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Comments from Scientists, Academics, and Clinicians on the Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP) 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 Diethylhexyl Phthalate (DEHP), (hereafter referred to as the *DEHP 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] DEHP 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 DEHP exposure from which a point of departure (POD) was derived.[3]

In the DEHP 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 DEHP 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 733 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 Diethylhexyl Phthalate (DEHP), p. 11.
[3] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 132.
[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 DEHP 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 DEHP.

The DEHP Draft Risk Evaluation also relies on dose-response and risk characterization methods that violate TSCA's "best available science" requirement. EPA did not apply benchmark dose (BMD) modeling for estimating non-cancer risks of DEHP, and instead inappropriately used a dose level that EPA identified as a no-observed-adverse-effect level (NOAEL) as the POD without considering any other toxicological endpoints, many of which had similar or lower NOAELs. It 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 DEHP exposure, and found that EPA's current approach results in acceptance of exposures producing an unacceptable upper bound risk of 1-in-80, a level 12,500 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 DEHP 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 DEHP, 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]

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 DEHP Draft Risk

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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.

[10] 15 U.S.C. § 2602(12).

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 DEHP 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 DEHP 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 Diethylhexyl Phthalate (DEHP) 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 DEHP.**
    a. **EPA did not conduct a comprehensive and up-to-date literature search.**
    b. **EPA relied on assessments conducted by other agencies 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 733 PECO-relevant DEHP health effects studies from evidence integration without valid scientific justification.**
    e. **EPA's methods for evaluation of study quality need to incorporate further improvements that have been 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 DEHP 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 DEHP 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 DEHP, including reproductive, developmental, metabolic, and neurotoxicity studies.**
        i. **EPA inappropriately excluded all epidemiology studies from dose-response assessment.**

ii. **EPA inappropriately excluded animal toxicology studies from dose-response assessment.**
iii. **EPA did not provide a clear summary judgment for each outcome.**

b. **EPA failed to make appropriate use of benchmark dose modeling to specify a non-cancer point of departure for risk characterization.**
c. **EPA's non-cancer margin of exposure (MOE) calculations are unreliable due to EPA's failure to conduct scientifically appropriate benchmark dose modeling.**
d. **EPA should apply best available methods to generate quantitative estimates of non-cancer risks for varying levels of exposure to DEHP.**

3. **EPA's approach systematically underestimates real-world DEHP 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 improperly determined that disposal of DEHP does not pose an unreasonable risk to workers by disregarding high-end exposure and risk estimates.**
   b. **EPA improperly determined that consumer exposure to DEHP in furniture does not pose an unreasonable risk to infants and toddlers by disregarding high-intensity exposure and risk estimates.**

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

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

    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 DEHP 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 DEHP Draft Risk Evaluation.

To identify epidemiology studies of DEHP, EPA relied on a Health Canada assessment completed in 2020 and the ATSDR assessment completed in 2022,[14,15,16] and a literature search that was conducted in 2019 and has not been updated since. As stated in EPA's systematic review protocol for DEHP:

> The search for peer-reviewed and gray literature relevant references was completed in September and May 2019, respectively.[17]

EPA has not conducted a search for studies relevant to the DEHP Draft Risk Evaluation in the five-plus years prior to its release for public comment, and therefore the literature compiled for use in evaluating DEHP 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 Di-ethylhexyl Phthalate (DEHP), p. 22.
[15] Health Canada (2020). Screening assessment - Phthalate substance grouping.
[16] ATSDR (2022). Toxicological Profile for Di(2-Ethylhexyl)Phthalate (DEHP).
[17] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), p. 9.

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

> EPA reviewed the epidemiological conclusions from existing assessments of DEHP…and considered whether information from newer published literature would change those conclusions, since the ATSDR (2022) literature search through June 2020 is more recent than the 2019 TSCA literature search. OPPT used these previous assessments to facilitate efficient and scientific risk evaluation. Therefore, data quality evaluation and extraction were conducted 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 ATSDR (2022), and included literature published up to June 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 wasn't conducted for any references published before 2018.[18]

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 assessments conducted by other agencies including Health Canada and ATSDR. The Health Canada document is not a systematic review or and it does not appear to have been peer reviewed. The ATSDR assessment is not a systematic review. EPA did not assess the quality of the studies published before 2018 or extract their data. The DEHP draft protocol indicates that 262 PECO-relevant pre-2018 epidemiology studies were excluded from the risk evaluation;[19] 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 assessments by other agencies 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

[18] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), p. 22.
[19] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), p. 23.

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 DEHP. A further concern is that these inconsistent procedures for identifying epidemiological evidence were ultimately relevant only to the identification of DEHP 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 process that involved more extensive use of the 2022 ATSDR assessment and prior assessments by other agencies:

> Previous phthalates risk assessments have been conducted by authoritative sources including U.S. EPA (1988), U.S. CPSC (2014, 2010), ATSDR (2022); NTP-CERHR (2006); NASEM (2017), California OEHHA (2022), Environment and Climate Change Canada/ Health Canada (2020; 2015); ECB (2008), ECHA (2017a, b, 2010), EFSA (2019, 2005), the Danish EPA (2011); and Australia NICNAS (2010). Based on these existing assessments, a total of 12 key studies…for point of departure (POD) refinement…moved directly to the data evaluation and extraction step under TSCA.[20]

> OPPT also used the ATSDR toxicological profile for DEHP (ATSDR, 2022) as a starting point for literature review because the assessment included literature through June 2020, which included references up until EPA's last literature search in 2019, and employed a systematic review process [*sic*] that focused on relevant health outcomes across a range of human health hazards … and identified 164 studies (constituting 201 animal toxicology experiments), which are included as Levels of Significant Exposure (LSE) …At the time of this protocol, OPPT has reviewed 110 of these studies…with the intention to review the remaining when available. References that underwent further filtering were oral studies from the ATSDR (2022) except for 1 study which was added by assessors to aide in meta-analysis during POD refinement (Gray et al., 2021).[21]

The text is unclear regarding how EPA's own search results were used in this process, but Figure 4-6 indicates that 364 PECO-relevant toxicology studies not included in the ATSDR assessment were excluded from consideration for the TSCA risk evaluation, without explanation.[22]

Out of 110 studies identified by EPA using the ATSDR assessment, 82 of these studies were excluded from data extraction and study quality evaluation based solely on dose-response data (i.e. value of the LOAEL),[23] and 14 additional studies were excluded from data extraction and study quality evaluation based on consideration of additional study characteristics (e.g. reporting deficiencies, limited animal survival).[24] Therefore, only 14 out of 110 studies identified by

[20] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), p. 24.
[21] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), p. 24.
[22] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), Figure 4-6, box 2c.
[23] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), p. 25.
[24] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), pp. 25-26.

ATSDR were considered by EPA for hazard identification and dose-response assessment of DEHP.[25]

According to the protocol, toxicology studies published after June 2020 were not included at all, with one exception (Gray et al., 2021). The process by which the 2021 study was identified is not described. In addition, the DEHP data quality evaluation file for DEHP includes 2 later studies (Laws et al. 2023; Santacruz-Marquez et al. 2024).[26] These studies from 2023-2024 are not mentioned in the protocol, and the process by which they entered the hazard assessment is not clear. EPA has not applied a clear, comprehensive, or consistent approach to identifying the toxicology evidence relevant to assessing the health effects of DEHP.

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 appear to have been 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 toxicology studies submitted to the docket. It appears that any toxicological findings on DEHP published in the past 5 years (with the exception of studies by Gray et al., Laws et al., and Santacruz-Marquez 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.[27] Collectively, EPA's practices run a high risk of failing to include all relevant health effects studies and/or treating relevant studies differently in the DEHP Draft Risk Evaluation.

b. EPA relied on assessments conducted by other agencies to exclude studies, without supporting justification and inconsistent with the best available science.

