> Shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science.[26]

However, it appears that the two Health Canada assessments were not systematic reviews, and it is unclear if they were peer reviewed. EPA also does not provide adequate justification for its use of previous DBP assessments to substitute for conducting its own comprehensive systematic review to identify and evaluate health effects evidence.

The 2023 NASEM report *Building Confidence in New Evidence Streams for Human Health Risk Assessment* demonstrates an appropriate process for evaluating the quality of previous assessments. After conducting a comprehensive search for prior reviews satisfying a pre-specified PECO (population, exposure, comparator, outcome) statement, the NASEM applied AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) to assess the methodological quality of each relevant review.[27] AMSTAR 2 was also applied by the NASEM in multiple prior reports on environmental health assessment.[28,29,30] In order to establish that it is appropriate to use previous assessments as part of a TSCA risk evaluation, EPA must apply this type of process to determine whether the previous assessments are consistent with the best available science, as required by TSCA.[31]

c. EPA used deficient inclusion and exclusion criteria for health effects evidence that inappropriately excluded important toxicity endpoints.

The DBP draft systematic review protocol does not provide the PECO statement that was used to identify epidemiology studies published from 2018-2019 and toxicology studies published from 2014-2019. A PECO statement was provided in the broader 2021 TSCA Draft Systematic Review Protocol, which EPA has never revised to address public comments and more than 200 SACC recommendations.

PECO statements play a critical role in conducting a systematic review as they provide criteria for screening the literature search results to identify which studies are relevant (included in the risk evaluation) and not relevant (excluded from further consideration). The PECO statement for DBP and other phthalates is deficient and excludes a broad range of important toxicity outcomes from consideration in the draft risk evaluation.

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[26] 15 U.S.C. § 2625(h).
[27] NASEM (2023). Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests.
[28] NASEM (2019). Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene.
[29] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations.
[30] NASEM (2022). Guidance on PFAS Exposure, Testing, and Clinical Follow-Up.
[31] 15 U.S.C. § 2625(h).

The outcome component of the PECO statement for DBP health effects evidence provides the following criteria for inclusion and exclusion of studies:

> **Human:** All health outcomes (cancer and non-cancer) at the organ level or higher.
> **Animal and Plants:** All apical biological effects (effects measured at the organ level or higher)
> and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth.
> **Screener note:**
> - Measurable biological effects relevant for humans, animals and plants may include but are not limited to: mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects.
> - Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.[32] (emphasis added)

By limiting the relevant human and animal studies to those with "apical" effects or those with effects at the "organ level or higher," EPA appears to be excluding studies of important biochemical markers and other outcomes at the cellular level that are strong indicators of hazards and which have commonly been used as critical effects in previous EPA hazard assessments, including TSCA risk evaluations (see examples below).

EPA's PECO statement provides very limited guidance for screeners on what effects are to be considered "apical" or "organ-level." The PECO says: "Apical endpoints include but are not limited to reproduction, survival, and growth" and "Measurable biological effects relevant for humans, animals and plants may include but are not limited to: mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects."[33] The 2021 TSCA Draft Systematic Review Protocol provides no further guidance on which outcomes are to be considered apical or organ-level, and which outcomes are to be considered cellular-level.

The NASEM has defined an apical end point as "An observable outcome in a whole organism, such as a clinical sign or pathologic state, that is indicative of a disease state that can result from exposure to a toxicant,"[34] and identified "tumors, birth defects, and neurologic impairments"[35] as examples. No biochemical measures or early biological changes were mentioned among the examples.

[32] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, Table_Apx H-47.
[33] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, Table_Apx H-47.
[34] National Research Council (2007). Toxicity Testing in the 21st Century: A Vision and a Strategy, p. 38.
[35] National Research Council (2007). Toxicity Testing in the 21st Century: A Vision and a Strategy, p. 177.

The definition of an apical effect appears to be narrower than the definition of an adverse effect provided by the EPA IRIS program: "a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to response to an additional environmental challenge."[36] The definition of adverse effect includes, for example, "a biochemical change;" such effects appear to be excluded from the DBP Draft Risk Evaluation as they would likely be considered cellular-level effects rather than organ-level or apical effects.

Biochemical and/or cellular-level outcomes have been identified as critical effects in numerous past EPA hazard assessments, including some of the completed TSCA risk evaluations. Examples of these outcomes and past assessments include:

- reduced male fetal testosterone or adult male testosterone levels (2018 and 2019 IRIS staff published systematic reviews of health effects of phthalates, 2023 draft approach to cumulative risk assessment of phthalates under TSCA)[37,38,39]
- reduced thyroid hormone levels (2020 TSCA risk evaluation of HBCD; 2021 toxicity assessment of PFBS) [40,41]
- decreased erythrocyte counts and hemoglobin (2020 TSCA risk evaluation of perchloroethylene)[42]
- measures of immune function, such as increases in immunoglobulin E, lymphocytes, natural killer cells, and interlukin-4 levels (2020 TSCA risk evaluation of perchloroethylene)[43]
- decreased sperm quality or concentration (2020 TSCA risk evaluations of trichloroethylene and perchloroethylene; 2018 and 2019 IRIS staff published systematic reviews of health effects of phthalates)[44,45,46,47]

[36] U.S. EPA. IRIS Glossary. https://www.epa.gov/iris/iris-glossary.
[37] Radke EG, Braun JM, Meeker JD, Cooper GS. Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence. Environ Int. 2018 Dec;121(Pt 1):764-793.
[38] Yost EE, Euling SY, Weaver JA, Beverly BEJ, Keshava N, Mudipalli A, Arzuaga X, Blessinger T, Dishaw L, Hotchkiss A, Makris SL. Hazards of diisobutyl phthalate (DIBP) exposure: A systematic review of animal toxicology studies. Environ Int. 2019 Apr;125:579-594.
[39] U.S. EPA (2023). Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act, p. 102.
[40] U.S. EPA (2020). Risk evaluation for cyclic aliphatic bromide cluster (HBCD).
[41] U.S. EPA (2021). Human health toxicity values for perfluorobutane sulfonic acid and related compound potassium perfluorobutane sulfonate. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=350888.
[42] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[43] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[44] U.S. EPA (2020). Risk Evaluation for Trichloroethylene.
[45] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[46] Radke EG, Braun JM, Meeker JD, Cooper GS. Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence. Environ Int. 2018 Dec;121(Pt 1):764-793.
[47] Yost EE, Euling SY, Weaver JA, Beverly BEJ, Keshava N, Mudipalli A, Arzuaga X, Blessinger T, Dishaw L, Hotchkiss A, Makris SL. Hazards of diisobutyl phthalate (DIBP) exposure: A systematic review of animal toxicology studies. Environ Int. 2019 Apr;125:579-594.

- acetylcholinesterase inhibition (numerous assessments of pesticides, including cumulative risk assessments of organophosphate and carbamate pesticides)[48,49]

EPA must either document that it has considered outcomes like altered thyroid hormone levels and other biochemical changes or cellular-level effects to be included in the animal and human evidence streams in the DBP Draft Risk Evaluation, or provide a justification for why these outcomes should not be considered as potential hazards of DBP.

Tagging biochemical and cellular-level outcomes as "supplemental, mechanistic," as directed in the PECO statement above, constrains the role of biochemical outcomes and other cellular changes to possibly providing biological support for apical outcomes, rather than considering precursors to apical outcomes as critical effects. Further, under EPA's proposed method, if no studies have been conducted of apical outcomes related to a biochemical outcome that has been studied, it is unclear whether the biochemical outcome will be considered at all. EPA says that supplemental studies "**may** be reviewed, evaluated for data quality, and incorporated into risk evaluations **as needed** for each chemical assessment"[50] (emphasis added), but it is unclear how a determination would be made to incorporate these studies into the risk evaluation, particularly in the absence of a related apical outcome study. Even if included to support a hazard conclusion based on apical outcomes, it appears that EPA rules out considering such studies for deriving a point of departure.

Exclusive reliance on studies of apical endpoints is also inconsistent with the best available science.[51] An important theme of the NASEM 2007 *Toxicity Testing in the 21st Century* report was that toxicity testing should move away from reliance on testing of apical outcomes. Accordingly, EPA's research programs and other U.S. health agencies have invested heavily in this new direction. Government and academic toxicology labs now rarely conduct studies of apical endpoints because the science has shifted towards examining more sensitive endpoints representing upstream biological changes ("key events") that lead to apical outcomes. In addition, a restriction to consider only apical or organ-level studies may bias the evidence base of the TSCA risk evaluations toward inclusion of industry-funded guidelines studies that are generally focused on apical endpoints.

d. EPA inappropriately excluded at least 446 PECO-relevant health effects studies of DBP from evidence integration without valid scientific justification.

In past TSCA risk evaluations, EPA's practice was to exclude some health effects studies from consideration based on study quality evaluations; studies could be excluded based on a single perceived methodological shortcoming. EPA's draft systematic review protocol for DBP says

[48] U.S. EPA (2006). Organophosphorus cumulative risk assessment. https://www.regulations.gov/document/EPA-HQ-OPP-2006-0618-0002.
[49] U.S. EPA (2008). Revised N-methyl carbamate cumulative risk assessment. https://www.regulations.gov/document/EPA-HQ-OPP-2008-0347-0029.
[50] U.S. EPA (2021). Draft systematic review protocol supporting TSCA risk evaluations for chemical substances, p. 345.
[51] 15 U.S.C. § 2625(h).

that, in response to recommendations from the NASEM, SACC and public comments, all relevant studies are included:

> One main clarification is that *all references that undergo systematic review are considered for use in the risk evaluation*, even those that do not meet the various discipline and sub-discipline screening criteria or those that are categorized as supplemental information at title and abstract (TIAB) or full-text screening.[52]

This would be an important improvement that would strengthen the scientific basis of TSCA risk evaluations; however, full consideration of EPA's systematic review procedures, as outlined in the draft protocol and hazard assessment, indicates that hundreds of PECO-relevant health effects studies of DBP were excluded from the risk evaluation through procedures lacking scientific justification.

EPA applied a procedure that it calls "further filtering" of PECO-relevant to exclude significant portions of the bodies of evidence for both epidemiology and toxicology:

> References that met the PECO screening criteria and were categorized as having epidemiology information and/or animal toxicity information for the evaluation of human health hazard went through a fit-for-purpose further filtering step to determine which studies would move forward to data quality evaluation and data extraction.[53]

> To streamline the identification of studies containing potentially relevant data that had not previously been evaluated by an authoritative agency, modifications were implemented to the process described in the 2021 Draft Systematic Review Protocol…Following PECO-based screening, references that met PECO screening criteria for epidemiology underwent a two-step further filtering process to identify the subset of potentially relevant references that proceeded to data quality evaluation.[54]

> The main purpose of this further filtering step was to allow for the refinement of the references that would be considered for data quality evaluation and extraction.[55]

The protocol does not provide any explanation for why the application of the PECO statement was insufficient for determining studies to include in the DBP Draft Risk Evaluation or why this "further filtering" process (which was not included in the 2021 TSCA draft systematic review method) was applied.

EPA used the further filtering process to exclude 212 epidemiology studies of DBP from consideration solely because they were published before 2018:

[52] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 5.
[53] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 23.
[54] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 23.
[55] U.S. EPA (2024). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 25.

> Of the 334 references that met DBP PECO screening criteria for epidemiology, step 1 of the further filtering process identified 122 references that had a publication date of 2018 or later, which proceeded to step 2 of the further filtering process.[56]

An additional 6 epidemiology studies were excluded through the filtering process based on their use of serum biomarkers, leaving 116 out of 334 PECO-relevant epidemiology studies for which data extraction and study quality evaluation were conducted.[57] Overall, EPA discarded 218 studies out of the 334 epidemiology studies it identified as PECO relevant, or 65%.

In the initial step of further filtering of the DBP toxicology evidence, 164 studies out of the 251 PECO-relevant studies identified by EPA were removed from consideration without any explanation other than "did not support POD refinement for hazard."[58]

Implementation of the next further filtering step for toxicology studies is unclear. EPA provides a further filtering form for that includes a series of questions regarding the methods and outputs of a study. The form concludes with the Yes/No question "Should this reference move on to data extraction and evaluation?"[59] but no instructions are given for how the assessor is to answer this question.

EPA advanced 64 studies published from 2014 to 2019 to "partial extraction" and 52 of these studies were excluded from further consideration based only on dose-response data (i.e., value of the LOAEL), with 12 studies remaining.[60] EPA then says that none of the 12 toxicology studies further examined in the filtering procedure were included in the risk evaluation due to "limitations and/or uncertainties that impacted interpretation."[61] Overall, EPA discarded 228 studies out of the 251 toxicology studies it identified as PECO-relevant, or more than 90%.[62] The vast majority of these studies were excluded for unexplained reasons or based on their dose-response data.

EPA's exclusion of and 218 epidemiology studies 228 toxicology studies from the DBP hazard assessment – studies already determined by EPA to be relevant to assessing the human health hazard of DBP - contradicts EPA's claim that all relevant studies are considered in the DBP Draft Risk Evaluation. EPA does not provide valid scientific justifications for exclusion of relevant evidence. In addition, EPA's "further filtering" considerations are implicit amendments to the PECO statement that were not made available for public comment or peer review before the assessment was conducted, which is contrary to best practices for systematic review.

e. EPA's methods for evaluation of study quality need to incorporate further improvements recommended by the National Academies.

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[56] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 24.
[57] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 24.
[58] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), Figure 4-6.
[59] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), Table 4-1.
[60] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), Figure 4-6., boxes 3b and 4b.
[61] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 27.
[62] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), Figure 4-6.

The DBP Draft Risk Evaluation incorporates two recently-implemented critical improvements to the assessment of study quality that were applied in other recent TSCA risk evaluations: quantitative scoring of study quality is no longer used; and study quality domains for evaluation of health effects studies have been aligned with the domains used by EPA's Integrated Risk Information System (IRIS). These changes respond to important recommendations of the NASEM and the SACC.

In the DBP Draft Risk Evaluation EPA appears to backslide on one important improvement addressing NASEM recommendations that had been implemented in some other recent risk evaluations.

EPA revised study quality evaluation criteria have removed consideration of statistical significance, consistent with NASEM recommendations for TSCA risk evaluations. Now, EPA reintroduces statistical significance in the DBP protocol as a new criterion for determining studies that advance to data extraction:

> An update to the 2021 Draft Systematic Review Protocol is that the criteria for extracting data were refined. **The criteria for extracting data from DBP epidemiology studies** were that the reference met PECO screening criteria and further filtering criteria, and had an overall quality determination of High, Medium, or Low, **and found statistically significant associations** between DBP and an adverse health outcome.[63] (emphasis added)

This contrasts with the similar statement found in the recent DINP protocol, which makes no mention of statistical significance:

> Epidemiology references with an overall quality determination (OQD) of High, Medium, or Low underwent data extraction; data wasn't extracted from Uninformative references.[64]

EPA therefore now says that studies lacking statistical significance will be excluded from further consideration. Statistical significance testing is not a scientifically valid basis for including or excluding a study from a risk evaluation and has been criticized by leading statisticians.[65] Further, the NASEM's review of EPA's approach to systematic review under TSCA explicitly stated that EPA should not consider statistical significance in study quality evaluation:

> Statistical power and statistical significance are not markers of risk of bias or quality. Statistical significance is not a measure of association or strength of association and should not be used to evaluate studies.[66]

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[63] U.S. EPA (2024). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 56.
[64] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), p. 54.
[65] Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature, 2019 Mar;567(7748):305-307. doi: 10.1038/d41586-019-00857-9.
[66] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 40. https://doi.org/10.17226/25952.