EPA reviewed several prior assessments of DEHP toxicology and epidemiology studies as part of conducting the DEHP Draft Risk Evaluation, including assessments by ATSDR and agencies in Europe, Canada, and Australia. Epidemiology studies published before 2019 were not considered by EPA unless they were included in the previous assessments. Studies published before these dates that were not identified in searches conducted by ATSDR, Health Canada or other agencies that were excluded from these previous assessments for any reason were not considered at all by EPA. For toxicology studies, it appears that EPA search results were not

[25] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), Figure 4-6, boxes 2b and 5.

[26] U.S. EPA (2025). Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for Diethylhexyl Phthalate (DEHP).

[27] 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.

used at all in the process of identifying studies included in the DEHP Draft Risk Evaluation; thus the hazard and dose-response conclusions for DEHP are entirely reliant on the previous assessments.

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 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.[28]

However, it appears that that most or all of the assessments used by EPA were not systematic reviews. For example, the Health Canada and ATSDR assessments that were central to EPA's process of identify included studies are not systematic reviews. Further, in some cases (e.g. Health Canada) it is unclear if the previous assessments were peer reviewed. EPA also does not provide adequate justification for its use of previous DEHP 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.[29] AMSTAR 2 was also applied by the NASEM in multiple prior reports on environmental health assessment.[30,31,32] 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.[33]

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

The DEHP 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

[28] 15 U.S.C. § 2625(h).
[29] NASEM (2023). Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests.
[30] NASEM (2019). Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene.
[31] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations.
[32] NASEM (2022). Guidance on PFAS Exposure, Testing, and Clinical Follow-Up.
[33] 15 U.S.C. § 2625(h).

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 DEHP and other phthalates is deficient and excludes a broad range of important toxicity outcomes from consideration in the draft risk evaluation.

The outcome component of the PECO statement for DEHP 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.[34] (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."[35] 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.

[34] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, Table_Apx H-47.
[35] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, Table_Apx H-47.

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,"[36] and identified "tumors, birth defects, and neurologic impairments"[37] as examples. No biochemical measures or early biological changes were mentioned among the examples.

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."[38] The definition of adverse effect includes, for example, "a biochemical change;" such effects appear to be excluded from the DEHP 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)[39,40,41]
- reduced thyroid hormone levels (2020 TSCA risk evaluation of HBCD; 2021 toxicity assessment of PFBS) [42,43]
- decreased erythrocyte counts and hemoglobin (2020 TSCA risk evaluation of perchloroethylene)[44]
- measures of immune function, such as increases in immunoglobulin E, lymphocytes, natural killer cells, and interlukin-4 levels (2020 TSCA risk evaluation of perchloroethylene)[45]

[36] National Research Council (2007). Toxicity Testing in the 21st Century: A Vision and a Strategy, p. 38.
[37] National Research Council (2007). Toxicity Testing in the 21st Century: A Vision and a Strategy, p. 177.
[38] U.S. EPA. IRIS Glossary. https://www.epa.gov/iris/iris-glossary.
[39] 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.
[40] 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.
[41] 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.
[42] U.S. EPA (2020). Risk evaluation for cyclic aliphatic bromide cluster (HBCD).
[43] 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.
[44] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[45] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).

- 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)[46,47,48,49]
- acetylcholinesterase inhibition (numerous assessments of pesticides, including cumulative risk assessments of organophosphate and carbamate pesticides)[50,51]

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 DEHP Draft Risk Evaluation, or provide a justification for why these outcomes should not be considered as potential hazards of DEHP.

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"[52] (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.[53] 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

[46] U.S. EPA (2020). Risk Evaluation for Trichloroethylene.
[47] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[48] 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.
[49] 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.
[50] U.S. EPA (2006). Organophosphorus cumulative risk assessment. https://www.regulations.gov/document/EPA-HQ-OPP-2006-0618-0002.
[51] U.S. EPA (2008). Revised N-methyl carbamate cumulative risk assessment. https://www.regulations.gov/document/EPA-HQ-OPP-2008-0347-0029.
[52] U.S. EPA (2021). Draft systematic review protocol supporting TSCA risk evaluations for chemical substances, p. 345.
[53] 15 U.S.C. § 2625(h).

generally focused on apical endpoints.

d. EPA inappropriately excluded at least 733 PECO-relevant DEHP health effects studies 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 DEHP says 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.[54]

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 DEHP 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.[55]

> To streamline the identification of studies containing potentially relevant data that had not previously been evaluated by EPA, 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.[56]

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

[54] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), p. 5.
[55] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), p. 22.
[56] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), p. 22.

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

> the first step of further filtering was based only on publication date…. All DEHP references that met PECO screening criteria for epidemiology with a publication date of 2020 or later proceeded to the next step of further filtering. All other DEHP references (references with a publication date before 2018) didn't proceed to data quality evaluation.[57]

EPA excluded 262 PECO-relevant epidemiology studies due to being published before 2018.[58]

An additional 11 epidemiology studies were excluded through the filtering process based on their use of serum or breast milk biomarkers, leaving 122 out of 395 PECO-relevant epidemiology studies for which data extraction and study quality evaluation were conducted.[59] Overall, EPA discarded 273 studies out of the 395 epidemiology studies it identified as PECO relevant, or 69%.

In the initial step of further filtering of the DEHP toxicology evidence, 364 studies out of the 486 PECO-relevant studies identified by EPA were removed from consideration without any explanation other than "Did not support POD refinement for hazard."[60]

EPA then excluded another 82 studies based solely on dose-response considerations (i.e., value of the LOAEL), and 14 additional studies were excluded based on other study characteristics.[61] Overall, EPA discarded 460 studies out of the 486 DEHP toxicology studies it identified as PECO-relevant, or nearly 95%.[62] The vast majority of these studies were excluded for unexplained reasons or based on their dose-response data.

EPA's exclusion of 273 epidemiology studies and 460 toxicology studies from the DEHP hazard assessment – studies already determined by EPA to be relevant to assessing the human health hazard of DEHP – contradicts EPA's claim that all relevant studies are considered in the DEHP 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 that have been recommended by the National Academies.

[57] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), p. 22.
[58] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), p. 23.
[59] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), p. 23.
[60] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), Figure 4-6.
[61] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), p. 25.
[62] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), Figure 4-6.

The DEHP 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 DEHP 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 DEHP 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 [DEHP] 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 [DEHP] 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 Di-ethylhexyl Phthalate (DEHP), 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.[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 DEHP 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 DEHP. 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 integration" for the subsequent process of drawing conclusions considering all evidence streams.

[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 Di-ethylhexyl Phthalate (DEHP), p. 56.
[73] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 36.

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 DEHP 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 DEHP 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 DEHP endpoints, including a pre-specified set of descriptors that are considered for each endpoint.

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

Along with the DEHP 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 provided an opportunity for early identification and correction of the many critical deficiencies

[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 Di-ethylhexyl Phthalate (DEHP), pp. 112-115.
[77] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 33.
[78] 15 U.S.C. § 2625(h).

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, which 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]

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

[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

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 DEHP 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 DEHP, including reproductive, developmental, metabolic, and neurotoxicity studies.

EPA's approach to hazard identification for DEHP 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 700 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.[84]
>
> Hazard information related to potential health and environmental hazards of the chemical substance will be reviewed in a manner consistent with best available science.[85]

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

[84] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA), 40 CFR § 702.39(c)(1).

[85] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA), 40 CFR § 702.39(c)(2).

includes both epidemiologic and toxicological evidence, as discussed below. And third, EPA did not provide a clear summary judgment for each outcome.

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

In the DEHP draft systematic review protocol, EPA identified 395 human epidemiology studies of DEHP.[86] EPA initially excluded any studies published before 2018 from consideration, without justification, leaving 122 studies published from 2018 to 2022 (only 1 study published in 2022; no studies published from 2023 to 2025 were included) that were advanced to data quality evaluation. EPA rated the quality of more than 100 DEHP epidemiology studies as "High" or "Medium."[87]

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.[88]

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.[89] 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

[86] U.S. EPA (2025). Draft Systematic Review Protocol for Di-ethylhexyl Phthalate (DEHP), p. 23.
[87] U.S. EPA (2025). Data Quality Evaluation Information for Human Health Hazard Epidemiology for Di - ethylhexyl Phthalate (DEHP).
[88] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 13.
[89] 15 U.S.C. §2625(h).

> finalized the requirement to use and document systematic review methods to assess reasonably available information.[90]

EPA's broad exclusion of DEHP 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 DEHP 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.

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).[91]

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.[92]

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

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[90] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA). 89 FR 37028.

[91] 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.

[92] 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.

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 DEHP as indicated by EPA's study quality ratings.

Moreover, EPA's explanation considers only alleged limitations of the DEHP 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 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 DEHP from dose-response analysis, EPA has violated TSCA's requirement to use the best available science.[93] EPA cannot broadly exclude epidemiologic studies from dose-response assessment in the DEHP 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.

EPA conducted its hazard identification based on a list of only 201 toxicology studies identified in the ATSDR 2022 assessment of DEHP as providing "Levels of Significant Exposure" (LSE). ATSDR already had excluded studies from this list based on its assessment of study dose levels, study quality and reporting deficiencies.[94] EPA then immediately discarded 151 of the ATSDR-identified studies based solely on dose-response data:

> Using this cut-off criterion of LOAEL less than or equal to 20 mg/kg-day, EPA identified a total of 50 animal toxicology studies from among the 201 studies in ATSDR's Table of LSE for further consideration in hazard identification and dose-response.[95]

Of these 50 animal toxicology studies, EPA considered 24 animal studies of DEHP male reproductive toxicity published up to 2022 for dose-response analysis.[96] From this set of studies, EPA ultimately selected a no-observed-adverse-effect level (NOAEL) of 4.8 mg/kg-d (human equivalent dose (HED) of 1.1 mg/kg-d) for male reproductive effects from a study by Blystone et al. as the POD, citing that it was supported by a set of studies by Andrade and Grande with NOAELs of 5 mg/kg-d and consistent with several other studies with lowest-observed-adverse-

[93] 15 U.S.C. § 2625(h).
[94] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 21.
[95] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 33.
[96] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 140.

effect levels (LOAELs) of 10-14 mg/kg-d. In making this selection, EPA discounted lower male reproductive NOAELs from studies by Hsu (0.03 mg/kg-d), Akingbemi et al. (1 mg/kg-d) and Christiansen et al. (3 mg/kg-d) from consideration of dose-response assessment without adequate scientific rationale.

The exclusion of Hsu et al. (2016) and Christiansen et al. (2010) is particularly problematic. In the Christiansen et al. study, EPA acknowledged a NOAEL of 3 mg/kg-day for male developmental endpoints, including decreased anogenital distance (AGD), increased nipple retention, and incidences of mild external genital dysgenesis in male rats developmentally exposed to DEHP across two independent experiments conducted 8 months apart:

> When data from both studies were combined, AGD was significantly decreased and nipple retention was significantly increased at 10 mg/kg-day and above…and EPA agrees with the determination of the LOAEL at 10 mg/kg-day based on increased nipple retention and decreased AGD, with the NOAEL established at 3 mg/kg-day.[97]

However, EPA then went on dismiss the NOAEL, citing inconsistency in the magnitude of effects across the two experiments and asserting that the dose reflected choices in dose selection rather than true sensitivity:

> Given the inconsistencies between the two studies in the endpoints of AGD and nipple retention, EPA did not consider the NOAEL of 3 mg/kg-day in the study by Christiansen et al. (2010) as the POD. Again, the more sensitive NOAEL of 3 mg/kg-day provided by the study by Christiansen et al. (2010) is more of a reflection of lower dose selection. Instead, the study by Christiansen et al. (2010) supports the consensus NOAEL of 5 mg/kg-day (or 4.8 mg/kg-day) based on studies by Andrade and Grande (2006b; 2006c; 2006a; 2006) and the three-generation reproduction study (Blystone et al., 2010; TherImmune Research Corporation, 2004).[98]

EPA's rationale for dismissing the NOAEL and claiming that this study aligned with the "consensus" NOAEL of 5 mg/kg-day is scientifically unsupported. First, EPA acknowledged that the NOAEL reported by the study authors was appropriately determined. EPA cannot simultaneously accept the validity of a NOAEL and dismiss it based solely on its relative position within a dose range. Notably, the same study has been used by ECHA and Health Canada to derive regulatory PODs, affirming its scientific credibility and relevance. Instead of disregarding this study, EPA should incorporate it into benchmark dose modeling and dose-response assessment (see discussion in section b below).

EPA similarly excluded Hsu et al. 2016, which found statistically significant sperm structural abnormalities and DNA damage in exposed adult male rats at doses ≥0.1 mg/kg-day, identifying a NOAEL of 0.03 mg/kg-day, which is more than 100 times lower than the oral POD selected by EPA for DEHP (4.8 mg/kg-day). EPA dismissed this study based on the absence of comparable findings in the Blystone et al. three-generation reproductive toxicity study, stating:

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[97] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p.146.
[98] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p.146.

> EPA considered this study to have high uncertainty regarding the plausibility and replicability of the effects on sperm….[since] sperm abnormalities were not observed in the three-generation reproduction study (Blystone et al, 2010; TherImmune Research Corporation, 2004).[99]

EPA's dismissal of the Hsu et al. (2016) study is scientifically unfounded and inconsistent with TSCA's best available science mandate. A failure to replicate specific endpoints in a separate study, particularly one with a different experimental paradigm, is not valid grounds to dismiss positive findings from another well-conducted study. EPA's approach violates best available methods in evidence evaluation, which requires transparent, systematic integration of all relevant data. Rather than excluding Hsu et al., EPA should also consider it as a candidate for benchmark dose (BMD) modeling and dose-response assessment. Had EPA incorporated the Hsu et al. NOAEL into its dose-response assessment for DEHP, the resulting oral POD could have been at least 100-fold lower than the selected POD of 4.8 mg/kg-d (assuming benchmark dose modeling was not employed), with significant implications for risk characterization across conditions of use.

EPA also dismissed evidence from studies related to other adverse health outcomes beyond male reproductive harm, including female reproductive harm (6 studies), nutritional/metabolic toxicity (16 studies), liver toxicity (19 studies), cardiovascular/kidney toxicity (4 studies), neurotoxicity (3 studies), and immunotoxicity (3 studies). Of these, 21 studies reported NOAELs or LOAELs below 4.8 mg/kg-day, suggesting these endpoints may be more sensitive indicators of DEHP toxicity than male reproductive toxicity. Nonetheless, EPA disregarded all of them from consideration in POD derivation, in many cases, because study outcomes were not also observed in other toxicological or epidemiologic studies in the scientific literature.

For example, EPA dismissed the study by Zhang et al. (2014), which identified a NOAEL of 0.04 mg/kg-d for delayed germline progression in female mice exposed to DEHP during pregnancy—a study that ATSDR relied on to derive a chronic oral minimal risk level (MRL) in its 2022 Toxicological Profile for DEHP.[100] Although the study only examined a single dose and thus may not be suitable for BMD modeling, it clearly provides evidence of a sensitive adverse outcome that EPA could have used to support POD selection. Instead, EPA dismissed consideration of this study because the examined outcomes "were not examined in other oral studies in rodents."[101] EPA also summarized the "paucity of epidemiological data evaluating the effects of DEHP exposure on female developmental and reproductive outcomes"[102] citing several epidemiologic studies that did not observe similar outcomes as Zhang et al.