EPA introduces a new, unvetted criterion (not included, for example, in the recent risk evaluations of DIDP and DINP) for exclusion that contradicts NASEM advice regarding consideration of statistical significance.

EPA should not use statistical significance or overall study quality evaluations to exclude studies from consideration in its TSCA risk evaluations.

In addition, EPA needs to incorporate two further improvements to study quality evaluation recommended by the NASEM.

First, EPA should incorporate assessment of financial conflict of interest (COI) as a risk of bias domain for evaluating studies. Empirical research shows that industry sponsorship can bias research through various mechanisms, including how a study is designed and conducted, selective reporting of the results, skewed or incomplete analyses of study data, misleading or selective presentation of conclusions, and signaling of preferred outcomes in framing the questions to be investigated.[67]

The NASEM has highlighted the "large body of evidence showing that financial COIs lead to systemic biases in research"[68] and recommended that "funding sources should be considered in the risk-of-bias assessment conducted for systematic reviews that are part of an IRIS assessment."[69] To ensure that EPA assessments account for the possible bias in the evidence base, industry sponsorship and author financial COI should incorporated as a study quality evaluation domain that could affect the validity of a study's findings and conclusions.

Importantly, including funding as a risk of bias domain does not mean excluding industry-sponsored studies from EPA's risk evaluations; it only means documenting funding as one of many domains of potential bias and evaluating its impact on the overall quality of the body of evidence.

Second, EPA has continued to apply an overall quality determination (OQD) of High, Medium, Low, or Uninformative to each study. To adhere to best practices in systematic review, EPA should not derive an overall study rating, and instead implement the domain-based approach of the Navigation Guide.[70] This was a specific recommendation in the NASEM report on TSCA systematic review:

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[67] Odierna DH, Forsyth SR, White J, Bero LA. The cycle of bias in health research: a framework and toolbox for critical appraisal training. Account Res. 2013;20(2):127-141; Fabbri A, Lai A, Grundy Q, Bero LA. The influence of industry sponsorship on the research agenda: a scoping review. Am J Public Health. 2018;108(11):e9-e16; Psaty BM, Prentice RL. Minimizing bias in randomized trials: the importance of blinding. JAMA. 2010;304(7):793-794; Psaty BM, Kronmal RA. Reporting mortality findings in trials of rofecoxib for Alzheimer disease or cognitive impairment: a case study based on documents from rofecoxib litigation. JAMA. 2008;299(15):1813-1817.

[68] NASEM (2023). Sponsor Influences on the Quality and Independence of Health Research: Proceedings of a Workshop, p. 9.

[69] National Research Council (2014). Review of EPA's Integrated Risk Information System (IRIS) Process, p. 79.

[70] Lam, J., Koustas, E., Sutton, P., Padula, A. M., Cabana, M. D., Vesterinen, H., Griffiths, C., Dickie, M., Daniels, N., Whitaker, E., Woodruff, T. J. (2021). Exposure to formaldehyde and asthma outcomes: A systematic review, meta-analysis, and economic assessment. PloS one, 16(3), e0248258. https://doi.org/10.1371/journal.pone.0248258.

> There are many tools for assessing risk of bias, such as those used by the Navigation Guide, OHAT, and the IRIS Program, and there is no consensus on the best tool for risk-of-bias analysis. However, there are best practices. For example, tools are preferred that rely on the evaluation of individual domains rather than the creation of overall quality scores (Eick et al. 2020). Such tools provide a structured framework within which to make qualitative decisions on the overall quality of studies and to identify potential sources of bias. Overall quality scores may not adequately distinguish between studies with high and low risk of bias in meta-analyses (Herbison et al. 2006). Importantly, there is also a lack of empirical evidence on the use of quality scores (Jüni et al. 1999).[71]

Importantly, an "uninformative" rating can be based on a "critically deficient" rating for any study quality metric, regardless of the ratings for other metrics, which can be highly misleading.

EPA has also continued its practice of excluding some studies based on study quality evaluations:

> data was not extracted from Uninformative references.[72]

EPA's choice not to conduct data extraction for some studies based on the overall quality determination is equivalent to excluding these studies from evidence integration. Labeling studies as "Uninformative" or excluding studies based on the rating for a single study quality metric could erroneously lead to disregarding studies that constitute the best available science.

Accordingly, EPA must revise its approach to TSCA study quality evaluation to avoid disregarding studies based on pre-assigned labels that are unwarranted. By replacing the overall study quality determination with a domain- or metric-based approach, as the NASEM recommended for the TSCA program in 2021,[73] risk assessors can evaluate the ratings for each study in each domain at the evidence synthesis step to reach conclusions across the body of evidence, informed by the strengths and limitations of all relevant studies. These improved procedures should be applied to DBP and are necessary for consistency with EPA's claim that all relevant studies are considered in the risk evaluation.

EPA should immediately implement the NASEM recommendation to use a domain-based approach instead of an overall quality determination.

f. EPA continues to use unclear terminology regarding evidence synthesis and integration.

EPA's use of unclear terminology for evidence synthesis and integration is an additional scientific shortcoming of the approach to systematic review for DBP. The NASEM has recommended the use of the term "evidence synthesis" for assembling the evidence and drawing conclusions from a single evidence stream (e.g. toxicology, epidemiology), and "evidence

[71] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 36.
[72] U.S. EPA (2024). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 55.
[73] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 36.

integration" for the subsequent process of drawing conclusions considering all evidence streams. The SACC review of EPA's 2021 Draft TSCA Method document reiterated this recommendation:

> The EPA did not follow the recommendation of NASEM to separate evidence synthesis from evidence integration. To quote NASEM: "Evidence synthesis deals with more homogeneous data within a single stream, and evidence integration deals with more heterogeneous data from multiple streams."[74]
>
> The EPA could improve the clarify, transparency, and efficiency of its process by adopting the NASEM recommendation to use "synthesis" for drawing conclusions separately for each evidence stream (i.e., human, animal, and mechanistic evidence) and use 'integration' for drawing conclusions considering all evidence streams in combination – in context of the risk evaluation process/needs.[75]

In the DBP systematic review protocol, however, EPA disregards the advice of both the NASEM and the SACC by continuing to use the term "evidence integration" for both steps.[76] The Draft DBP Hazard Assessment further confuses matters by using the term "hazard identification"[77] instead of "evidence integration."

This is one more area in which EPA's approach differs from best practices in systematic review, violating the best available science requirement under TSCA.[78] In addition, failing to adopt consistent and vetted terminology decreases the clarity of the risk evaluation and creates confusion for peer reviewers and the public regarding the procedures applied to drawing conclusions from a single stream of evidence.

EPA should adopt a standardized procedure, such as the approach used by the IRIS program, for evidence integration for all DBP endpoints, including a pre-specified set of descriptors that are considered for each endpoint.

g. EPA released an incomplete draft systematic review protocol for DBP that was not made publicly available in advance of the draft risk evaluation.

Along with the DBP Draft Risk Evaluation, EPA released a draft chemical-specific systematic review protocol. Publication of a chemical-specific protocol is consistent with best available scientific methods in systematic review and responds to recommendation of the NASEM and the SACC. However, the comments above demonstrate many flaws and deficiencies in the protocol and the procedures applied to conducting the risk evaluation. Public release of the protocol for public comment and peer review in advance of conducting the risk evaluation would have

[74] U.S. EPA (2022). Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2022-2, p. 83. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0044.
[75] U.S. EPA (2022). Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2022-2, p. 88. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0044.
[76] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), pp. 106-107.
[77] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), p. 27.
[78] 15 U.S.C. § 2625(h).

provided an opportunity for early identification and correction of the many critical deficiencies described above. For future TSCA risk evaluations, EPA must publish a chemical-specific systematic review protocol for public comment before completing the draft risk evaluation, as recommended by the Institute of Medicine and the NASEM as a best practice for systematic review.[79,80]

The TSCA program should follow the established procedures of EPA's IRIS program, which makes a draft protocol for each assessment publicly available in advance of its release for public comment. Following the public comment process, the IRIS program then publishes an updated protocol, as needed. For example, for the IRIS assessments of five per- and polyfluoroalkyl substances (PFAS), a draft protocol was made available for public comment for 45 days. The IRIS program then followed up with a revised protocol to address public comments, with documentation of the changes, that was published before the release of the PFAS draft assessments.[81] EPA should be following this same approach for all TSCA risk evaluations.

h. EPA should prepare a new TSCA systematic review handbook that is aligned with the best available scientific methods and issue updated draft systematic review protocols for all risk evaluations currently in development.

To adhere to best practices in systematic review, including those specifically recommended to the TSCA program by the NASEM and SACC, EPA should issue a new TSCA systematic review methodology document that states methods to be applied consistently to all TSCA risk evaluations. The SACC recently highlighted this issue in its review of the 1,3-butadiene draft risk evaluation, saying that:

> the SACC has repeatedly identified its concerns with TSCA's systematic review protocol/process[82]

and that there is a

> need for the EPA to develop and execute an updated systematic review protocol for TSCA reviews before finalizing this draft Risk Evaluation.[83]

[79] Institute of Medicine (2011). Finding what works in health care: Standards for systematic reviews.
[80] National Research Council (2014). Review of EPA's Integrated Risk Information System (IRIS) process.
[81] U.S. EPA (2021). Systematic Review Protocol for the PFAS IRIS Assessments. https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345065 (accessed 1 February 2024).
[82] U.S.EPA (2025). Science Advisory Committee on Chemicals, Meeting Minutes and Final Report No. 2025-01. A Set of Scientific Issues Being Considered by the U.S. Environmental Protection Agency Regarding: Peer Review of the 2024 Draft Risk Evaluation for 1,3-Butadiene, p. 29. https://www.regulations.gov/document/EPA-HQ-OPPT-2024-0425-0123
[83] U.S.EPA (2025). Science Advisory Committee on Chemicals, Meeting Minutes and Final Report No. 2025-01. A Set of Scientific Issues Being Considered by the U.S. Environmental Protection Agency Regarding: Peer Review of the 2024 Draft Risk Evaluation for 1,3-Butadiene, p. 98. https://www.regulations.gov/document/EPA-HQ-OPPT-2024-0425-0123

EPA should also prepare a chemical-specific systematic review protocol for each TSCA risk evaluation it conducts, and these protocols should be complete, stand-alone documents that do not refer to the 2021 Draft TSCA Method for critical elements. The chemical-specific protocols for ongoing and future risk evaluations should also be released for public comment well before the draft risk evaluations are completed to allow for public input, scrutiny, and opportunities for improvement. We urge EPA to consistently adopt the practices of the IRIS program for systematic review protocol development and publication across all EPA programs and offices.

2. **EPA's non-cancer hazard identification and dose-response assessment for DBP is not consistent with the best available science.**

EPA's Draft Risk Evaluation includes a "Hazard Identification" section that is critically deficient in its scope and does not consider all relevant health effects studies in evaluating the hazards of DBP. The risk evaluation does draw an appropriate conclusion regarding male reproductive effects:

> reasonably available studies consistently demonstrate that oral exposure to DBP during the masculinization programming window can disrupt androgen action, leading to a spectrum of effects on the developing male reproductive system consistent with phthalate syndrome. Evidence from epidemiological studies indicates a *moderate* level of confidence in the association between DBP and health effects on the male reproductive system, such as AGD. Evidence from animal studies, including the robust database of studies in rats, demonstrates adverse effects on the male reproductive system following developmental exposure to DBP…available studies consistently demonstrate that oral exposure to DBP during the masculinization programming window can disrupt androgen action, leading to a spectrum of effects on the developing male reproductive system consistent with phthalate syndrome.[84]

EPA, however, did not conduct hazard identification for any other outcomes of DBP:

> EPA did not conduct a full evidence integration for health outcomes other than those of the male reproductive system following developmental exposure.[85]

EPA indicates that available studies provide evidence of other developmental and reproductive outcomes:

> These include decreases in litter size, changes in sex ratio, increases in pup mortality, decreases in fetal weight, resorptions, post-implantation loss, and increase in skeletal variations.[86]

EPA did not conduct hazard identification (evidence integration) for any of these outcomes.

[84] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), p. 56.
[85] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), p. 56.
[86] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), p. 36.

a. EPA did not adequately consider all reasonably available evidence for multiple potential non-cancer hazards of DBP.

EPA's approach to hazard identification for DBP is critically deficient in three major aspects. First, EPA did not consider all the reasonably available evidence for each outcome assessed. As discussed above, EPA removed more than 400 PECO-relevant health effects studies from consideration for hazard identification, without appropriate rationale. EPA cannot conduct appropriate hazard identification using a process that excludes that majority of relevant health effects studies. This process is entirely backwards and violates the TSCA risk evaluation framework rule, which says that

> The hazard assessment process includes the identification, evaluation, and synthesis of information to describe the potential health and environmental hazards of the chemical substance under the conditions of use.[87]
>
> Hazard information related to potential health and environmental hazards of the chemical substance will be reviewed in a manner consistent with best available science.[88]

The best available science for hazard assessment involves assembling **all** of the evidence relevant to a particular outcome, assessing the internal validity of the relevant evidence, conducting synthesis for each stream of evidence (i.e. toxicology, epidemiology), and integrating the evidence streams to draw clear conclusions regarding the quality and strength of evidence. These are also the key elements of hazard assessment identified by the framework rule. EPA shortcuts the entire process by excluding relevant evidence up-front so that the subsequent steps cannot be meaningfully executed. EPA's current draft hazard assessment leaves significant questions about what is to be found in the hundreds of studies that have been excluded, and is therefore critically deficient.

Second, of the evidence EPA did include in its hazard identification, it inappropriately excluded studies from further consideration in dose-response assessment without scientific rationale. This includes both epidemiologic and toxicological evidence, as discussed below.

i. EPA inappropriately excluded all epidemiology studies from dose-response assessment.