EPA also dismissed studies showing metabolic, hepatic, and neurotoxicity at doses well below 4.8 mg/kg-day. Of these endpoints, the exclusion of all studies demonstrating nutritional/metabolic harm was the most problematic given the strength and consistency of the evidence, including a number of studies demonstrating metabolic toxicity at levels well below the selected 4.8 mg/kg-day POD. This includes studies examining endpoints, like fasting glucose

[99] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p.143.
[100] ATSDR (2022). Toxicological Profile for Di(2-Ethylhexyl)Phthalate (DEHP), p. A-13.
[101] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 68.
[102] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 68.

levels and glucose levels following a glucose tolerance test, that EPA acknowledged were "consistent" and "sensitive" across multiple studies:

> A subset of effects on glucose-insulin homeostasis (including impaired glucose tolerance, increased fasting glucose levels, and impaired insulin resistance) were consistent and sensitive across studies.[103]

This subset of studies includes NOAEL and/or LOAEL values that were substantially lower than 4.8 mg/kg-day, including two studies with LOAELs at 0.05 mg/kg-day,[104] values 100 times lower than the selected POD. EPA also acknowledged that these findings were corroborated in the epidemiologic evidence:

> Available human epidemiologic studies show some limited evidence of an association between exposure to DEHP and clinical outcomes related to the nutritional and metabolic effects observed in laboratory animal studies, such as metabolic syndrome, diabetes, altered glucose metabolism, altered insulin metabolism, and adiposity.[105]

Despite this, EPA made a final conclusion that the toxicologic evidence would not be considered further because:

> [A]n adverse outcome pathway demonstrating effects of DEHP of other phthalates on glucose homeostasis is not well established, and the largely mechanistic endpoints measured in these studies did not manifest themselves in adverse apical outcomes in the animals in these studies (e.g., no clinical signs of toxicity such as lethargy, polyuria, etc.). Finally, the human-relevance of these effects is difficult to determine given the lack of robust epidemiological evidence supporting effects of DEHP on diseases related to glucose homeostasis, such as diabetes, altered glucose metabolism, altered insulin metabolism, adiposity, and metabolic syndrome.[106]

These are not scientifically justifiable reasons to dismiss an entire evidence base that EPA itself admitted was consistent and sensitive. First, a fully developed adverse outcome pathway is *not* a prerequisite for POD/endpoint selection, especially when the animal data are strong and reproducible. Second, altered glucose homeostasis does not have be accompanied by apical outcomes like lethargy to be considered a hallmark of diabetes. Animal models of diabetes, especially those testing potential therapies, use blood glucose levels as the "most common end-point of measurement"[107] and could be used on its own to characterize diabetes risk. Along with blood glucose alterations, the studies EPA cited also consistently demonstrate impaired insulin resistance, further underscoring the evidence base as sufficient to characterize diabetes risk. In addition, EPA cannot dismiss toxicological evidence based on a lack of "robust epidemiological evidence" to support it while simultaneously limiting the epidemiologic evidence for

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[103] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 95.
[104] Zhang et al, 2017; Gu et al, 2016.
[105] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 94.
[106] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 95.
[107] King A. J. (2012). The use of animal models in diabetes research. British journal of pharmacology, 166(3), 877–894. https://doi.org/10.1111/j.1476-5381.2012.01911.x

consideration in dose-response assessment. Robust epidemiologic evidence is also *not* a requirement for POD/endpoint selection from animal toxicology studies, as outlined by best practices in systematic review.[108]

EPA also inappropriately dismissed neurotoxicity evidence, including a study by Feng et al (2020), which found statistically significant impairments in locomotion, spatial learning, and memory from DEHP exposures as low as 0.18 mg/kg-day. These findings were detected using well-established and widely accepted behavioral assays, the Open Field Test (OFT) and the Morris Water Maze (MWM) test, which have been foundational in neurotoxicology research for decades. This study additionally investigated potential underlying mechanisms, and found statistically significant, dose-responsive alterations to the cAMP-PKA-ERK1/2-CREB signaling pathway, a molecular mechanism critical to learning and memory.[109] EPA inappropriately dismissed this study for a number of reasons, including stating that the findings from the OFT and the MWM were "not specific to a neurotoxic effect and may indicate general decreased activity" or "decreased general condition".[110] This rationale is scientifically unsound. The OFT and MWM are robust, scientifically validated screening tests for neurobehavior, learning, and memory, and their consistent application across neurotoxicity studies reinforces, not undermines, the relevance of these results.

EPA later dismisses all cited neurotoxicity evidence based on the following uncertainties:

> All three studies were in mice, with no studies of rats or other species.[111]
>
> EPA determined that the vast majority of the findings in the study by Feng (2020) were most pronounced in the pubertal type 2 diabetes mellitus (P-T2DM) ICR mice; whereas the P-normal mice, while showing some statistically significant effects, were much more similar to controls and not reaching a level of adversity compared to the pubertal type 2 diabetes mellitus (P-T2DM) ICR mice.[112]
>
> EPA considers the effects in the three low-dose neurotoxicity studies of mice (Feng et al., 2020; Barakat et al., 2018; Tanida et al., 2009) to be inconsistent with dose-response for neurotoxic endpoints in other studies.[113]

[108] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, Chapters 6 and 7.
[109] Feng, W, et.al (2020). Typical neurobehavioral methods and transcriptome analysis reveal the neurotoxicity and mechanisms of di(2-ethylhexyl) phthalate on pubertal male ICR mice with type 2 diabetes mellitus. Archives of Toxicology, 94(4), 1279–1302. https://doi.org/10.1007/s00204-020-02683-9.
[110] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 118.
[111] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 119.
[112] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 119.
[113] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 120.

> [A] conclusion on the association between DEHP and neurological outcomes could not be reached due to the lack of substantive epidemiological data particularly on adults.[114]

First, it is arbitrary and unscientific for EPA to dismiss this entire evidence base because the three studies they selected only examined one species of rodent. Second, the presence of more pronounced effects in disease-susceptible animal models does not invalidate the statistically significant findings observed in healthy controls at very low levels of DEHP exposure (as low as 0.18 mg/kg-day, a level nearly 30 times lower than the selected 4.8 mg/kg-day POD). Third, EPA did not compare the findings from Feng et al. to other dose-response studies for the examined endpoints, and therefore cannot exclude this study because of inconsistencies with other dose-response studies. Moreover, EPA's dismissal based on lack of epidemiological data is inappropriate given that EPA did not conduct a robust evaluation of the epidemiologic evidence and no epidemiologic studies were included in dose-response evaluation. EPA therefore cannot use findings from an incomplete evidence base to dismiss entire categories of toxicological evidence. By disregarding statistically and biologically significant behavioral and mechanistic evidence of neurotoxicity, EPA fails to uphold its responsibility under TSCA to consider the best available science and all reasonably available information.

Overall, EPA's unduly narrow and methodologically flawed approach to hazard identification is alarming. Rather than applying a transparent systematic review framework, including consistent methods for evidence integration, EPA systematically dismissed critical health effects studies solely because their outcomes were not replicated in a limited and selectively curated subset of the literature. This circular logic imposes an unreasonable standard, requiring novel or sensitive endpoints must be independently validated by duplication in a literature base that EPA itself has already severely limited in scope.

This approach is inconsistent with the best available science and also violates TSCA's mandate to consider all reasonably available information. EPA cannot credibly conclude that DEHP lacks certain health effects while excluding or dismissing studies that offer direct evidence of those effects, especially when such studies have been used as the basis for protective actions by other authoritative bodies, including ATSDR, ECHA, and Health Canada. By disregarding high-quality data without adequate justification, EPA's risk evaluation severely underestimates the true hazard potential of DEHP and undermines public health protection, particularly for susceptible subpopulations.

In summary, EPA's current draft risk evaluation for DEHP fails to meet its obligations under TSCA to use the best available science and consider all reasonably available information. By arbitrarily excluding all epidemiologic evidence and a wide array of high-quality toxicological studies, including those demonstrating effects on female reproductive health, metabolism, liver function, neurodevelopment, and other endpoints, from dose response assessment, EPA has underestimated the hazards associated with DEHP and failed to protect public health. The Agency's reliance on an overly narrow set of studies and its dismissal of sensitive endpoints that have been recognized by other regulatory authorities undermines the credibility and scientific integrity of the evaluation.

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[114] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 120.

To comply with TSCA, EPA must revise its hazard assessment, starting with an improved evaluation of the scientific evidence, including:

- Implementing a gold-standard systematic review methodology that comprehensively evaluates *all* relevant health effects studies from *all* evidence streams;
- Conducting risk of bias and evidence integration analyses that do not arbitrarily exclude studies based on perceived methodological limitations or subjective judgments about study quality; and
- Applying benchmark dose modeling to sensitive endpoints, including those beyond male reproductive toxicity, such as female reproductive, metabolic, hepatic, and neurological effects (see section b below).

iii. EPA did not provide a clear summary judgment for each outcome.

Regarding the conclusions of hazard identification, the DEHP systematic review protocol references EPA's 2021 draft TSCA systematic review method for evidence integration procedures. The 2021 method identifies a specific set of hazard descriptors or "summary judgments" that are to be used for characterizing the evidence for each human health hazard assessed:[115]

- Evidence demonstrates
- Evidence indicates likely
- Evidence suggests but is not sufficient to conclude
- Evidence is inadequate
- Strong evidence supports no effect.

EPA's 2021 draft systematic review method explains that each health outcome assessed in a draft risk evaluation should be summarized with one of those five phrases:

> For each health effect or specific cancer type of potential concern, the first sentence of the narrative should include the summary judgment…These summary judgments provide a succinct and clear representation of the decisions from the more detailed analyses of whether (or not) the evidence indicates that chemical exposure has the potential to cause the human health effect(s) under the necessary conditions of exposure.[116]

EPA's hazard identification section for DEHP, however, does not make use of the summary judgment phrases or any other standardized hazard descriptors, and therefore lacks clear conclusions. EPA's conclusions for hazards of DEHP are:

[115] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, Table 7-14.

[116] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, p. 120.

> the effects on the developing female reproductive tract will not be considered further by EPA in dose-response analysis to derive a POD for human health risk assessment.[117]
>
> EPA is not further considering effects on metabolic syndrome and altered glucose/insulin homeostasis for dose-response analysis or for use in estimating risk to human health.[118]
>
> EPA is not further considering effects on the kidneys or cardiovascular outcomes for dose-response analysis or for use in estimating risk to human health.[119]
>
> EPA is not further considering liver effects for dose-response analysis or for use in estimating DEHP risk to human health.[120]
>
> EPA will not further consider the neurotoxicity studies…in dose-response analysis.[121]
>
> EPA is not considering the three immunotoxicity studies…further in dose-response analysis.[122]

EPA's conclusions lack use of any of its pre-specific summary judgment phrases (e.g., evidence indicates likely; evidence suggests but is not sufficient to conclude) or other clear hazard descriptors (e.g. probably toxic, possibly toxic), and generally skip past hazard identification to focus on EPA's decisions regarding whether to consider these outcomes in dose-response analysis – a separate step from evidence integration.

EPA's hazard identification is therefore critically deficient, violating basic principles and best practices in systematic review, both because it failed to consider all relevant evidence, and because it failed to apply standard summary judgments. EPA should start over on identifying hazards of DEHP by considering all relevant studies, conducting appropriate data extraction and study evaluation, and carrying through evidence synthesis and evidence integration to draw clear hazard conclusions for multiple DEHP hazards.

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

EPA should follow its own well-established guidance[123] and recommendations of the NASEM and SACC by conducting benchmark dose (BMD) modeling for all studies and endpoints listed

[117] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 71.
[118] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 95.
[119] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 102.
[120] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 112.
[121] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 120.
[122] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 125.
[123] U.S. EPA (2012). Benchmark Dose Technical Guidance.

in Table 4-3, any of which could conceivably yield a BMD lower confidence limit (BMDL) below EPA's chosen POD of 4.8 mg/kg-d. 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,[124]1,4-dioxane,[125] n-methylpyrrolidone,[126] and 1,3-butadiene.[127]

EPA discounted several studies that provide credible evidence that the selected NOAEL value of 4.8 mg/kg-d is not adequately protective of human health. Regarding a set of studies demonstrating male reproductive effects at the lowest dose tested, EPA says:

> Although these 11 studies consistently support a LOAEL of 10 mg/kg-day for DEHP, they are limited by dose-selection and did not test sufficiently low doses to establish a NOAEL. Therefore, EPA did not select any of these studies for deriving the POD because other, more sensitive developmental studies are available that evaluated doses below 10 mg/kg-day and allowed for a developmental NOAEL to be established. Instead, these studies comprise a robust database indicating a consensus LOAEL of 10 mg/kg-day and serve to refine the threshold at which treatment-related effects of DEHP occur.[128]

EPA has drawn an inappropriate conclusion regarding dose-response based on LOAELs when a more robust conclusion could be supported by BMD modeling. Multiple studies supporting a LOAEL of 10 mg/kg-d strongly suggest that if lower doses had been tested, they would indicate a NOAEL lower than 4.8 mg/kg-d. The appropriate treatment of these studies in dose-response assessment is not to reference them as supporting EPA's preferred POD or EPA's presumption of a threshold for effects (multiple studies with a LOAEL and no NOAEL actually undermine this presumption), but to conduct BMD modeling – which overcomes the limitations of study dose selection to better inform POD selection.

EPA did not conduct any BMD modeling for DEHP except for 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 DEHP resulting in a 5% decrease in fetal testosterone with a BMD of 17 mg/kg-day and a BMDL of 11 mg/kg-day. [129] EPA chose not to use the meta-regression BMDL as the POD because it identified a more sensitive POD for male reproductive effects. Selection of a lower POD is an appropriate scientific decision, but the comparison of a BMDL to a set of NOAELs and LOAELs, without

[124] U.S. EPA (2020). Risk Evaluation for Trichloroethylene, Tables 3-8 to 3-14.
[125] U.S. EPA (2020). Final Risk Evaluation for 1,4-Dioxane, Table 3-9.
[126] U.S. EPA (2020). Risk Evaluation for n-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP), Table 3-11.
[127] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene, Table 4-1.
[128] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), pp. 143-144.
[129] 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.

attempting BMD modeling of the data from which EPA identified the NOAELs and LOAELs, is not scientifically appropriate.

EPA's dose-response assessment for DEHP is not consistent with the best available science, as stated in EPA guidance[130] and reports from the NASEM.[131,132] EPA's 2012 Benchmark Dose Technical Guidance is unequivocal in describing the limitations of NOAEL/LOAELs and in stating a strong preference for BMDLs rather than NOAEL/LOAELs.

The BMD guidance represents the best available science, and it clearly states the significant limitations of NOAELs and 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 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%.[133]

[130] U.S. EPA (2012). Benchmark Dose Technical Guidance.
[131] NASEM (2017). Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals, p. 158.
[132] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 129.
[133] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 4.

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.[134]
>
> 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.[135]
>
> 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.[136]
>
> 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 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.[137]

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.[138]

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.[139]

[134] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 6.
[135] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 12.
[136] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 30.
[137] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 40.
[138] U.S. EPA (2020). Risk Evaluation for n-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP), p. 262.
[139] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, p. 8-1.

> Basis of the POD: A modeled BMDL is preferred over a NOAEL, which is in turn preferred over a LOAEL.[140]

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.[141]

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 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.[142]

EPA all disregarded all of the above guidance in its overall approach to dose-response assessment for DEHP. Its selection of 4.8 mg/kg-day as the POD is based on a summary of dose-response data from 17 studies, each of which is characterized only with a NOAEL or LOAEL.[143] 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.[144]

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[140] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, p. 8-18.
[141] NASEM (2017). Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals, p. 158.
[142] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 129.
[143] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), Table 4-3.
[144] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 15.

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 DEHP are very similar to those of its previous 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.[145]
>
> EPA should apply benchmark dose modeling to derive chronic non-cancer points of departure and select the one that is most sensitive (lowest).[146]

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:

> Shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science.[147]

EPA's dose-response analysis for DEHP 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.[148]
>
> EPA will document that the risk evaluation is consistent with the best available science.[149]

EPA's dose-response analysis for DEHP 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

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[145] 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.

[146] 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.

[147] 15 U.S.C. § 2625(h).

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

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

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's non-cancer margin of exposure (MOE) calculations are unreliable due to EPA's failure to conduct scientifically appropriate benchmark dose modeling.