In the DBP draft systematic review protocol, EPA identified 334 human epidemiology studies of DBP.[89] EPA initially excluded any studies published before 2018 from consideration, without justification, leaving 116 studies published from 2018 to 2022 (only 1 study published in 2022; no studies published from 2023 – 2025 were included) that were advanced to data quality

[87] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA), 40 CFR § 702.39(c)(1).
[88] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA), 40 CFR § 702.39(c)(2).
[89] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 24.

evaluation. EPA rated the quality of more than 100 DBP epidemiology studies as "High" or "Medium."[90]

EPA then disregarded its own study quality evaluations by excluding all of these studies from its dose-response analysis, without any consideration of the strengths and weaknesses of each individual study:

> The Agency did not use epidemiology studies quantitatively for dose-response assessment, primarily due to uncertainty associated with exposure characterization. Primary sources of uncertainty include the source(s) of exposure; timing of exposure assessment that may not be reflective of exposure during outcome measurements; and use of spot-urine samples, which due to rapid elimination kinetics may not be representative of average urinary concentrations that are collected over a longer term or calculated using pooled samples. Additionally, the majority of epidemiological studies examine one phthalate and one exposure period at a time such that they are treated as if they occur in isolation, which contributes additional uncertainty due to co-exposure that may confound results for the majority of epidemiologic studies.[91]

EPA's blanket exclusion of an entire category of studies is scientifically inappropriate and violates the TSCA requirement to use the best available science, which includes systematic review conducted with best practices.[92] The preamble to EPA's 2024 final framework rule for conducting risk evaluations re-stated EPA's commitment to systematic review:

> EPA believes that integrating appropriate and applicable systematic review methods into the TSCA risk evaluations is critical to meeting the scientific standards as described in TSCA section 26(h) and (i)…. The principles of systematic review are well-established and include "transparent and explicitly documented methods, consistent and critical evaluation of all relevant literature, application of a standardized approach for grading the strength of evidence, and clear and consistent summative language" (Ref. 26). EPA has finalized the requirement to use and document systematic review methods to assess reasonably available information.[93]

EPA's broad exclusion of DBP epidemiology studies from dose-response analysis is contrary to the framework rule preamble and disregards the structured, consistent systematic review process that is required to evaluate the quality of relevant epidemiological studies according to pre-specified criteria. EPA evaluated the quality of individual studies, following systematic review methods outlined in the DBP protocol. It then effectively ignored its systematic review process and excluded all epidemiology studies from dose-response assessment with an argument that demonstrates a bias against environmental epidemiology, rather than a thoughtful approach to evidence evaluation that is consistent with best practices in systematic review.

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[90] U.S. EPA (2025). Data Quality Evaluation Information for Human Health Hazard Epidemiology for Dibutyl Phthalate (DBP).
[91] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), p. 13.
[92] 15 U.S.C. § 2625(h).
[93] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA). 89 FR 37028.

In 2024, EPA's SACC criticized EPA's decision to disregard epidemiology studies in the draft risk evaluation of diisononyl phthalate (DINP):

> Several recent human epidemiology studies of DINP non-cancer effects, including developmental effects were excluded from the dose-response assessment. These studies were excluded because of uncertainty about exposure. However, the studies focused on measurement of urinary biomarkers of phthalates, including metabolites of DINP. While there are technical issues when using urinary biomarkers for determination of exposure, this is a common approach and the gold standard for phthalates to understand the association between the chemicals and outcomes relevant in people. EPA individually assessed the merits of 53 epidemiology studies of DINP, published from 2018 to 2021, applying a pre-specified set of study quality domains and metrics that closely mirrors the approach used by EPA's IRIS program, which has been favorably reviewed by the NASEM. EPA's overall quality determination was "Medium" or "High" for 46 of these epidemiology studies. Each study was individually assessed for its exposure measurement methods (Domain 2) and treatment of potential confounding (Domain 4).[94]

The SACC then provided this recommendation to EPA:

> EPA has disqualified epidemiology studies in a manner inconsistent with its own pre-specified procedures. EPA's own overall quality determinations indicate that these studies are suitable for use. EPA should include these studies in its identification of studies potentially suitable for informing a POD.[95]

As pointed out by the SACC, the issues that EPA raises in an attempt to disqualify the entire set of epidemiology studies are accounted for in the systematic review process using pre-specified procedures to assess the quality of each study, including domains for exposure assessment and potential confounding. In the DINP hazard assessment, EPA's own study quality assessments indicated that the excluded studies were consistent with existing standards for use of studies in dose-response assessment, and the same is true for DBP as indicated by EPA's study quality ratings.

Moreover, EPA's explanation considers only alleged limitations of the DBP epidemiologic studies as a class, without considering strengths of these studies (e.g., they are conducted in humans rather than laboratory animals, at exposure levels routinely experienced by humans) or mitigating considerations (e.g. regression models that control for co-exposures; implications of exposure misclassification) that apply to the limitations. For example, the use of spot-urine samples is a limitation that is expected to result in some degree of exposure misclassification, but to the extent this occurs, it is likely to result in imprecision in effect estimates, rather than

[94] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 91.

[95] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 92.

overstatement of effects. In general, the uncertainties in exposure characterization may result in exposure misclassification, but that does not mean the studies are not useful or informative and potentially strong candidates for determination of the point of departure (POD).

By excluding relevant epidemiology studies of DBP from dose-response analysis, EPA has violated TSCA's requirement to use the best available science.[96] EPA cannot broadly exclude epidemiologic studies from dose-response assessment in the DBP Draft Risk Evaluation, and must consider each relevant study on an individual basis as a candidate for POD derivation.

ii. EPA inappropriately excluded animal toxicology studies from dose-response assessment.

As discussed above, EPA removed at least 446 relevant health effects studies from consideration for hazard identification, without appropriate rationale. EPA separately says that it considered 63 "new" toxicology studies of DBP (published 2014-2019) for hazard identification:

> EPA reviewed literature published between 2014 to 2019 for new information on sensitive human health hazards…EPA identified 63 new PECO-relevant animal toxicology studies that provided information pertaining to various primary hazard outcomes, including: reproduction/development, neurological, metabolic/nutritional, cardiovascular, and the immune system.[97]

EPA, however, immediately discarded 51 of the 63 studies based on dose-response information, leaving it with 7 studies of reproductive/developmental outcomes, 3 studies of neurological outcomes, 3 studies of nutritional/metabolic outcomes, 1 study of cardiovascular outcomes, and 2 studies of immune system outcomes (some of the 12 remaining studies evaluated multiple outcomes).[98] EPA's decision to not conduct hazard identification for outcomes other than male reproductive effects was based only on review of this small set of DBP toxicology studies, which was inappropriately narrowed by considering only studies published within a 5-year span, then screening out studies based only on their lowest-observed-effect levels (LOELs). Nevertheless, even from this small subset of studies, 12 NOAELs and/or LOAELs were identified for non-male reproductive endpoints that were lower than the chosen 9 mg/kg-day POD.

EPA dismissed all of these studies from consideration in dose-response assessment/POD derivation largely based on scientifically unsupported rationale. For example, EPA cited that "Only male animals were evaluated"[99] as a significant limitation and rationale for dismissing many of these studies. This rationale is arbitrary and not supported by established toxicological principles or EPA's own precedent, which routinely accepts single-sex animal data for hazard identification and dose-response analysis. Moreover, excluding studies solely on the basis of sex

[96] 15 U.S.C. § 2625(h).
[97] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), p. 18.
[98] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), pp. 18-19.
[99] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), pp. 118.

without evaluating the strength and consistency of the findings and the larger body of evidence is in direct conflict with best practices in evidence integration.[100]

EPA should start over on identifying hazards of DBP other than male reproductive effects by considering all relevant studies, conducting appropriate data extraction and study evaluation, and carrying through evidence synthesis and evidence integration for multiple DBP hazards.

b. EPA failed to make appropriate use of benchmark dose modeling to specify a non-cancer point of departure for risk characterization.

EPA considered 11 animal studies of DBP male reproductive toxicity published from 1997 to 2014 for dose-response analysis.[101] Four of these studies provided no-observed-adverse-effect levels (NOAEL) or lowest-observed-adverse-effect levels (LOAELs) in the range of 1-10 mg/kg-d. EPA also considered a benchmark dose, lower confidence limit (BMDL) from its update of a meta-regression approach developed by the NASEM that used data from 14 studies of reduced fetal testosterone for 6 anti-androgenic phthalates to derive relative potency factors (RPFs) in the draft phthalates cumulative risk assessment. The meta-regression estimates the dose of DBP resulting in a 5% decrease in fetal testosterone with a BMD of 14 mg/kg-day and a BMDL of 9 mg/kg-day (human equivalent dose (HED) of 2.1 mg/kg-d).[102]

EPA selected the meta-regression BMDL for reduced fetal testosterone of 9 mg/kg-d as the point of departure to use for risk characterization of DBP, and gave only limited consideration to values from the 11 individual animal studies that examined a broad range of male reproductive outcomes including sperm effects, testicular pathology and nipple retention. EPA mentioned various limitations applying to several of the individual studies, including "these studies are limited by poor dose-selection,"[103] and ultimately explained its selection of the meta-regression BMDL by noting that it falls within the range of the lowest NOAEL/LOAELs and benefits from the advantages of BMD modeling:

> Notably, the $BMDL_5$ of 9 mg/kg-day falls within the narrow range of the NOAEL or LOAELs (*i.e.,* 1 to 10 mg/kg-day) identified in additional studies that evaluated effects on the developing male reproductive system…which provides support and confidence in both the effect and the dose at which it occurs. Additionally, the $BMDL_5$ is not constrained to one of the experimental doses within a given study, as a NOAEL or LOAEL would be, which may better define the POD.[104]

EPA is correct that an important advantage of the BMDL is that, unlike a NOAEL or LOAEL it may take a value other than the doses tested in an animal study; however, this statement also

[100] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, Chapters 6 and 7.
[101] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), Table 4-1.
[102] U.S. EPA (2025). Revised Draft 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), pp. 19-25.
[103] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), p. 60.
[104] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), pp. 62-63.

highlights the critical deficiencies of EPA's approach to dose-response analysis. EPA inappropriately evaluated the dose-response data for the 11 individual studies using only NOAELs and LOAELs instead of conducting BMD analysis for these studies. The appropriate treatment of these studies in dose-response assessment is not to reference them as supporting EPA's preferred POD, but to conduct BMD modeling – which overcomes the limitations of study dose selection to better inform POD selection.

EPA's dose-response assessment for DBP is not consistent with the best available science, as stated in EPA guidance,[105] reports from the NASEM,[106,107] and recommendations of the SACC.[108] EPA should conduct BMD modeling for all studies and endpoints listed in Table 4-1, any of which could conceivably yield a BMDL below EPA's chosen POD of 9 mg/kg-d. For example, the table identified 2 studies (Moody et al. 2013 and Lee et al. 2004), both rated as "Medium" quality,[109] that demonstrate effects on sperm at doses of 1 mg/kg-d and 3 mg/kg-d. EPA should not select a POD without conducting BMD modeling of these 2 studies. EPA should also conduct BMD modeling for other candidate studies and endpoints – not restricted to male reproductive effects - and then use the lowest overall BMDL, or a set of BMDLs (representing different studies, endpoints and organ systems) as the POD for risk characterization of DEHP. This is the approach taken in multiple previous TSCA risk evaluations, such as those for trichloroethylene,[110] 1,4-dioxane,[111] n-methylpyrrolidone,[112] and 1,3-butadiene.[113]

EPA's 2012 Benchmark Dose Technical Guidance represents the best available science and is unequivocal in describing the limitations of NOAEL/LOAELs and in stating a strong preference for BMDLs rather than NOAEL/LOAELs.

> The NOAEL is actually of little practical utility in describing toxicological dose-response relationships; it does not represent a biological threshold and cannot establish that lower exposure levels are necessarily without risk. Specific limitations of the NOAEL/LOAEL approach are well known and have been discussed extensively (Crump 1984; Gaylor 1983; Kimmel and Gaylor 1988; Leisenring and Ryan 1992; U.S. EPA 1995a):
>
> - The NOAEL/LOAEL is highly dependent on sample size. The ability of a bioassay to distinguish a treatment response from a control response decreases as sample size decreases, so the NOAEL for a compound (and thus the POD, when based on a

[105] U.S. EPA (2012). Benchmark Dose Technical Guidance.
[106] NASEM (2017). Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals, p. 158.
[107] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 129.
[108] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 92.
[109] U.S. EPA (2025). Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for Dibutyl Phthalate (DBP).
[110] U.S. EPA (2020). Risk Evaluation for Trichloroethylene, Tables 3-8 to 3-14.
[111] U.S. EPA (2020). Final Risk Evaluation for 1,4-Dioxane, Table 3-9.
[112] U.S. EPA (2020). Risk Evaluation for n-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP), Table 3-11.
[113] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene, Table 4-1.

NOAEL) will tend to be higher in studies with smaller numbers of animals per dose group.

- More generally, the NOAEL/LOAEL approach does not account for the variability and uncertainty in the experimental results that are due to characteristics of the study design such as dose selection, dose spacing, and sample size.
- NOAELs/LOAELs do not correspond to consistent response levels for comparisons across studies/chemicals/endpoints, and the observed response level at the NOAEL or LOAEL is not considered in the derivation of RfDs/RfCs.
- Other dose-response information from the experiment, such as the shape of the dose-response curve (e.g., how steep or shallow the slope is at the BMD, providing some indication of how near the POD might be to an inferred threshold), is not taken into account…
- While the NOAEL has typically been interpreted as a threshold (no-effect level), simulation studies (e.g., Leisenring and Ryan 1992; study designs involving 10, 20, or 50 replicates per dose group) and re-analyses of developmental toxicity bioassay data (Gaylor 1992; Allen et al. 1994a; studies involving approximately 20 litters per dose group) have demonstrated that the rate of response above control at doses fitting the criteria for NOAELs, for a range of study designs, is about 5–20% on average, not 0%.[114]

The Benchmark Dose Technical Guidance further states that use of a BMD/BMDL as a POD is preferred and a NOAEL or LOAEL should be considered as a POD only if BMD modeling is conducted and is unable to produce a BMD estimate, and requires justification:

> Because of the limitations of the NOAEL/LOAEL approach discussed earlier, the BMD approach is preferred to the NOAEL/LOAEL approach…there are some instances in which reliable BMDs cannot be estimated and the NOAEL/LOAEL approach might be warranted…In such cases, the NOAEL/LOAEL approach might be used, while recognizing its limitations and the limitations of the dataset.[115]
>
> Resorting to the NOAEL/LOAEL approach does not resolve a data set's inherent limitations, but it conveys that there are limitations with the data set.[116]
>
> At times, modeling will not yield useful results and the NOAEL/LOAEL approach might be considered, although the data gaps and inherent limitations of that approach should be acknowledged.[117]
>
> In some cases, modeling attempts may not yield useful results. When this occurs and the most biologically relevant effect is from a study considered adequate but not amenable to modeling, the NOAEL (or LOAEL) could be used as the POD. The modeling issues that

[114] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 4.
[115] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 6.
[116] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 12.
[117] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 30.

> arose should be discussed in the assessment, along with the impacts of any related data limitations on the results from the alternate NOAEL/LOAEL approach.[118]

EPA cited the Benchmark Dose Technical Guidance in a previous TSCA risk evaluation to describe the preference for a BMD over a NOAEL:

> As outlined in EPA guidance, the BMD approach overcomes many of the limitations inherently associated with the NOAEL/LOAEL approach, and thus is the preferred method for establishing a POD for use in risk assessment.[119]

EPA's 2022 handbook for conducting chemical hazard assessments for the Integrated Risk Information System (IRIS) reinforces these key points:

> As discussed in detail in Section 1.2 of EPA's Benchmark Dose Technical Guidance (U.S. EPA, 2012b), dose-response modeling (i.e., benchmark dose modeling) is the preferred approach for deriving points of departures given several limitations in the no-observed adverse-effect level/ lowest-observed-adverse-effect level (NOAEL/LOAEL) approach.[120]
>
> Basis of the POD: A modeled BMDL is preferred over a NOAEL, which is in turn preferred over a LOAEL.[121]

Reports from the NASEM also state the advantages of BMD modeling. The NASEM report on low-dose toxicity of endocrine active chemicals (which is the source of the meta-regression used to estimate RPFs in EPA's draft phthalates CRA document) discusses the deficiencies of the NOAEL/LOAEL approach for risk estimation:

> The use of LOAELs and NOAELs is less than ideal because they depend highly on individual study-design characteristics; therefore, apparent differences among studies might be explained by design differences, such as sample size or dose spacing, rather than true inconsistency.[122]

In the 2009 report *Science and Decisions*, the National Academies highlighted the adoption of the BMD approach as an important improvement in risk assessment methodology:

> Another refinement in dose-response assessment has been the derivation of the RfD or low-dose cancer risk from a POD that is calculated using BMD methodology (EPA 2000a). In noncancer risk assessment, this approach has the advantage of making better use of the dose-response evidence available from bioassays than do calculations based on NOAELs. It also provides additional quantitative insight into the risk presented in the

[118] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 40.
[119] U.S. EPA (2020). Risk Evaluation for n-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP), p. 262.
[120] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, p. 8-1.
[121] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, p. 8-18.
[122] NASEM (2017). Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals, p. 158.

> bioassay at the POD because for quantal end points the POD is defined in terms of a given risk for the animals in the study.[123]

EPA all disregarded all of the above guidance in its overall approach to dose-response assessment for DBP. Its selection of 9 mg/kg-day as the POD from the NASEM meta-regression model does not consider the candidate PODs that would be provided by BMD modeling of 11 studies, each of which EPA has characterized only with a NOAEL or LOAEL.[124]

EPA's BMD guidance clearly states that identification of the most sensitive endpoint cannot be based on comparisons of NOAELs and LOAELs, and that all candidate values should be evaluated based on BMD modeling:

> The apparent relative sensitivities of endpoints based on NOAELs/LOAELs may not correspond to the same relative sensitivities based on BMDs or BMDLs after BMD modeling; therefore, relative sensitivities of endpoints cannot necessarily be judged a priori. For example, differences in slope (at the BMR) among endpoints could affect the relative values of the BMDLs. Selected endpoints from different studies that have the potential to be used in the determination of a POD(s) should all be modeled.[125]

The scientifically appropriate method for selecting the POD based on the most sensitive study/endpoint combination would be to estimate a BMDL for each endpoint, and then select the lowest value, rather than selecting the lowest NOAEL.

The deficiencies of EPA's dose-response analysis for DBP are very similar to those of its previous draft risk evaluation of DINP. In its review of that assessment, the SACC commented that much more thorough BMD modeling of multiple studies was necessary to inform selection of the point of departure:

> EPA should use all available dose range studies from which BMD-based POD should be developed, compared with each other to select the lowest BMD-based POD as the basis for the derivation for the HED.[126]

> EPA should apply benchmark dose modeling to derive chronic non-cancer points of departure and select the one that is most sensitive (lowest).[127]

By disregarding existing EPA guidance and NASEM recommendations that state BMD modeling is the most scientifically appropriate approach for determining the POD, EPA violates the TSCA section 26(h) scientific standards which direct that the Agency:

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[123] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 129.
[124] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), Table 4-1.
[125] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 15.
[126] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 92.
[127] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 92.

> Shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science.[128]

EPA's dose-response analysis for DBP also violates the TSCA risk evaluation framework rule, which states:

> EPA will use applicable EPA guidance when conducting risk evaluations, as appropriate and where it represents the best available science.[129]
>
> EPA will document that the risk evaluation is consistent with the best available science.[130]

EPA's dose-response analysis for DBP does not use the applicable EPA guidance and is not consistent with the best available science. EPA's non-cancer hazard assessment requires extensive revisions to consider hazards other than male reproductive effects without unwarranted exclusions of studies, BMD modeling of a broad selection of studies for male reproductive effects and other hazards, and selection of one or more PODs informed by the BMD modeling.

c. EPA should apply best available methods to generate quantitative estimates of non-cancer risks for varying levels of exposure to DBP.

In its TSCA risk evaluations, EPA typically calculates a margin of exposure (MOE) for each condition of use (COU). The MOE is calculated as:

> Margin of Exposure = Non-cancer point of departure / Human exposure.

The MOE approach is a scientifically deficient method for characterizing risk as it does not provide a quantitative estimate of risk. In its recent review of the 1,3-butadiene risk evaluation, the SACC said:

> The MOE approach is not the best available method for characterizing risk and is inconsistent with amended TSCA's requirements to use the 'best available science' and to ensure protection of PESS.[131]

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[128] 15 U.S.C. § 2625(h).

[129] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA), 40 CFR § 702.37(a)(1).

[130] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA), 40 CFR § 702.37(a)(2).

[131] U.S.EPA (2025). Science Advisory Committee on Chemicals, Meeting Minutes and Final Report No. 2025-01. A Set of Scientific Issues Being Considered by the U.S. Environmental Protection Agency Regarding: Peer Review of the 2024 Draft Risk Evaluation for 1,3-Butadiene, p.99. https://www.regulations.gov/document/EPA-HQ-OPPT-2024-0425-0123

> The EPA should utilize a more informative approach by applying the probabilistic dose-response assessment methods of the World Health Organization's IPCS to estimate the risk of adverse effects at various levels of exposure.[132]

Use of the MOE, which relies on a POD with no extrapolation to lower doses, is a simplistic approach that only compares the POD to the exposure level and judges whether this ratio is "interpreted as a human health risk of concern" or if "risk is not considered to be of concern and mitigation is not needed."[133]

The MOE does not estimate the proportion of the exposed population projected to experience a specified health endpoint or the number of individuals affected, and it perpetuates the scientifically flawed notion that a "safe" or "no risk" level of chemical exposure can be identified for a diverse exposed population.[134,135]

The National Academies[136] and the World Health Organization[137] (WHO) have outlined more robust methods for risk estimation that more accurately account for variability in the human population and have been demonstrated in published case studies.[138,139,140,141] We applied the WHO methodology to the DBP endpoint of reduced fetal testosterone, using the BMD (14 mg/kg-d) and BMDL (9 mg/kg-d) values derived by EPA through application of the NASEM meta-regression model,[142] to estimate risk-specific doses for several levels of incidence (e.g. 1%, 0.1%, etc.).

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[132] U.S.EPA (2025). Science Advisory Committee on Chemicals, Meeting Minutes and Final Report No. 2025-01. A Set of Scientific Issues Being Considered by the U.S. Environmental Protection Agency Regarding: Peer Review of the 2024 Draft Risk Evaluation for 1,3-Butadiene, p. 25. https://www.regulations.gov/document/EPA-HQ-OPPT-2024-0425-0123

[133] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 134.

[134] Woodruff, T. J., Rayasam, S. D. G., Axelrad, D. A., Koman, P. D., Chartres, N., et al. (2023). A science-based agenda for health-protective chemical assessments and decisions: overview and consensus statement. Environ Health, 21(Suppl 1), 132. https://doi.org/10.1186/s12940-022-00930-3.

[135] McGartland, A., Revesz, R., Axelrad, D. A., Dockins, C., Sutton, P., Woodruff, T. J. (2017). Estimating the health benefits of environmental regulations. Science, 357(6350), 457-458. https://doi.org/10.1126/science.aam8204.

[136] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, Chapter 5.

[137] WHO. (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition. https://www.who.int/publications/i/item/9789241513548.

[138] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. doi:10.1289/EHP3368.

[139] Nielsen, G. H., Heiger-Bernays, W. J., Levy, J. I., White, R. F., Axelrad, D. A., Lam, J., Chartres, N., Abrahamsson, D. P., Rayasam, S. D. G., Shaffer, R. M., Zeise, L., Woodruff, T. J., Ginsberg, G. L. (2023). Application of probabilistic methods to address variability and uncertainty in estimating risks for non-cancer health effects. Environ Health, 21(Suppl 1), 129. https://doi.org/10.1186/s12940-022-00918-z.

[140] 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.

[141] Ginsberg, G. L. (2012). Cadmium risk assessment in relation to background risk of chronic kidney disease. J Toxicol Environ Health A, 75(7),374-390.

[142] U.S. EPA (2025). Revised Draft 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), Table 2-2.

Our analysis (see Technical Appendix for details; all reported doses are HEDs) of male reproductive effects from chronic DBP exposure found that:

- 0.10 mg/kg-day is the lower bound (95% confidence) chronic human dose at which a 5% reduction in fetal testicular testosterone is expected in 5% of the exposed population
- 0.04 mg/kg-day is the lower bound (95% confidence) chronic human dose at which a 5% reduction in fetal testicular testosterone is expected in 1% of the exposed population
- 0.03 mg/kg-day is the lower bound (95% confidence) chronic human dose at which a 5% reduction in fetal testicular testosterone is expected in 0.5% of the exposed population
- 0.01 mg/kg-day is the lower bound (95% confidence) chronic human dose at which a 5% reduction in fetal testicular testosterone is expected in 0.1% of the exposed population
- 0.005 mg/kg-day is the lower bound (95% confidence) chronic human dose at which a 5% reduction in fetal testicular testosterone is expected in 0.01% (1-in-10,000) of the exposed population
- 0.002 mg/kg-day is the lower bound (95% confidence) chronic human dose at which a 5% reduction in fetal testicular testosterone is expected in 0.001% (1-in-100,000) of the exposed population.

The implications of these risk values can be understood by comparison with the exposure levels considered by EPA to represent negligible risk. EPA's assessment uses a POD of 2.1 mg/kg-day (HED) and a benchmark MOE of 30,[143] meaning that EPA concludes "risk is not considered to be of concern and mitigation is not needed"[144] for any exposure below 0.07 mg/kg-day (2.1 mg/kg-day / 30 = 0.08 mg/kg-day). Our analysis indicates that 0.07 mg/kg-day is the lower-bound dose for the 2.8% (1-in-36) risk level. This risk far exceeds EPA's usual target range of protection for carcinogenic risks of 1-in-10,000 to 1-in-1,000,000.[145]

EPA should apply the WHO framework using the DBP meta-regression BMDL for reduced fetal testicular testosterone, other male reproductive toxicity endpoints and other toxicity endpoints, including developmental toxicity, neurotoxicity, and immunotoxicity endpoints using appropriate BMD/BMDL estimates. The risk-specific dose estimates can in turn be used to characterize the risks associated with the estimated levels of DBP exposure.

3. EPA's approach systematically underestimates real-world DBP exposures and risks.

The DBP Draft Risk Evaluations fails to adequately consider and quantify multiple known or foreseeable exposures to DBP, thereby understating the extent of these exposures. This oversight

[143] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 133.
[144] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 134.
[145] U.S. EPA (2024). Unreasonable Risk Determination of the Draft Risk Evaluation for Formaldehyde, p. 13.

violates TSCA's mandates to "integrate and assess available information on . . . exposures for the conditions of use" of a chemical,[146] and EPA's regulatory mandate to "assess all exposure routes and pathways relevant to [a] chemical substance under the conditions of use."[147] EPA must consider the following DBP exposures, which it failed to adequately assess in the DBP Draft Risk Evaluation. **These scenarios are described in greater detail in the comments of Earthjustice:**

A. **EPA failed to evaluate worker exposures to DBP, including: exposures without the use of personal protective equipment (PPE), exposures via ingestion, and exposure estimates factoring in appropriate work durations.** EPA's inclusion of PPE in its risk evaluations contradicts TSCA's requirements to assess chemical risks without considering risk management measures. PPE should only be considered during the risk management phase, not the risk evaluation phase. Relying on PPE to mitigate risks before evaluating them violates TSCA's mandate and the best available science. EPA must evaluate occupational exposures without assuming the effectiveness or use of PPE to provide a more accurate risk assessment. Next, EPA's reliance on a 31-year working lifetime for its risk evaluations fails to address the longer careers of many workers, thus understating exposures and risks. Nearly 20% of individuals aged 65 and older remain employed, and those aged 75 and above represent the fastest-growing segment of the workforce. To capture the true risks to workers, EPA must use a working lifetime of at least 40 years in its exposure assessments. EPA also ignores ingestion as a route of exposure for workers, focusing only on inhalation and dermal exposures to DBP. Workers can ingest chemicals through various unintentional behaviors, such as nail-biting and eating on the worksite. The EPA must use best available exposure models to quantify these ingestion exposures and provide a more comprehensive risk assessment.

B. **EPA failed to consider DBP exposures from plastic agricultural films:** EPA does consider exposures from plastic agriculture films that contain DBP, such as plastic mulch and greenhouse sheeting. These films can leach phthalates into soil and air, contributing to significant dermal, oral, and inhalation exposures for workers and consumers. EPA must quantify these exposure pathways and their environmental impacts, including the disposal of these agricultural films, to provide a comprehensive risk assessment.

C. **EPA failed to consider exposure to DBP from microplastics:** EPA fails to account for exposures to DBP from microplastics, which are a known and reasonably foreseen source of DBP exposure[148] that can exacerbate the harmful effects of DBP from other sources. The weight of the scientific evidence shows that microplastics are highly persistent, mobile, and exert serious harms to human health, including metabolic

[146] 15 U.S.C. § 2605(b)(4)(i).
[147] 40 C.F.R. § 702.39(d)(9).
[148] Liu, Y., et al., *Phthalates Released from Microplastics Can't Be Ignored: Sources, Fate, Ecological Risks, and Human Exposure Risks*, 179 TrAC Trends in Analytical Chemistry Art.

disorders, reproductive harm, and cancer,[149] many of the same health effects that are linked to DBP. Microplastics have been located virtually everywhere they have been studied, including in the human body[150,151,152,153] and in environmental media like surface water, coastal beaches, sediment, fresh water, air, and food.[154] Microplastics can also persist and bioaccumulate in living organisms, increasing the risk for long-term exposures to chemicals found within common microplastics, like DBP.[155] EPA's failure to consider this exposure pathway violates TSCA's mandate to integrate and assess all relevant information for reasonably foreseeable uses. The agency must evaluate the risks associated with microplastics in its final risk assessment.

D. **EPA understates DBP exposures in vehicles:** EPA underestimates exposures to DBP in vehicles by only considering limited sources like car mats and replacement tires, while ignoring other significant sources such as automotive upholstery and over 300 auto parts. The DBP Draft Risk Evaluation also fail to account for off-gassing of DBP at elevated temperatures inside vehicles. EPA must consider all known and reasonably foreseen exposures within vehicles to provide a comprehensive risk assessment.