To inform its determination of unreasonable risks of non-cancer effects from chronic exposure, EPA calculated a margin of exposure (MOE) for each DEHP condition of use (COU) using the POD (HED) of 1.1 mg/kg-day. The MOE is calculated as:

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

As discussed below, the MOE approach is a scientifically deficient method for characterizing risk and is inconsistent with amended TSCA's requirements to use the "best available science"[150] and to ensure protection of "potentially exposed and susceptible subpopulations" (PESS).[151]

In the DEHP Draft Risk Evaluation, the many shortcomings of EPA's MOE approach are exacerbated by EPA's failure to conduct appropriate dose-response modeling. EPA's calculated MOEs for DEHP are in question because of EPA's use of a NOAEL as the POD. Application of BMD modeling could result in a POD that is significantly lower than the NOAEL, which in turn would significantly reduce the calculated MOEs. COUs that currently have calculated MOEs up to 100 or even greater could conceivably be reduced to below EPA's benchmark MOE of 30 when recalculated with an appropriate POD, and should be provisionally considered contributors to unreasonable risk until EPA has conducted BMD modeling of multiple non-cancer endpoints and, preferably, conducted a probabilistic dose-response analysis, as described below, to replace the MOE approach.

DEHP COUs identified as not contributing to unreasonable risk and for which application of an improved POD could result in calculated MOEs less than 30 include:[152]

- Commercial use – automotive, fuel, agriculture, outdoor use products – lawn and garden care products;
- Commercial use – construction, paint, electrical, and metal products – batteries and capacitors;
- Commercial use – construction, paint, electrical, and metal products – construction and building materials covering large surface areas, including paper articles; metal articles; stone, plaster, cement, glass and ceramic articles;
- Commercial use – construction, paint, electrical, and metal products – machinery, mechanical appliances, electrical/electronic articles;
- 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;

[150] 15 U.S.C. § 2625(h).
[151] 15 U.S.C. § 2602(12).
[152] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), Tables 4-17, 4-18, and 6-1.

- Commercial use – packaging, paper, plastic, toys, hobby products – packaging (excluding food packaging) and other articles with routine direct contact during normal Use, including rubber articles; plastic articles (hard); plastic articles (soft);
- Commercial use – packaging, paper, plastic, toys, hobby products – packaging (excluding food packaging), including paper articles;
- Commercial use – packaging, paper, plastic, toys, hobby products – toys, playground, and sporting equipment;
- Commercial use – other uses – laboratory chemicals.
- Consumer use – construction, paint, electrical, and metal products – machinery, mechanical appliances, electrical/electronic articles
- Consumer use – furnishing, cleaning, treatment care products – fabric, textile, and leather products; furniture and furnishings
- Consumer use – packaging, paper, plastic, toys, hobby products – packaging (excluding food packaging) and other articles with routine direct contact during normal use, including rubber articles; plastic articles (hard); plastic articles (soft).

In addition, the Draft Occupational Exposure Value Derivation in Appendix F is similarly not scientifically defensible due to the failure to conduct BMD modeling in selecting a POD.[153] At a minimum, the draft occupational exposure value must be recalculated after conducting BMD modeling for multiple candidate endpoints and selection of a POD based on the BMDL values.

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

As discussed above, the draft DEHP risk evaluation continues EPA's practice of relying on the scientifically deficient MOE approach for non-cancer dose-response analysis and risk characterization in TSCA risk evaluations. The MOE approach 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.[154]
>
> 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.[155]

[153] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 327.

[154] 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

[155] 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

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."[156] 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.[157,158]

The National Academies[159] and the World Health Organization[160] (WHO) have outlined more robust methods for risk estimation that more accurately account for variability and vulnerability across the human population and have been demonstrated in published case studies.[161,162 ,163,164] We applied the WHO methodology to the DEHP endpoint of increased male reproductive tract malformations to estimate risk-specific doses for several levels of incidence (e.g. 1%, 0.1%, etc.) and at doses relevant to the DEHP Draft Risk Evaluation. Because EPA has not estimated BMDLs for the chronic effects of DEHP, we use the NOAEL of 4.8 mg/kg-d in rats from the critical study (Blystone et al.) identified by EPA as the starting point for this analysis; however we emphasize that selection of the POD and application of the WHO methodology would be better informed by BMD modeling for a range of studies and endpoints. We also applied the WHO methodology to the alternate POD of female reproductive effects, a LOAEL of 0.04 mg/kg-d in mice from a study by Zhang et al.[165] that was used as the POD in the 2022 ATSDR assessment of DEHP.[166]

Our analysis based on the Blystone et al. NOAEL of 4.8 mg/kg-d (see Technical Appendix for details) found that:

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[156] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 138.

[157] 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.

[158] 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.

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

[160] 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.

[161] 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.

[162] 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.

[163] 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.

[164] 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.

[165] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), Table 1-2.

[166] ATSDR (2022). Toxicological Profile for Di(2-Ethylhexyl)Phthalate (DEHP), p. A-13.

- 0.13 mg/kg-day is the lower bound (95% confidence) chronic human dose at which increased male reproductive tract malformations are expected in 10% of the exposed population;
- 0.08 mg/kg-day is the lower bound (95% confidence) chronic human dose at which increased male reproductive tract malformations are expected in 5% of the exposed population;
- 0.03 mg/kg-day is the lower bound (95% confidence) chronic human dose at which increased male reproductive tract malformations are expected in 1% of the exposed population;
- 0.012 mg/kg-day is the lower bound (95% confidence) chronic human dose at which increased male reproductive tract malformations are expected in 0.1% of the exposed population;
- 0.005 mg/kg-day is the lower bound (95% confidence) chronic human dose at which increased male reproductive tract malformations are expected in 0.01% 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 1.1 mg/kg-day (the HED for the NOAEL of 4.8 mg/kg-d) and a benchmark MOE of 30, meaning that EPA concludes "risk is not considered to be of concern and mitigation is not needed"[167] for any DEHP exposure below 0.04 mg/kg-day (1.1 mg/kg-day / 30 = 0.04 mg/kg-day). Our analysis finds that an exposure of 0.04 mg/kg-day is the lower-bound dose for the 1.25% (1-in-80) 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.[168]

Example results for the alternate analysis (see Technical Appendix for details), based on the Zhang et al. LOAEL of 0.04 mg/kg-d for female reproductive effects, include:

- 0.0001 mg/kg-day is the lower bound (95% confidence) chronic human dose at which increased female reproductive effects are expected in 5% of the exposed population;
- 0.00004 mg/kg-day is the lower bound (95% confidence) chronic human dose at which increased female reproductive effects are expected in 1% of the exposed population.

EPA should apply the WHO framework to multiple male and female reproductive endpoints of DEHP (including but not limited to those included in Table 4-3 of the DEHP draft non-cancer hazard assessment), using BMDLs instead of the NOAELs/LOAELs as the starting point, and should also apply the framework to other non-cancer endpoints of DEHP with BMD-derived PODs for comparison.

3. EPA's approach systematically underestimates real-world DEHP exposures.

[167] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 138.
[168] U.S. EPA (2024). Unreasonable Risk Determination of the Draft Risk Evaluation for Formaldehyde, p. 13.

The DEHP Draft Risk Evaluations fails to adequately consider and quantify multiple known or foreseeable exposures to DEHP, thereby understating the extent of these exposures. This oversight violates TSCA's mandates to "integrate and assess available information on . . . exposures for the conditions of use" of a chemical,[169] and EPA's regulatory mandate to "assess all exposure routes and pathways relevant to [a] chemical substance under the conditions of use."[170] EPA must consider the following DEHP exposures, which it failed to adequately assess in the DEHP Draft Risk Evaluation. **These scenarios are described in greater detail in the comments of Earthjustice:**

A. **EPA failed to evaluate worker exposures to DEHP, 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 DEHP. 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 DEHP exposures from plastic agricultural films:** EPA does consider exposures from plastic agriculture films that contain DEHP, 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 exposures to DEHP from prior-sanctioned use in food packaging:** EPA's exclusion of DEHP exposures from food packaging materials for food with high water content in its risk evaluation is based on an incorrect interpretation of TSCA's definition of "chemical substance."[171] While food additives are excluded, DEHP's prior-sanctioned uses in food packaging are not. These uses

[169] 15 U.S.C. § 2605(b)(4)(i).
[170] 40 C.F.R. § 702.39(d)(9).
[171] 15 U.S.C. § 2602(2).

must be considered in the risk evaluation as they represent a significant exposure pathway that cannot be ignored. EPA must include these exposures in its final risk assessment to comply with TSCA's requirements.