E. **EPA understates DBP exposures to people in apartments, mobile housing, and other smaller homes:** EPA's assumption that everyone lives in a home of 492 cubic meters underestimates exposures for those living in smaller spaces, like apartments and mobile homes. Smaller living spaces result in higher concentrations of chemicals and greater inhalation exposures to DBP. EPA must use a more representative home size, such as 154 cubic meters, to accurately assess risks for individuals in smaller living environments.

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[149] California State Policy Evidence Consortium (CalSPEC). Microplastics occurrence, health effects, and mitigation policies: An evidence review for the California state legislature. January 2023. Sacramento, CA; Chartres, N., Cooper, C. B., Bland, G., Pelch, K. E., Gandhi, S. A., BakenRa, A., & Woodruff, T. J. (2024). Effects of Microplastic Exposure on Human Digestive, Reproductive, and Respiratory Health: A Rapid Systematic Review. *Environmental science & technology*, *58*(52), 22843–22864. https://doi.org/10.1021/acs.est.3c09524

[150] Jenner, L. C., Rotchell, J. M., Bennett, R. T., Cowen, M., Tentzeris, V., & Sadofsky, L. R. (2022). Detection of microplastics in human lung tissue using μFTIR spectroscopy. Science of the Total Environment, 831, 154907. https://doi.org/https://doi.org/10.1016/j.scitotenv.2022.154907

[151] Ragusa, A., Svelato, A., Santacroce, C., Catalano, P., Notarstefano, V., Carnevali, O., Papa, F., Rongioletti, M. C. A., Baiocco, F., Draghi, S., D'Amore, E., Rinaldo, D., Matta, M., & Giorgini, E. (2021). Plasticenta: First evidence of microplastics in human placenta. Environment International, 146, 106274. https://doi.org/https://doi.org/10.1016/j.envint.2020.106274

[152] Ragusa A, Notarstefano V, Svelato A, Belloni A, Gioacchini G, Blondeel C, Zucchelli E, De Luca C, D'Avino S, Gulotta A, Carnevali O, Giorgini E. Raman Microspectroscopy Detection and Characterisation of Microplastics in Human Breastmilk. Polymers (Basel). 2022 Jun 30;14(13):2700. doi: 10.3390/polym14132700. PMID: 35808745; PMCID: PMC9269371.

[153] Leslie, H. A., van Velzen, M. J. M., Brandsma, S. H., Vethaak, A. D., Garcia-Vallejo, J. J., & Lamoree, M. H. (2022). Discovery and quantification of plastic particle pollution in human blood. Environment International, 163, 107199. https://doi.org/https://doi.org/10.1016/j.envint.2022.107199

[154] Hale RC, et al. A Global Perspective on Microplastics. *Journal of Geophysical Research: Oceans*. 2020;125(1):e2018JC014719. https://doi.org/10.1029/2018JC014719.

[155] Alijagic, A., Suljević, D., Fočak, M., Sulejmanović, J., Šehović, E., Särndahl, E., & Engwall, M. (2024). The triple exposure nexus of microplastic particles, plastic-associated chemicals, and environmental pollutants from a human health perspective. Environment International, 188, 108736. https://doi.org/10.1016/j.envint.2024.108736.

F. **EPA failed to quantify exposures from groundwater, biosolids, and landfills:** EPA's decision not to conduct quantitative assessments of DBP exposures from biosolids and landfills is flawed. Despite limited monitoring data, the agency has previously used modeling to assess ecological risks and should apply the same methods to evaluate human health risks from these pathways and provide a more accurate risk assessment.

G. **EPA failed to measure down-the-drain exposures from products containing DBP:** EPA does not measure exposures from the down-the-drain disposal of consumer products containing DBP, despite acknowledging their potential release into the environment. The Agency has used exposure models for similar assessments in the past and must apply these methods to estimate down-the-drain exposures for DBP and provide a quantitative assessment of these releases and their associated risks.

H. **EPA failed to adequately quantify all reasonably foreseeable DBP exposures in young age groups:** First, EPA failed to quantify exposures from human breast milk for all relevant age groups. The agency must use models to estimate transfers from mothers to infants and toddlers, considering the full range of potential exposures beyond 1 year of age, as many toddlers continue to breastfeed beyond their first birthday. EPA also failed to evaluate fish ingestion rates for infants under one year old or for children in subsistence fishing populations. Infants can start eating solid foods, including fish, at a few months old and are more susceptible to harm from chemical exposures. EPA must separately evaluate the risks to these younger age groups and model exposures for children in subsistence fishing communities. EPA also failed to consider oral and dermal exposures to DBP from swimming for children under six years old. Evidence shows that young children swim and recreate in surface waters, leading to significant exposures. EPA must expand its assessment to include these younger age groups, as they are more likely to ingest water and experience higher exposure levels. EPA also failed to consider several foreseeable consumer exposures in children and toddlers. These include exposures from tire crumb rubber on playgrounds, synthetic leather clothing, and mouthing of various household items. The EPA must account for these additional exposure pathways to provide a comprehensive risk assessment for DBP.

a. EPA considered aggregate exposure to only a limited extent.

EPA failed to adequately consider aggregate exposures to DBP from multiple sources, conditions of use, and exposure pathways.

The DBP Draft Risk Evaluation states:

> EPA defines aggregate exposure as "the combined exposures to an individual from a chemical substance across multiple routes and across multiple pathways (40 CFR § 702.33)." For the draft DBP risk evaluation, EPA considered aggregate risk across all routes of exposure for each individual consumer and occupational COU evaluated for acute, intermediate, and chronic exposure durations. EPA did not consider aggregate

> exposure for the general population. As described in Section 4.1.3, the Agency employed a risk screen approach for the general population exposure assessment.
>
> EPA did not consider aggregate exposure scenarios across COUs because the Agency did not find any evidence to support such an aggregate analysis, such as statistics of populations using certain products represented across COUs, or workers performing tasks across COUs. However, EPA considered combined exposure across all routes of exposure for each individual occupational and consumer COU to calculate aggregate risks.[156]

In an important improvement, EPA considered aggregate exposure to DBP by combining worker exposure estimates for the inhalation and dermal routes of exposure, and consumer exposure estimates for the inhalation, ingestion, and dermal routes of exposure.

EPA's approach, however, does not fully characterize aggregate exposure and the resulting risks. EPA considered exposures to only individual COUs without combining exposures to multiple COUs or exposures that occur to the same individuals in different settings. EPA aggregated across DBP exposure pathways for consumers and separately for workers, but it did not aggregate exposures for workers who also experience consumer and general population exposures, and did not aggregate exposures for consumers who have exposure to multiple consumer products or who experience general population exposures. EPA says that these exposures were not aggregated because it did not have data indicating such co-exposures.

EPA should not require chemical-specific evidence to conduct aggregate exposure assessment. It can reasonably model scenarios in which exposures are combined across products and across worker, consumer, and general population exposures. For example, some individuals with occupational exposure to DBP are likely to live close to where they work and would, therefore, also be exposed as members of the general population and may also use DBP-containing consumer products.

By failing to recognize that some individuals may be exposed in multiple ways – that is, experiencing combinations of general population, consumer and worker exposures – EPA is systematically underestimating exposures and risks to some of the most-exposed people in the population. This approach is not consistent with the requirements of TSCA to apply the best available science,[157] and to identify and eliminate unreasonable risks to potentially exposed or susceptible subpopulations,[158] which include groups with higher exposure levels. TSCA also requires EPA to eliminate unreasonable risks resulting from "the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance…or…any combination of such activities."[159] EPA can meet these TSCA requirements only by fully considering aggregate exposures. If EPA does not estimate risks from aggregate exposures across COUs and exposure

[156] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 127.
[157] 15 U.S.C. § 2625(h).
[158] 15 U.S.C. § 2605(b)(4)(A).
[159] 15 U.S.C. § 2605(a).

settings in the final DBP risk evaluation, the resulting underestimation would then be a consideration that must be incorporated into the unreasonable risk determination.

b. EPA failed to conduct a background exposure assessment, underestimating risk to potentially exposed or susceptible subpopulations.

Phthalates such as DBP are ubiquitous contaminants worldwide to which the general population is continuously exposed through multiple pathways, including water, air, and inhalation and/or ingestion of household dust.[160] DBP is primarily used as a plasticizer in polyvinyl chloride (PVC) plastic and in manufacturing adhesives, paints and coatings, plastic and rubber products, and plastic resins.[161]

EPA failed to account for these multiple sources of exposure in their assessment of unreasonable risk in the DBP Draft Risk Evaluation. Instead, EPA stated that certain significant pathways of exposure to the general population, including cosmetics, medical devices, food and food packaging materials, were not considered because they constitute "non-TSCA" uses.[162] EPA's rationale for this decision is that these other pathways of exposure will be assessed and managed by statutes such as the Clean Air Act and the Federal Food, Drug, and Cosmetic Act. However, exposures via these pathways are highly relevant and reasonably foreseeable across the human population, and cannot be excluded when evaluating the human health risks posed by DBP as no such regulations are in place nor are they planned. EPA is required under TSCA to account for all "reasonably foreseeable" pathways of exposure.[163] EPA must also conduct risk evaluations using "scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science."[164] The NASEM recommends consideration of background exposures when conducting a risk evaluation for both individual chemicals and categories of chemicals through a cumulative risk assessment,[165] citing that background exposures at "even small doses may have a relevant biological effect."[166]

Given the widespread exposure to DBP across the general population and susceptible populations through food, plastic food storage products, cosmetics, and other "non-TSCA" uses, the failure to consider exposures from those uses would be contrary to TSCA's requirements to consider all reasonably foreseeable exposure pathways and to identify and address risks to PESS. EPA cannot adequately evaluate the conditions of use that are subject to TSCA regulation or control their unreasonable risks if it ignores the background exposures that can contribute to a baseline level of exposures and risks DBP in the human body, even if EPA may not be able to directly regulate some of these uses under TSCA. EPA must consider all exposures that are currently happening for the general population and potentially exposed or susceptible subpopulations or it will significantly underestimate risk.

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[160] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 10.
[161] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 10.
[162] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 239.
[163] 15 U.S.C. § 2602(4).
[164] 15 U.S.C. § 2625(h).
[165] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, pp. 135, 136, and 214.
[166] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 130.

The SACC criticized a similar omission of background exposures from the recent DINP Draft Risk Evaluation:

> Total exposure to phthalates is much more complex and involves many exposure sources, including those beyond the regulatory authority of Toxic Substances Control Act (TSCA). However, those exposures should be included as "background" or some other designation, rather than being invisible in the risk assessment. The science should not be redacted because of legislative compartmentalization of the contributors to real risk.[167]

In the preamble to the 2024 final risk evaluation framework rule, EPA acknowledged the importance of background exposures, and that these exposures can be incorporated in TSCA risk evaluations:

> it may be appropriate to consider potential background exposures from non-TSCA uses that are not within the scope of the risk evaluation as part of an aggregate exposure assessment. Likewise, EPA could consider the disproportionate impacts that background exposures may have on overburdened communities to inform the final unreasonable risk determination.[168]

EPA routinely considers exposures from products or sources that it does not regulate in assessments. For example, in its assessment and regulation of the pesticide fumigant sulfuryl fluoride, EPA's Office of Pesticide Programs (OPP) considered all sources of exposure to fluoride, including ones EPA does not regulate (such as toothpaste). Considering these exposures was critical for accurate risk calculation and decision making—OPP proposed to terminate pesticidal uses of sulfuryl fluoride because children's total exposure to fluoride (mainly from drinking water and toothpaste) exceeded the risk cup of acceptable exposure levels.[169] EPA's plan to exclude from consideration uses of DBP subject to statutes such as the Federal Food Drug and Cosmetics Act ignores the reality of human exposure and violates TSCA.

Thus, EPA must revise the DBP Draft Risk Evaluation so it addresses all sources and pathways of DBP exposure, including background exposures. TSCA, with its specific charge to consider potentially exposed or susceptible subpopulations, has a critical role to play in the protection of the general public and more susceptible groups such as infants and toddlers that are facing DBP exposure. As we have previously detailed, established scientific principles for exposure assessment require that all known pathways of exposures be included in the assessment, or exposure will not be accurately quantified, and risk will be underestimated, particularly to potentially exposed or susceptible subpopulations.[170]

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[167] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 16.

[168] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act.

[169] Sulfuryl Fluoride; Proposed Order Granting Objections to Tolerances and Denying Request for Stay, 76 Fed. Reg. 3,422-01 (Jan. 19, 2011).

[170] US EPA. (2019). Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC); Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4 Dioxane; Notice of Availability and Public Meetings. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences,

EPA importantly incorporates estimates of "non-attributable" exposures to phthalates, which include exposures from non-TSCA uses of phthalates such as food packaging and cosmetics, in the phthalates cumulative risk assessment (CRA) by estimating background phthalate intakes from NHANES biomonitoring data. EPA combines estimates of exposure from TSCA conditions of use for any single phthalate with NHANES background exposure estimates for the other phthalates included in the CRA. This approach is useful for incorporating background exposures to multiple phthalates, but is insufficient for capturing high-end exposures to combinations of phthalates.

The limitations of NHANES for the phthalates CRA are demonstrated by a comparison of NHANES diisononyl phthalate (DINP) 95th percentile exposures to consumer exposures from the DINP draft risk evaluation. EPA estimates 95th percentile exposure to DINP from NHANES data for women 16-49 years old as 5.6 μg/kg-day.[171] In comparison, EPA's DINP draft risk evaluation identifies multiple consumer conditions of use with much greater exposures[172] – in some cases, even for low exposure scenarios:

> Carpet backing: high, medium and low exposure scenarios all substantially greater than 10 μg/kg-day
> Indoor furniture: high exposure scenario greater than 10 μg/kg-day, medium exposure scenario approximately 5 μg/kg-day
> Specialty wall coverings: high exposure scenario greater than 10 μg/kg-day, medium exposure scenario greater than 5 μg/kg-day
> Vinyl flooring: high and medium exposure scenarios both substantially greater than 10 μg/kg-day
> Polyurethane injection resin: high and medium exposure scenarios both substantially greater than 10 μg/kg-day
> Roofing adhesives: high, medium and low exposure scenarios all substantially greater than 10 μg/kg-day.

This comparison reveals that the NHANES estimates represent generally routine and population-wide exposures primarily from non-TSCA uses and are insufficient to capture the higher exposures resulting from TSCA conditions of use for phthalates. Inclusion of NHANES data in the CRA is useful to capture some aspects of exposure to multiple phthalates, but EPA's approach assumes that no individuals are exposed to more than 1 out of the 6 phthalates through TSCA conditions of use. This assumption is not plausible when considering real-world consumer use of multiple products within and across phthalate conditions of use identified in the draft CRA document. For example, EPA indicates that 5 out of the 6 phthalates are used in consumer arts, crafts and hobby materials; 3 phthalates are used in consumer cleaning products;

University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA- HQ-OPPT-2019-0237-0059 and https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0056.

[171] U.S. EPA (2025). Revised Draft 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), Table 4-2.

[172] U.S. EPA (2024). Draft Risk Evaluation for Diisononyl Phthalate (DINP), Figure 4-12.

and all 6 are used in consumer paints and coatings.[173] In most instances, consumers engaged in hobbies, home cleaning or home painting will use multiple products in a day, thus there is a likelihood of many consumers exposed to multiple phthalates in a day. Further, many workers who are exposed to one phthalate in the workplace are likely exposed to other phthalates from TSCA conditions of use at home. EPA's CRA approach disregards these scenarios, which are not captured by the NHANES data.

A further limitation to the use of NHANES in the CRA is that NHANES does not provide phthalates data for children younger than 3 years old. Table 5-2 indicates that exposures for infants and toddlers are assumed to be the same as the exposures estimated from NHANES for children ages 3-5 years. This assumption is very likely to underestimate exposures to young children who typically have greater exposure per unit body weight to any contaminants such as phthalates that are present in house dust and food.

4. EPA failed to adequately identify and quantify risks to potentially exposed or susceptible subpopulations (PESS), as required by TSCA.

EPA has failed to meet its requirement under TSCA to identify, consider, and account for risk to "potentially exposed or susceptible subpopulations" (PESS) in the DBP Draft Risk Evaluation.[174] EPA excluded multiple potential PESS, and among the PESS identified, EPA did not apply a transparent methodology for quantifying the risk of harm to each identified PESS using the best available science. This omission is consistent with previous risk evaluations where EPA regularly underestimated the risk to PESS due to a lack of adequate identification and consideration of PESS. By not adequately identifying and considering risks to PESS, EPA is violating TSCA's requirements. EPA must, therefore, adopt a consistent framework for identifying PESS and quantifying the risk of harm to PESS from DBP exposures.

Identification and consideration of PESS for each chemical assessed is a critical aspect of conducting risk evaluation under TSCA, as TSCA requires EPA to:

> determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other nonrisk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation.[175]

In the final 2024 TSCA Risk Evaluation Framework Rule, EPA defined PESS as:

> Potentially exposed or susceptible subpopulation means a group of individuals within the general population identified by EPA who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects

[173] U.S. EPA (2025). Revised Draft 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), Table_Apx D-4.
[174] 15 U.S.C. § 2605(b)(4)(A).
[175] 15 U.S.C. § 2605(b)(4)(A).

> from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, the elderly, or overburdened communities.[176]

EPA needs to develop and apply a consistent approach to identify all PESS. To date, EPA has not employed a consistent or structured approach to identifying PESS in its TSCA risk evaluations, including scope documents for ongoing risk evaluations. EPA's approach and terminology for identifying PESS varied considerably in the first 10 TSCA risk evaluations. These inconsistencies included differences in whether health conditions related to a chemical's hazards were considered in identifying PESS, and whether fenceline communities were included as PESS.[177] To remedy the problem of inconsistent and incomplete identification of PESS, Rayasam *et al.* recommended that:

> EPA should prepare a comprehensive methodology to identify PESS and quantify their risks consistently within and across the TSCA risk evaluations.[178]

EPA has not yet proposed such a methodology. The DBP Draft Risk Evaluation is particularly deficient in its failure to present any structured approach for the identification of PESS. The DBP Draft Risk Evaluation indicates that the following groups were identified as PESS:

> females of reproductive age; pregnant women; infants; children and adolescents; people who frequently use consumer products and/or articles containing high concentrations of DBP; people exposed to DBP in the workplace; people in close proximity to releasing facilities, including fenceline communities; and Tribes and subsistence fishers whose diets include large amounts of fish.[179]

The DBP Draft Risk Evaluation does include consideration of various categories of "biological susceptibility" in Table 5-1 of the draft hazard assessment document, which is a useful initial step towards developing a consistent, structured approach to identifying PESS in TSCA risk evaluations.[180] However, the evaluation is still deficient in identifying PESS, and has taken a step backwards with the exclusion of more detailed evaluations of PESS based on both greater exposure and greater susceptibility that were included in recent risk evaluations. The DBP draft hazard assessment Table 5-1 gives explicit consideration to each of the following categories: lifestage, pre-existing disease or disorder, lifestyle activities, socio-demographic factors,

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[176] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act, § 702.33.

[177] Rayasam, S. D. G., Koman, P. D., Axelrad, D. A., Woodruff, T. J., Chartres, N. (2022). Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. Environmental science & technology, 56(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079.

[178] Rayasam, S. D. G., Koman, P. D., Axelrad, D. A., Woodruff, T. J., Chartres, N. (2022). Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. Environmental science & technology, 56(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079].

[179] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 12.

[180] U.S. EPA (2025). Draft Non-Cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), p. 75, Table 5-1.

nutrition, genetics/epigenetics, and other chemical and non-chemical stressors. However, EPA failed to fully consider all PESS within each category identified for DBP.[181]

Further, the DBP Draft Risk Evaluation does not provide any careful consideration of how risk estimates should be adjusted to account for risks to susceptible groups, beyond the selection of the POD and, in some cases, the use of a default 10X uncertainty factor for intraspecies (human) variability. While the selection of POD for DBP may ensure protection for some populations, EPA itself acknowledged that it cannot guarantee absolute protection, especially for those with greater susceptibility and/or exposure. The full discussion of this issue is:

> For non-cancer endpoints, EPA used a default value of 10 for human variability (UF_H) to account for increased susceptibility when quantifying risks from exposure to DBP. The Risk Assessment Forum, in *A Review of the Reference Dose and Reference Concentration Processes* discusses some of the evidence for choosing the default UF of 10 when data are lacking and describe the types of populations that may be more susceptible, including different life stages (e.g., children, elderly). However, U.S. EPA (2002) did not discuss all the factors presented in Table 5-1. Although U.S. EPA (2002) did not discuss all the factors presented in Table 5-1, EPA considers the POD proposed for use in characterizing risk from exposure to DBP to be protective of effects on the developing male reproductive system consistent with phthalate syndrome in humans. Thus, **uncertainty remains regarding whether additional susceptibility factors would be covered by the default UF_H value of 10 chosen for use in the draft DBP risk evaluation**.[182] (emphasis added)

Instead of increasing the use of science-based uncertainty factors to account for the wide range of vulnerability and variability in the human population that EPA itself has acknowledged, EPA uses inadequate default uncertainty factors, which will result in an underestimation of risk, particularly for PESS. The 10X default human variability (UF_H) uncertainty factor that EPA relies on to account for intra-species variability is based on a scientific recommendation made nearly 70 years ago. Since then, decades of scientific evidence suggests that this adjustment factor falls short of capturing the full range of human responses to chemical exposures, especially for susceptible subgroups.[183] Based on observed toxicokinetic differences in chemical metabolism between younger age groups and adults, California EPA's Office of Environmental Health Hazard Assessment (OEHHA) now relies on an intra-species adjustment factor that is three times higher than the one currently used by EPA.[184] The World Health Organization's

[181] U.S. EPA (2025). Draft Non-Cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), p. 75, Table 5-1.

[182] U.S. EPA (2025). Draft Non-Cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), p. 73-74.

[183] Varshavsky, J. R., Rayasam, S. D. G., Sass, J. B., Axelrad, D. A., Cranor, C. F., Hattis, D., Hauser, R., Koman, P. D., Marquez, E. C., Morello-Frosch, R., Oksas, C., Patton, S., Robinson, J. F., Sathyanarayana, S., Shepard, P. M., & Woodruff, T. J. (2023). Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. Environmental Health, 21(Suppl 1), 133. https://doi.org/10.1186/s12940-022-00940-1.

[184] Cal. Env't Protection Agency, Technical Support Document for the Derivation of Noncancer Reference Exposure Levels (2008), https://oehha.ca.gov/media/downloads/crnr/noncancertsdfinal.pdf.

International Programme on Chemical Safety (IPCS) examined human variability in toxicokinetic and toxicodynamic responses to chemical exposures using a probabilistic method, and found that variability at the 99th percentile across the general population was up to more than four times higher than what is reflected in EPA's default intra-species adjustment factor.[185] Accordingly, the WHO recommends using larger uncertainty factors, up to 42X, just to account for normal variability in the human response to chemical exposures among healthy adults.[186,187] Had EPA applied this uncertainty factor to its risk calculations in the DBP Draft Risk Evaluation, several conditions of use would have been associated with MOEs that were below the benchmark MOE, indicating unreasonable risk. For example, among consumer uses, the following conditions of use would have MOEs less than the benchmark (Benchmark MOE=126):

- **Construction, paint, electrical, and metal products:**
  - Automotive adhesives
  - Construction adhesives
  - Adhesives for small repairs
  - Metal coatings
  - Indoor flooring sealing and refinishing products
  - Sealing and refinishing sprays (outdoor use)
- **Furnishing, cleaning, treatment care products:**
  - Synthetic leather clothing
  - Synthetic leather furniture
  - Wallpaper (in-place)
  - Spray cleaner
  - Waxes and polishes
- **Packaging, paper, plastic, toys, hobby products:**
  - Footwear components
  - Miscellaneous items, including a pen, pencil case, hobby cutting board, costume jewelry, tape, garden hose, disposable gloves, and plastic bags/pouches
  - Children's toys (new)
  - Children's toys (legacy)
  - Miscellaneous items, including a football, balance ball, and pet toys
- **Other uses: Chemiluminescent light sticks**
  - Small articles with semi routine contact; glow sticks
- **Other uses: Automotive articles**
  - Synthetic leather seats

[185] WHO. (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition. https://www.who.int/publications/i/item/9789241513548.

[186] WHO. (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition. https://www.who.int/publications/i/item/9789241513548.

[187] Varshavsky, J. R., Rayasam, S. D. G., Sass, J. B., Axelrad, D. A., Cranor, C. F., Hattis, D., Hauser, R., Koman, P. D., Marquez, E. C., Morello-Frosch, R., Oksas, C., Patton, S., Robinson, J. F., Sathyanarayana, S., Shepard, P. M., & Woodruff, T. J. (2023). Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. Environmental Health, 21(Suppl 1), 133. https://doi.org/10.1186/s12940-022-00940-1.

For many of the identified PESS, EPA concluded that, due to a lack of chemical specific data, no further adjustment is necessary. This includes for individuals with increased susceptibility due to lifestyle activities (smoking, alcohol consumption, physical activity), socio-demographic status (race/ethnicity, socioeconomic status), poor nutrition (diet, malnutrition), and other chemical and nonchemical stressors (build environment, social environment). First, TSCA does not require chemical-specific quantitative data to identify or evaluate risks to PESS. Instead, TSCA requires EPA to rely on the "best available science" when evaluating risks to PESS. The best available science demonstrates that both intrinsic factors, which include biological traits like age, genetic makeup, and pre-existing health conditions, and extrinsic factors, which include psychosocial stress from experiencing income inequality, violence, racism, healthcare inequity, or food insecurity, can individually or collectively increase susceptibility to harm from chemical exposures.[188]

EPA should therefore focus first on identifying susceptible subpopulations based on either chemical-specific evidence or the broader literature on intrinsic and extrinsic susceptibility factors, but should not be contingent on chemical-specific data.[189] Then, as a separate step, EPA should consider how to adequately account for the elevated risks for each group, in some cases by using *additional* scientifically-supported uncertainty factors to those that are already being used to adequately account for human variability among healthy adults (e.g. 42X). The best available scientific evidence indicates that EPA should incorporate one or more additional uncertainty factors to account for multiple chemical and non-chemical stressors when assessing risk to potentially exposed or susceptible subpopulations, beyond the 42X to address intra-species variability.[190] This includes assessment of risk to individuals with increased susceptibility due to factors like race/ethnicity, or poor nutrition—categories that EPA failed to evaluate in the DBP Draft Risk Evaluation. This is particularly relevant when assessing risk to residents of fenceline communities or other susceptible subgroups

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[188] Woodruff, T. J., Rayasam, S. D. G., Axelrad, D. A., Koman, P. D., Chartres, N., Bennett, D. H., Birnbaum, L. S., Brown, P., Carignan, C. C., Cooper, C., Cranor, C. F., Diamond, M. L., Franjevic, S., Gartner, E. C., Hattis, D., Hauser, R., Heiger-Bernays, W., Joglekar, R., Lam, J., … Zeise, L. (2023). A science-based agenda for health-protective chemical assessments and decisions: Overview and consensus statement. Environmental Health,21(1), 132. https://doi.org/10.1186/s12940-022-00930-3; Rachel Morello-Frosch et al., Understanding the Cumulative Impacts of Inequalities in Environmental Health: Implications for Policy, 30 Health Affs. 879 (2011), https://www.healthaffairs.org/doi/pdf/10.1377/hlthaff.2011.0153; Cliona M. McHale et al., Assessing Health Risks from Multiple Environmental Stressors: Moving from G×E to I×E, 775 Mutational Rsch. 11 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5863617/; Devon C. Payne-Sturges et al., Methods for Evaluating the Combined Effects of Chemical and Nonchemical Exposures for Cumulative Environmental Health Risk Assessment, 15 Int'l. J. Env't Rsch. & Pub. Health 2797 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6313653/; Gilbert C. Gee et al., Environmental Health Disparities: A Framework Integrating Psychosocial and Environmental Concepts, 112 Env't Health Persps. 1645 (2004), https://doi.org/10.1289/ehp.7074; Gina M. Solomon et al., Cumulative Environmental Impacts: Science and Policy to Protect Communities 37 Ann. Rev. Pub. Health 83, 87–88 (2016), https://www.annualreviews.org/doi/pdf/10.1146/annurev-publhealth-032315-021807; Patricia D. Koman et al., Population Susceptibility: A Vital Consideration in Chemical Risk Evaluation Under the Lautenberg Toxic Substances Control Act, 17 PLoS Biology 1, 4 (2019), https://journals.plos.org/plosbiology/article?id=10.1371/.

[189] Varshavsky et al. Current Practice and Recommendations for Advancing How Human Variability and Susceptibility Are Considered in Chemical Risk Assessment, 21(Suppl 1) Env't Health Article No. 133, at 3 (2023), https://doi.org/10.1186/s12940-022-00940-1.

[190] *Id.*

who experience disproportionately high levels of chemical and non-chemical stressors compared to the general population.