D. **EPA failed to consider exposure to DEHP from microplastics:** EPA fails to account for exposures to DEHP from microplastics, which are a known and reasonably foreseen source of DEHP exposure[172] that can exacerbate the harmful effects of DEHP 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 disorders, reproductive harm, and cancer,[173] many of the same health effects that are linked to DEHP. Microplastics have been located virtually everywhere they have been studied, including in the human body[174,175,176,177] and in environmental media like surface water, coastal beaches, sediment, fresh water, air, and food.[178] Microplastics can also persist and bioaccumulate in living organisms, increasing the risk for long-term exposures to chemicals found within common microplastics, like DEHP.[179] 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.

E. **EPA understates DEHP exposures in vehicles:** EPA underestimates exposures to DEHP 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 DEHP Draft Risk Evaluation also fail to account for off-gassing

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[172] 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.

[173] 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

[174] 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

[175] 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

[176] 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.

[177] 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

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

[179] 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.

of DEHP at elevated temperatures inside vehicles. EPA must consider all known and reasonably foreseen exposures within vehicles to provide a comprehensive risk assessment.

F. **EPA understates DEHP 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 DEHP. EPA must use a more representative home size, such as 154 cubic meters, to accurately assess risks for individuals in smaller living environments.

G. **EPA failed to quantify exposures from groundwater, biosolids, and landfills:** EPA's decision not to conduct quantitative assessments of DEHP 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.

H. **EPA failed to measure down-the-drain exposures from products containing DEHP:** EPA does not measure exposures from the down-the-drain disposal of consumer products containing DEHP, 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 DEHP and provide a quantitative assessment of these releases and their associated risks.

I. **EPA failed to adequately quantify all reasonably foreseeable DEHP 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 DEHP 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 DEHP.

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

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

The DEHP 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 DEHP 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.[180]

In an important improvement, EPA considered aggregate exposure to DEHP 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 DEHP 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 DEHP 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 DEHP-containing consumer products.

[180] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 131-132.

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,[181] and to identify and eliminate unreasonable risks to potentially exposed or susceptible subpopulations,[182] 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."[183] 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 settings in the final DEHP 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 DEHP 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.[184] DEHP is primarily used as a plasticizer in manufacturing adhesives, paints and coatings, plastic and rubber products, and plastic resins, it is also used as a stabilizing agent in the manufacturing of these products.[185]

EPA failed to account for these multiple sources of exposure in their assessment of unreasonable risk in the DEHP 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.[186] 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 DEHP 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.[187] 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."[188] The NASEM recommends consideration of background exposures when conducting a risk evaluation for both individual chemicals and categories of chemicals through a cumulative risk

[181] 15 U.S.C. § 2625(h).
[182] 15 U.S.C. § 2605(b)(4)(A).
[183] 15 U.S.C. § 2605(a).
[184] U.S. EPA (2024). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 11.
[185] U.S. EPA (2024). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p.11.
[186] U.S. EPA (2024). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 240.
[187] 15 U.S.C. § 2602(4).
[188] 15 U.S.C. § 2625(h).

assessment,[189] citing that background exposures at "even small doses may have a relevant biological effect."[190]

Given the widespread exposure to DEHP 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 DEHP in the human body, even if EPA may not be able to directly regulate some of these uses under TSCA. EPA's must consider all exposures that are currently happening for the general population and potentially exposed or susceptible subpopulations or it will significantly underestimate risk.

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.[191]

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.[192]

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.[193] EPA's

[189] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, pp. 135, 136, and 214.
[190] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 130.
[191] 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.
[192] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act.
[193] Sulfuryl Fluoride; Proposed Order Granting Objections to Tolerances and Denying Request for Stay, 76 Fed. Reg. 3,422-01 (Jan. 19, 2011).

plan to exclude from consideration uses of DEHP 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 DEHP Draft Risk Evaluation so it addresses all sources and pathways of DEHP 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 DEHP 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.[194]

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.[195] In comparison, EPA's DINP draft risk evaluation identifies multiple consumer conditions of use with much greater exposures[196] – 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

[194] 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, 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.

[195] 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.

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

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; and all 6 are used in consumer paints and coatings.[197] 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 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 DEHP Draft Risk Evaluation.[198] 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 DEHP exposures.

[197] 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.
[198] 15 U.S.C. § 2605(b)(4)(A).

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.[199]

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 from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, the elderly, or overburdened communities.[200]

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.[201] 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.[202]

EPA has not yet proposed such a methodology. The DEHP Draft Risk Evaluation is particularly deficient in its failure to present any structured approach for the identification of PESS. The DEHP 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 DEHP, people exposed to DEHP in the workplace, people in close proximity to releasing

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[199] 15 U.S.C. § 2605(b)(4)(A).

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

[201] 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.

[202] 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].

> facilities (fenceline communities), and Tribes and subsistence fishers whose diets include large amounts of fish.[203]

The DEHP 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.[204] 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 DEHP 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, nutrition, genetics/epigenetics, and other chemical and non-chemical stressors. However, EPA failed to fully consider all PESS within each category identified for DEHP.[205]

Further, the DEHP 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 DEHP 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 DEHP. 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 (2002b) did not discuss all the factors presented in Table 5-1. Thus, **uncertainty remains regarding whether these additional susceptibility factors would be covered by the default UF_H value of 10 chosen for use in the DEHP risk evaluation**.[206] (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

[203] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 13.
[204] U.S. EPA (2025). Draft Non-Cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 161, Table 5-1.
[205] U.S. EPA (2025). Draft Non-Cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 161, Table 5-1.
[206] U.S. EPA (2025). Draft Non-Cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), p. 159

factor falls short of capturing the full range of human responses to chemical exposures, especially for susceptible subgroups.[207] 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.[208] The World Health Organization's 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.[209] 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.[210,211] Had EPA applied this uncertainty factor to its risk calculations in the DEHP 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):

- **Furnishing, cleaning, treatment care products: Furniture textile components for**
    - Acute, ingestion, high-end exposure for infants (<1 year)
    - Acute, inhalation, acute, high-end exposure for ages <1 year—15 years old
    - Acute, aggregate dermal, ingestion, inhalation, high-end exposure for ages <1 year—15 years old
    - Chronic, ingestion, high-end exposure for infants (<1 year)
    - Chronic, inhalation, high-end exposure for ages <1 year—10 years old
    - Chronic, aggregate dermal, ingestion, and inhalation high-end exposure for ages <1 year—15 years old
    - Chronic, aggregate dermal, ingestion, and inhalation medium-end exposure for preschoolers (3-5 years)
- **Construction, paint, electrical, and metal products: Insulated cords for**
    - Acute, ingestion, high-end exposure for infants (<1 year)

[207] 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.

[208] 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.

[209] 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.

[210] 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.

[211] 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.