As one example, EPA correctly considered Black, non-Hispanic women as a highly exposed group to DBP and multiple other phthalates. However, EPA failed to fully account for the risk experienced by these groups by not adequately accounting for their increased susceptibility to harm from phthalate exposures. Black women are more likely to experience poverty, racism, healthcare inequities, certain disease disparities, and disproportionate chemical exposures compared to other racial groups in the U.S. population.[191] Factoring an additional 10X UF to account for increased susceptibility due to these intrinsic and extrinsic factors would have resulted in risk calculations that are more protective of this group. For example, the following consumer use conditions of use would have MOEs less than the benchmark (Benchmark MOE=1,260) in this scenario *in addition to those listed above*:

- **Furnishing, cleaning, treatment care products:**
  - Vinyl flooring
  - Wallpaper (installation)
- **Packaging, paper, plastic, toys, hobby products:**
  - Shower curtains
- **Other uses: Novelty articles**
  - Adult toys

5. EPA's determination of unreasonable risk inappropriately discounts and disregards high-end exposures without justification and violates TSCA's requirement to assess risks to groups with greater exposures.

a. EPA's failure to use high-end risk estimates resulted in incorrect determinations of no unreasonable risk for 10 occupational conditions of use.

In the DBP Draft Risk Evaluation, EPA determined that 20 occupational conditions of use (COUs) "may significantly contribute to unreasonable risk," and 11 worker COUs do not contribute to unreasonable risk. For each COU, EPA provides a "central tendency" and "high-end" exposure estimate (Table 4-3); EPA's risk characterization then uses both the central tendency and high-end exposures for estimating risk (Table 6-1). EPA's explanation of these key terms is as follows:

> The central tendency is expected to represent occupational exposures in the center of the distribution for a given COU…The Agency preferred to provide the 50th percentile of the distribution. However, if the full distribution was unknown, EPA used either the mean,

[191] Nguyen, V. K., Kahana, A., Heidt, J., Polemi, K., Kvasnicka, J., Jolliet, O., & Colacino, J. A. (2020). A comprehensive analysis of racial disparities in chemical biomarker concentrations in United States women, 1999-2014. Environment international, 137, 105496. https://doi.org/10.1016/j.envint.2020.105496; Chinn, J. J., Martin, I. K., & Redmond, N. (2021). Health Equity Among Black Women in the United States. *Journal of women's health (2002)*, *30*(2), 212–219. https://doi.org/10.1089/jwh.2020.8868

> mode, or midpoint of the distribution to represent the central tendency depending on the statistics available for the distribution. The high-end exposure is expected to represent occupational exposures that occur at probabilities above the 90th percentile, but below the highest exposure for any individual (U.S. EPA, 1992). For this draft risk evaluation, EPA provided high-end results at the 95th percentile. If the 95th percentile was not reasonably available, EPA used a different percentile greater than or equal to the 90th percentile but less than or equal to the 99th percentile, depending on the statistics available for the distribution. If the full distribution is not known and the preferred statistics are not reasonably available, EPA estimated a maximum or bounding estimate in lieu of the high-end.[192]

EPA later reports, however, that it generally did not use the high-end estimates for determining unreasonable risk:

> for most occupational COUs, central-tendency risk estimates were used to preliminarily determine unreasonable risk.[193]

Specifically, EPA says that it considered high-end estimates in determining unreasonable risk for only 8 worker COUs; for the remaining 23 COUs only central tendency estimates were considered.[194]

For many COUs, exposures were so high that EPA determined there was unreasonable risk even when it considered only the central tendency. But for 10 COUs, EPA determined there was no unreasonable risk <u>because</u> it considered only central tendency. For the following COUs that EPA determined do not contribute to unreasonable risk, Table 6-1 shows that high-end inhalation risk estimates for all exposure durations are at levels indicating unreasonable risk:

- Disposal
- Processing – recycling
- Industrial use – other uses – automotive articles
- Industrial use – other uses – propellants
- Commercial use – furnishing, cleaning, treatment care products – floor coverings; construction and building materials covering large surface areas including stone, plaster, cement, glass and ceramic articles; fabrics, textiles, and apparel
- Commercial use – furnishing, cleaning, treatment care products – furniture and furnishings
- Commercial use – packaging, paper, plastic, toys, hobby products – packaging (excluding food packaging), including rubber articles; plastic articles (hard); plastic articles (soft); other articles with routine direct contact during normal use, including rubber articles; plastic articles (hard)
- Commercial use – packaging, paper, plastic, toys, hobby products – toys, playground, and sporting equipment
- Commercial use – other uses – automotive articles

[192] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 75.
[193] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 244.
[194] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 246.

- Commercial use – other uses – chemiluminescent light sticks.

EPA's decision to use only central tendency values for most occupational COUs disregards the Agency's obligation under TSCA to determine whether workers with greater-than-typical exposures are experiencing an unreasonable risk[195] and ignores the risks to 50% of the workers in these COUs.

EPA's Science Advisory Committee on Chemicals (SACC) recently commented on the unexpected and unjustified change from EPA's practice in previous TSCA risk evaluations that have been carried through recent evaluations including for dicyclohexyl phthalate (DCHP):

> For occupational exposures, central tendency and 95 centile exposures were evaluated, but only the central tendency conditions were carried through to the risk characterization. EPA should justify why the pivot from past practice, when it is noted that the benchmark was exceeded for some COUs using the 95th centile exposure conditions.[196]

The practice of utilizing high-end exposure estimates is scientifically well-supported and is consistent with both the requirements of TSCA[197] and previous TSCA risk evaluations. This approach is crucial for ensuring that the risk evaluation comprehensively addresses all potential risks, particularly to the most vulnerable and highly exposed groups within the workforce.

To adhere to the requirements of TSCA and to ensure robust protection for all workers, EPA's unreasonable risk determination for all COUs should employ high-end exposure estimates that represent at least the 95th percentile of exposure—and should be up to the 99th percentile, as the 95th percentile leaves 5% of workers with high exposures unaccounted for and at risk.[198] This adjustment is necessary to accurately reflect the risk for the most exposed individuals and to ensure that all COUs are evaluated with an appropriate consideration of variability in exposure.

It is also concerning that EPA chose to disregard high-end risk estimates at the final stages of the risk evaluation, only after finding (in Table 6-1) high risks for several scenarios. EPA's weight of scientific evidence conclusions regarding the worker exposure estimates are "moderate" or "moderate to robust" for each occupational exposure scenario,[199] and EPA summarizes its findings as:

> EPA has moderate to robust confidence in the assessed inhalation exposures, …Overall, EPA has moderate to robust confidence in the risk estimates calculated for worker and ONU inhalation and dermal exposure scenarios.[200]

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[195] 15 U.S.C. § 2605(b)(4)(A).
[196] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 19.
[197] 15 U.S.C. § 2605(b)(4)(A).
[198] Program on Reproductive Health and the Environment (2025). Health Protective Chemical Policy Reform. https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/PRHE-EPAreqs-HealthProtectivePolicyReform-v6.pdf
[199] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), Table 4-5.
[200] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 154.

EPA then describes the strengths of its occupational exposure assessment:

> The exposure scenarios and exposure factors underlying the inhalation and dermal assessment are supported by moderate to robust evidence. Occupational inhalation exposure estimates were informed by moderate or robust sources of directly applicable and surrogate monitoring data or modeling was used to estimate the inhalation exposure estimates. Exposure factors for occupational inhalation exposure include duration of exposure, body weight, and breathing rate, which were informed by moderate to robust data sources.[201]

Regarding the impact of uncertainties in modeled exposure estimates, EPA says:

> the effects of these uncertainties on the exposure estimates are unknown as the uncertainties may result in either overestimation or underestimation of exposures, depending on the actual distributions of each of the model input parameters.[202]

None of these EPA conclusions indicate any concerns about the high-end exposure estimates. Instead, the questions regarding the representativeness of some estimates are raised only in the Risk Characterization and Unreasonable Risk Determination sections of the Draft DBP Risk Evaluation – sections that can be drafted only after risks have been calculated using the central tendency and high-end exposure estimates. The placement of the statements raising doubts about the high-end exposure estimates seems to indicate that EPA developed these concerns only after finding that the high-end exposures led to risk estimates that represent unreasonable risks.

EPA does not provide evidence in the DBP Draft Risk Evaluation for its claims that the high-end estimates are not representative of exposures for at least some workers. EPA further does not present evidence that central tendency estimates will not underestimate exposures and risks for significant proportions of workers in each COU. If EPA does have evidence that its current "high-end" estimates are not representative of high-end exposures for a given COU, the appropriate action would be to then develop new high-end estimates rather than relying only on the central tendency estimates.

EPA must adopt a more transparent, consistent, and accountable approach to risk assessment. Uncertainties identified by EPA must be addressed early in the exposure assessment; all reasonably foreseeable exposures, including high-end exposures for each occupational exposure scenario and COU must be accounted for; and the unreasonable risk determination must not disregard half of its exposure estimates, including high-end exposure estimates developed in the exposure assessment component of conducting a risk evaluation.

In addition, EPA's unscientific and nontransparent attempts to justify disregarding the high-end estimates, including repeated mentions of uncertainties and lack of data, indicate that EPA failed in its obligation to ensure that it obtained the necessary data needed to conduct a defensible risk evaluation. EPA did not utilize its authority under TSCA to obtain data during or after the process that designated DBP as a high priority for risk evaluation. Given the potentially

[201] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 97.
[202] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 98.

significant data gaps, EPA's high-end exposure estimates make appropriate use of the reasonably available data and should be used as the basis for the unreasonable risk determination.

b. EPA improperly disregarded high-intensity exposure and risk estimates in its unreasonable risk determination for consumer exposures to DBP in paints and toys.

EPA determined that 4 consumer COUs may contribute to the unreasonable risk of DBP based on dermal exposures, and 9 consumer COUs do not pose an unreasonable risk.

EPA explicitly applied a process intended to avoid findings of unreasonable risk by revisiting any exposure estimates resulting in margins of exposure (MOEs) less than 30, and therefore below the "benchmark MOE" used by EPA in finding unreasonable risks. As stated by EPA:

> If MOEs are below the benchmark of 30 for the high-intensity use scenario, EPA reevaluates the approaches and inputs used and determines if refinement of those is needed. In addition, the Agency considers the medium-intensity use scenario as either a possible upper-bound estimate by reevaluating inputs and approaches or endeavors in the refinement of approaches by using other modeling tools or other input parameters within the same modeling tools.[203]

EPA should not disregard elements of its exposure assessment based on risk characterization results. TSCA requires EPA to use the "best available science"[204] considering "reasonably available"[205] information in conducting TSCA risk evaluations. EPA's process of exposure estimate "refinement" sets aside reasonably available information it has already determine to represent the best available science in an attempt to avoid risk characterization results that signal an unreasonable risk. EPA applied this invalid procedure to avoid unreasonable risk determinations for the consumer paints and coatings and children's toys COUs.

EPA found that consumer paints and coatings contribute to the unreasonable risk of DBP based on dermal exposure, but it disregarded potential high risks to infants and toddlers from inhalation exposures. EPA did not consider its high-intensity inhalation exposure estimates for this COU when making its unreasonable risk determination, even though it describes the quality of these estimates as "robust."[206] The high-intensity estimates indicate MOEs less than 30, and therefore below the benchmark MOE used by EPA in finding unreasonable risks. EPA's explanation for deciding not to use the high-intensity estimates, a decision it made only after seeing that these estimates resulting in high risks to infants and toddlers, hinges on assumptions about the high-end frequency of use of metal coatings.

In the exposure assessment section of the draft risk evaluation addressing this COU, EPA said:

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[203] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 167.
[204] 15 U.S.C. § 2625(h).
[205] 15 U.S.C. § 2625(k).
[206] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 110.

> parameters such as frequency and duration of use…are well understood and representative.[207]

EPA later characterizes the frequency of use assumption as reasonable:

> For metal coating products, daily use was not considered likely, but the product **could reasonably be used weekly** for hobby projects or a variety of small projects. Therefore, this product was modeled at a use frequency of 52 times per year.[208] (emphasis added)

EPA then reiterates the "robust" characterization of the inhalation estimate for metal coatings, but then continues on to discard the high-intensity estimate without supporting evidence:

> The overall confidence in this COU inhalation exposure estimate is robust because the CEM **default parameters represent actual use patterns and location of use**. The resulting chronic inhalation MOEs for bystanders from the high-intensity scenario were below the benchmark of 30 for infants and toddlers (children <2 years old; MOEs of 26 and 28, respectively). However, based on the conservative assumptions used in the assessment, **the frequency of use likely overestimates potential exposure**, and the medium-intensity is a **more representative scenario** of exposure for this COU. Medium-intensity exposure risk estimates for the metal coatings scenario were 130 and 140 for infants and toddlers, respectively. Therefore, EPA is preliminarily determining that this COU does not contribute to unreasonable risk for infants and toddlers for bystander inhalation exposure.[209] (emphasis added)

EPA contradicts itself in an effort to justify not determining unreasonable risk for the inhalation pathway, first saying that it has developed a reasonable estimate of high-intensity exposure and then saying it is likely to be an overestimate. EPA says that instead it will rely on only the medium-intensity use scenario. EPA's statement that the medium-intensity estimate is "more representative" only indicates that this estimate represents typical conditions, and is not a justification for disregarding conditions that apply for in homes where metal coatings are used with greater-than-typical frequency. By using only the medium-intensity scenario for unreasonable risk determination, EPA fails to consider whether above-average frequency of use poses an unreasonable risk, and leaves infants and toddlers in homes with greater-intensity use of metal paints at risk.

EPA's unreasonable risk determination similarly discounts high estimated acute risks to infants from aggregate exposure to DBP in toys. EPA first states that is has high confidence in its exposure estimates for toys:

> The overall confidence in this COU's inhalation and dust ingestion exposure estimate is robust because of a good understanding of the CEM model parameter inputs and representativeness of actual use patterns and location of use…The mouthing parameters

[207] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 170.
[208] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 248.
[209] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 249.

> used, such as duration of use …and surface area for infants … are very well understood. The chemical migration value is DBP specific, empirically derived, and the main sources of uncertainty are related to a large variability in empirical migration rate data for harsh, medium, and mild mouthing approaches.[210]

Then, after finding that aggregating ingestion, inhalation and dermal exposures results in a high risk to infants (MOE of 23, substantially less than EPA's benchmark MOE of 30), EPA finds reasons to disregard the risk estimate:

> The aggregated MOE overall confidence originates from compounding and intensifying the uncertainties rom each aggregated exposure route. The overestimation for all three high-intensity exposure routes suggest that the high-intensity use aggregate scenario may not reflect or capture realistic exposures. Given this information, the Agency is basing this preliminary risk determination on the medium-intensity use of toys, **as it is representative of the middle of the range of exposures**; therefore, EPA is preliminary determining that, for DBP, the COU Consumer use – packaging, paper, plastic, toys, hobby products – toys, playground, sporting equipment does not significantly contribute to unreasonable risk.[211] (emphasis added)

EPA decides to consider only typical exposures – "the middle of the range" – after finding that the high-intensity scenario results in high risk. By considering only typical exposures, EPA disregards risk to any infants with greater-than-typical exposures. Further, EPA claims that it is avoiding potential overestimation of aggregate exposure that might result from combining three high-intensity scenarios, an unsupported assertion. First, it can be expected that exposures via different pathways to the same DBP-containing toys are likely to be correlated; thus the exposures from the three pathways should not be assumed to be independent. Second, use of high-end estimates for all 3 pathways is not necessary for the aggregate MOE to be less than 30. Combining the high-end estimates for just ingestion and inhalation exposure, with no contribution from dermal exposure, results in an MOE of 29.

EPA should not disregard its high-intensity aggregate exposure and risk estimates - especially for infants and toddlers, who are identified as potentially exposed or susceptible subpopulations (PESS) in the DBP Draft Risk Evaluation - and should revise its determination to identify consumer metal paints (by inhalation) and children's toys (by aggregate exposure) as contributors to the unreasonable risk of DBP.

[210] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 173.
[211] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 250.

Technical Appendix: Application of IPCS framework to DBP non-cancer risks

In the *Draft Risk Evaluation for Dibutyl Phthalate (DBP)*, EPA characterizes risks of effects on the developing male reproductive system. The draft TSCA risk evaluation calculates a "margin of exposure" (MOE) to characterize risk for each exposure scenario, which is the ratio of the point of departure (POD) to the exposure level. For the DBP, EPA says that an MOE of 30 or more indicates that "risk is not considered to be of concern and mitigation is not needed."[212]

EPA's approach to risk characterization does not actually estimate risks of adverse effects in the population with chronic exposure to DBP, but instead simply applies a "bright line" judgment of whether or not the MOE is adequate. A more informative approach for both risk characterization and risk management would be to apply the probabilistic dose-response assessment methods of the International Programme on Chemical Safety (IPCS),[213] part of the World Health Organization (WHO), to estimate the risk of adverse effects at various levels of exposure. The IPCS methodology has previously been described and applied in several peer-reviewed journal articles.[214,215,216,217,218]

We applied the IPCS approach for continuous endpoints and the "approximate probabilistic" calculation (see IPCS report Fig 3.5, panel C)[219] to estimate risks of male reproductive effects from chronic oral exposure to DBP. The analysis involved the following steps:

1. Determination of IPCS POD and corresponding uncertainty adjustment
2. Application of interspecies adjustments
3. Application of intraspecies adjustments
4. Calculation of HD_M^I - the human dose (HD) of DBP associated with a particular magnitude of effect M at a particular population incidence I.

[212] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 134.

[213] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.

[214] Chiu WA, Slob W. A Unified Probabilistic Framework for Dose–Response Assessment of Human Health Effects. Environmental Health Perspectives, 2015 December;123(12): 1241–1254. doi:10.1289/ehp.1409385

[215] Nielsen, G. H., Heiger-Bernays, W. J., Levy, J. I., White, R. F., Axelrad, D. A., Lam, J., Chartres, N., Abrahamsson, D. P., Rayasam, S. D. G., Shaffer, R. M., Zeise, L., Woodruff, T. J., Ginsberg, G. L. (2023). Application of probabilistic methods to address variability and uncertainty in estimating risks for non-cancer health effects. Environ Health, 21(Suppl 1), 129. https://doi.org/10.1186/s12940-022-00918-z

[216] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. doi:10.1289/EHP3368

[217] Blessinger T, Davis A, Chiu WA, Stanek J, Woodall GM, Gift J, Thayer KA, Bussard D. Application of a unified probabilistic framework to the dose-response assessment of acrolein. Environment International, 2020 October;143:105953. doi: 10.1016/j.envint.2020.105953

[218] Chiu WA, Paoli GM. Recent Advances in Probabilistic Dose–Response Assessment to Inform Risk-Based Decision Making. Risk Analysis, 2021 April;41(4):596-609. doi: 10.1111/risa.13595

[219] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.

For each aspect of the analysis, including the values used to derive the IPCS POD and the adjustment factors applied to derive the HD_M^I, the IPCS methodology uses a 50th percentile value (P50) as a central estimate and the ratio of 95th percentile to 50th percentile (P95/P50) as a measure of uncertainty. All POD and HD_M^I values presented in this analysis are for continuous exposures.

STEP 1: Determination of IPCS POD and corresponding uncertainty adjustments

For continuous endpoints, the IPCS methodology uses a benchmark dose (BMD) as the POD.

EPA derived a BMD of 14 mg/kg-day and a lower confidence limit (BMDL) of 9 mg/kg-day (applied dose) for a 5% reduction in fetal testicular testosterone by incorporating updated data in a meta-regression model developed by the National Academies of Science, Engineering, and Medicine (NASEM).[220] We use these values in applied dose units, as adjustment for allometric scaling to derive a human equivalent dose (HED) is applied separately in the interspecies adjustment step below.

In the IPCS methodology, the BMD of 14 mg/kg-day is the central estimate (P50) of the POD, and uncertainty in the POD (P95/P50) is equal to the ratio of BMD / BMDL:

P95/P50 = BMD / BMDL = 14 mg/kg-day / 9 mg/kg-day = 1.56

Step 2: Application of interspecies (animal-to-human) adjustments

For interspecies (animal-to-human) adjustments, the IPCS methodology first considers a factor for body-size scaling, and then a factor for remaining toxicokinetic (TK) and toxicodynamic (TD) differences. The IPCS framework provides equations for calculating the body size scaling adjustment factor, based on the assumed human body weight and test species body weight. We applied EPA's assumptions for human body weight (80 kg) and rat body weight (0.25 kg)[221] to derive the appropriate central tendency (P50) factor and its uncertainty (P95/P50).

For the TK/TD differences remaining after bodyweight scaling, the IPCS report recommends a central estimate (P50) of 1 (i.e., no additional interspecies differences) and representing uncertainty with a P95/P50 factor of 3.[222] We incorporated these IPCS recommendations, which are entered In the IPCS approximate probabilistic calculation template as follows:

[220] U.S. EPA (2025). Revised Draft 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), Table 2-2.

[221] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP), p. 121.

[222] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.3.

Interspecies adjustments for probabilistic dose-response analysis of chronic oral exposure to DBP: reduced fetal testosterone		
Aspect	**P50**	**P95/P50**
$AF_{Interspecies\text{-}BS}$	5.64[a]	1.26[a]
$AF_{Interspecies\text{-}TK/TD}$	1	3

[a] Calculated from IPCS equation 4-2 using EPA assumptions regarding body weight of humans (80 kg) and rats (0.25 kg).

Step 3: Application of intraspecies (human variability) adjustments

In the IPCS methodology, the value of the human variability adjustment factor ($AF_{intraspecies}$) varies depending on the incidence of the adverse effect in the exposed population – with a larger adjustment factor necessary to extrapolate from the POD to lower levels of incidence. The IPCS report provides $AF_{intraspecies}$ for several incidence (I) values. The P50 and P95/P50 values for $AF_{intraspecies}$ provided by IPCS for several values of I, along with additional values of I of interest for this analysis, are provided in the following table:

Lognormal approximation of uncertainty distributions for intraspecies variability ($AF_{Intraspecies}$) for varying levels of population incidence (I)		
Incidence (I)	**$AF_{Intraspecies}$**	
	P50	**P95/P50**
5%[a]	4.98	2.82
2.8%[b]	6.46	3.33
1%[a]	9.69	4.32
0.5%[a]	12.36	5.06
0.1% (1-in-1,000)[a]	20.42	6.99
0.01% (1-in-10,000)[a]	37.71	10.39
0.001% (1-in-100,000)[b]	64.25	14.65

[a] IPCS Table 4.5
[b] Calculated for this analysis using the same methods that were used to derive IPCS Table 4.5

Step 4: Calculation of HD_M^I

The output of the IPCS methodology is generically described as an HD_M^I value – the human dose (HD) associated with a particular magnitude of effect M at a particular population incidence I. For this analysis, the "M" represents a 5% reduction in fetal testicular testosterone. The following tables present the HD_M^I results for I = 5% and 1% using the POD, $AF_{Interspecies}$, and $AF_{Intraspecies}$ values shown above. HD_M^I values for other levels of incidence can be determined by substituting the $AF_{Intraspecies}$ values appropriate for each level of incidence into the tables below and then recalculating HD_M^I using the substituted $AF_{Intraspecies}$.

The IPCS approach is a probabilistic method, so the HD_M^I is a distribution; selected values from that distribution are presented in the tables as follows:

- P05: 5th percentile estimate (lower confidence limit) of HD_M^I (this value is shown in **bold**)
- P50: 50th percentile estimate (median) of HD_M^I
- P95: 95th percentile estimate (upper confidence limit) of HD_M^I.

All HD_M^I values in the following tables are human equivalent doses (HEDs), as they incorporate interspecies body size scaling (see Step 2 above).

Calculation of HD_M^I for chronic oral exposure to DBP: reduced fetal testosterone (Incidence = 5%)		
Aspect	**P50**	**P95/P50**
BMD	14 mg/kg-d	1.56
$AF_{Interspecies-BS}$	5.64	1.26
$AF_{Interspecies-TK/TD}$	1	3
$AF_{Intra-I=5\%}$	4.98	2.82
HD_M^I	0.50 mg/kg-d[a]	4.91[b]
	P05	**P95**
HD_M^I [(c)]	**0.10 mg/kg-d**	2.4 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.56)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 2.82)^2]^{0.5}} = 4.91$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I for chronic oral exposure to DBP: reduced fetal testosterone (Incidence = 1%)		
Aspect	**P50**	**P95/P50**
BMD	14 mg/kg-d	1.56
$AF_{Interspecies-BS}$	5.64	1.26
$AF_{Interspecies-TK/TD}$	1	3
$AF_{Intra-I=1\%}$	9.69	4.32
HD_M^I	0.26 mg/kg-d[a]	6.66[b]
	P05	**P95**
HD_M^I [(c)]	**0.04 mg/kg-d**	1.7 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.56)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 4.32)^2]^{0.5}} = 6.66$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Interpretation of Results

The National Academies and the WHO/IPCS have both recommended using the lower confidence limit (LCL) on a probabilistic dose-response distribution for use in decision-making, in place of a traditional reference dose (RfD) or reference concentration (RfC). The National Academies said in *Science and Decisions* that:

> Multiple risk-specific doses could be provided…in the various risk characterizations that EPA produces to aid environmental decision-making.[223]
>
> A Risk-Specific Reference Dose: For quantal effects, the RfD can be defined to be the dose that corresponds to a particular risk specified to be de minimis (for example, 1 in 100,000) at a defined confidence level (for example, 95%) for the toxicity end point of concern.[224]

The WHO/IPCS said:

> The LCL of the HD_M^I can be used as a probabilistic RfD to replace the deterministic RfD. In this case, the probabilistic RfD is the dose that protects the population from a specified magnitude and incidence of effect with a pre-specified per cent coverage (confidence).[225]

Consistent with the guidance from the National Academies and the IPCS, we summarize the above results in the following table of the lower confidence limit (5th percentile or P05) risk-specific doses (HD_M^I) for multiple levels of risk (incidence or I).

[223] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 140.
[224] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 140.
[225] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, p. 12.

Risk-specific dose estimates for chronic oral exposure to DBP: reduced fetal testosterone	
Incidence (I)	**HD_M^I lower -confidence limit (P05)**
5%	0.10 mg/kg-day
2.8%	0.07 mg/kg-day
1%	0.04 mg/kg-day
0.5%	0.03 mg/kg-day
0.1% (1-in-1,000)	0.01 mg/kg-day
0.01% (1-in-10,000)	0.005 mg/kg-day
0.001% (1-in-100,000)	0.002 mg/kg-day

Based on application of the WHO/IPCS methodology to DBP male reproductive effects from chronic exposures, we find that:

- 0.10 mg/kg-day is the lower bound (95% confidence) chronic human dose at which a 5% reduction in fetal testicular testosterone is expected in 5% of the exposed population
- 0.04 mg/kg-day is the lower bound (95% confidence) chronic human dose at which a 5% reduction in fetal testicular testosterone is expected in 1% of the exposed population
- 0.03 mg/kg-day is the lower bound (95% confidence) chronic human dose at which a 5% reduction in fetal testicular testosterone is expected in 0.5% of the exposed population
- 0.01 mg/kg-day is the lower bound (95% confidence) chronic human dose at which a 5% reduction in fetal testicular testosterone is expected in 0.1% of the exposed population
- 0.005 mg/kg-day is the lower bound (95% confidence) chronic human dose at which a 5% reduction in fetal testicular testosterone is expected in 0.01% (1-in-10,000) of the exposed population
- 0.002 mg/kg-day is the lower bound (95% confidence) chronic human dose at which a 5% reduction in fetal testicular testosterone is expected in 0.001% (1-in-100,000) of the exposed population.

The implications of these risk values can be understood by comparison with the exposure levels considered by EPA to represent negligible risk. EPA's assessment uses a POD of 2.1 mg/kg-day

(HED) and a benchmark MOE of 30,[226] meaning that EPA concludes "risk is not considered to be of concern and mitigation is not needed"[227] for any exposure below 0.07 mg/kg-day (2.1 mg/kg-day / 30 = 0.08 mg/kg-day). Our analysis indicates that 0.07 mg/kg-day is the lower-bound dose for the 2.8% (1-in-36) risk level. This risk far exceeds EPA's usual target range of protection for carcinogenic risks of 1-in-10,000 to 1-in-1,000,000.[228]

The estimates of HD_M^I presented here were based entirely on input values and equations available from the WHO/IPCS methodology document and related publications, and from EPA's *Draft Non-Cancer Human Health Hazard Assessment for Dibutyl Phthalate (DBP)*. An important caveat to these calculations is that the values used to represent human variability may be understated. The IPCS default human variability distribution is based on 37 data sets for human toxicokinetic variability and 34 data sets for human toxicodynamic variability. Most of these data sets were obtained from controlled human exposure studies of pharmaceuticals conducted in small samples of healthy adults, representing considerably less variability than found in the general population.[229,230,231] If human variability is underestimated, then the actual dose associated with each incidence level (e.g. I =1%, I = 0.1%) will be lower than the values obtained from this analysis – or in other words, risk at each dose will be underestimated.

[226] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 133.
[227] U.S. EPA (2025). Draft Risk Evaluation for Dibutyl Phthalate (DBP), p. 134.
[228] U.S. EPA (2024). Unreasonable Risk Determination of the Draft Risk Evaluation for Formaldehyde, p. 13.
[229] WHO. (2017). *Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition.* https://www.who.int/publications/i/item/9789241513548
[230] Hattis, D., Lynch, M.K. (2007). Empirically observed distributions of pharmacokinetic and pharmacodynamic variability in humans—Implications for the derivation of single-point component uncertainty factors providing equivalent protection as existing reference doses. In Lipscomb, J.C. & Ohanian, E.V. (Eds.), *Toxicokinetics in risk assessment* (pp. 69-93). Taylor & Francis Group. https://doi.org/10.1201/b14275
[231] Axelrad, D. A., Setzer, R. W., Bateson, T. F., DeVito, M., Dzubow, R. C., Fitzpatrick, J. W., Frame, A. M., Hogan, K. A., Houck, K., Stewart, M. (2019). Methods for evaluating variability in human health dose-response characterization. Hum Ecol Risk Assess, 25, 1-24. https://doi.org/10.1080/10807039.2019.1615828