    - Acute, aggregate dermal, ingestion, and inhalation high-end exposure for infants (<1 year)
    - Chronic, ingestion, high-end exposure for infants (<1 year)
    - Chronic, aggregate dermal, ingestion, and inhalation high-end exposure for infants (<1 year)
- **Packaging, paper, plastic, toys, hobby products: Air beds for**
    - Acute, dermal, high-end exposure for infants (<1 year)
    - Acute, aggregate dermal, ingestion, and inhalation high-end exposure for ages <1 year—2 years
- **Packaging, paper, plastic, toys, hobby products: Shower curtains for**
    - Acute, inhalation, high-end exposure for ages <1 year—10 years
    - Acute, aggregate dermal, ingestion, and inhalation high-end exposure for ages <1 year—10 years
    - Chronic, inhalation, high-end exposure for ages <1 year—10 years
    - Chronic, aggregate dermal, ingestion, and inhalation high-end exposure for ages <1 year—10 years
- **Packaging, paper, plastic, toys, hobby products: Children's toys (legacy)**
    - Acute, ingestion, high-end exposure for infants (<1 year)
    - Acute, inhalation, high-end exposure for ages <1 year—5 years
    - Acute, aggregate dermal, ingestion, and inhalation high-end exposure for ages <1 year—5 years
    - Chronic, ingestion, high-end exposure for infants (<1 year)
    - Chronic, inhalation, high-end exposure for ages <1 year—5 years
    - Chronic, aggregate dermal, ingestion, and inhalation high-end exposure for ages <1 year—5 years
- **Packaging, paper, plastic, toys, hobby products: Children's toys (new)**
    - Acute, ingestion, high-end exposure for infants (<1 year)
    - Acute, aggregate dermal, ingestion, and inhalation high-end exposure for infants (<1 year)
    - Chronic, ingestion, high-end exposure for infants (<1 year)
    - Chronic, aggregate dermal, ingestion, and inhalation high-end exposure for infants (<1 year)

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.[212]

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.[213] 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.[214] 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 DEHP Draft Risk Evaluation. This is particularly relevant when assessing risk to residents of fenceline communities or other susceptible subgroups 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 DEHP 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

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[212] 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/.

[213] 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.

[214] *Id.*

compared to other racial groups in the U.S. population.[215] 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:

- **Construction, paint, electrical, and metal products: Inductance loop sealant;** for Acute, dermal, high-end exposure for ages 11+
- **Furnishing, cleaning, treatment care products: Clothing;** for Acute, dermal, medium-end exposure for ages 11+
- **Furnishing, cleaning, treatment care products: Furniture textile components for**
    - Acute, dermal, medium-end exposure for ages 3+
    - Acute, dermal, low-end exposure for ages 1-5 years
    - Acute, ingestion, high-end exposure for ages <1 year—5 years
    - Acute, ingestion, medium-end exposure for ages <1 year—5 years
    - Acute, inhalation, acute, high-end exposure for **all age groups**
    - Acute, inhalation, acute, medium-end exposure **for all age groups**
    - Acute, aggregate dermal, ingestion, inhalation, high-end exposure for **all age groups**
    - Acute, aggregate dermal, ingestion, inhalation, medium-end exposure for **all age groups**
    - Acute, aggregate dermal, ingestion, inhalation, low-end exposure for ages 1-5 years
    - Chronic, dermal, medium-end exposure for ages 3+
    - Chronic, dermal, low-end exposure for ages 1-5 years
    - Chronic, ingestion, high-end exposure for ages <1 year—5 years
    - Chronic, ingestion, medium-end exposure for ages <1 year—5 years
    - Chronic, inhalation, high-end exposure for **all age groups**
    - Chronic, inhalation, medium-end exposure for **all age groups**
    - Chronic, aggregate dermal, ingestion, and inhalation high-end exposure for **all age groups**
    - Chronic, aggregate dermal, ingestion, and inhalation medium-end exposure for **all age groups**
    - Chronic, aggregate dermal, ingestion, and inhalation low-end exposure for ages 1-5 years
- **Furnishing, cleaning, treatment care products: Vinyl flooring for**
    - Acute, dermal, high-end exposure for **all age groups**
    - Acute, inhalation, high-end exposure for **all age groups**
    - Acute, aggregate dermal and inhalation high-end exposure for **all age groups**

[215] 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

    - Chronic, dermal, high-end exposure for **all age groups**
    - Chronic, inhalation, high-end exposure for **all age groups**
    - Chronic, aggregate dermal, ingestion, and inhalation high-end exposure for **all age groups**
- **Furnishing, cleaning, treatment care products: Wallpaper (installation) for** Acute, dermal, high-end exposure for ages 11+
- **Construction, paint, electrical, and metal products: Insulated cords for**
    - Acute, ingestion, high-end exposure for ages <1 year—5 years
    - Acute, aggregate dermal, ingestion, and inhalation high-end exposure for ages <1 year—5 years
    - Chronic, ingestion, high-end exposure for ages <1 year—5 years
    - Chronic, aggregate dermal, ingestion, and inhalation high-end exposure for ages <1 year—5 years
- **Other: Novelty articles: Adult toys for**
    - Acute, ingestion, medium-end exposure for ages 16+
    - Acute, aggregate dermal and ingestion medium-end exposure for ages 16+
    - Chronic, ingestion, medium-end exposure for ages 16+
    - Chronic, aggregate dermal and ingestion medium-end exposure for ages 16+
- **Packaging, paper, plastic, toys, hobby products: Air beds for**
    - Acute, dermal, high-end exposure for **all age groups**
    - Acute, inhalation, high-end exposure for ages <1 year—5 years
    - Acute, aggregate dermal, ingestion, and inhalation high-end exposure for **all age groups**
    - Chronic, dermal, high-end exposure for infants (<1 year)
    - Chronic, inhalation, high-end exposure for ages <1 year—5 years
    - Chronic, aggregate dermal, ingestion, and inhalation high-end exposure for ages <1 year—15 years
- **Packaging, paper, plastic, toys, hobby products: Mobile phone covers for**
    - Acute, dermal, high-end exposure for ages <1 year—15 years, 21+ years
    - Chronic, dermal, high-end exposure for ages <1 year—15 years, 21+ years
- **Packaging, paper, plastic, toys, hobby products: Eraser**
    - Acute, ingestion, high-end exposure for ages 5—10 years
    - Chronic, ingestion, high-end exposure for ages 5—10 years
- **Packaging, paper, plastic, toys, hobby products: Shower curtains for**
    - Acute, inhalation, high-end exposure for **all age groups**
    - Acute, aggregate dermal, ingestion, and inhalation high-end exposure for **all age groups**
    - Chronic, inhalation, high-end exposure for **all age groups**
    - Chronic, aggregate dermal, ingestion, and inhalation high-end exposure for **all age groups**
- **Packaging, paper, plastic, toys, hobby products: Children's toys (legacy)**
    - Acute, dermal, high-end exposure for ages <1 year—5 years
    - Acute, ingestion, high-end exposure for ages <1 year—5 years

    - Acute, inhalation, high-end exposure for **all age groups**
    - Acute, aggregate dermal, ingestion, and inhalation high-end exposure for **all age groups**
    - Chronic, dermal, high-end exposure for ages <1 year—5 years
    - Chronic, ingestion, high-end exposure for ages <1 year—5 years
    - Chronic, inhalation, high-end exposure for **all age groups**
    - Chronic, aggregate dermal, ingestion, and inhalation high-end exposure for **all age groups**
- **Packaging, paper, plastic, toys, hobby products: Children's toys (new)**
    - Acute, dermal, high-end exposure for ages <1 year—5 years
    - Acute, ingestion, high-end exposure for ages <1 year—5 years
    - Acute, aggregate dermal, ingestion, and inhalation high-end exposure for ages <1 year—10 years
    - Chronic, dermal, high-end exposure for ages <1 year—5 years
    - Chronic, ingestion, high-end exposure for ages <1 year—5 years
    - Chronic, aggregate dermal, ingestion, and inhalation high-end exposure for ages <1 year—10 years
- **Construction, paint, electrical, and metal products: Auto coatings for**
    - Chronic, inhalation, high-end exposure for **all age groups**
    - Chronic, aggregate inhalation and dermal high-end exposure for **all age groups**
- **Construction, paint, electrical, and metal products: Concrete sealant for**
    - Acute, aggregate dermal and inhalation high-end exposure for ages 11+

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 improperly determined that disposal of DEHP does not pose an unreasonable risk to workers by disregarding high-end exposure and risk estimates.

In the DEHP Draft Risk Evaluation, EPA determined that 13 occupational conditions of use (COUs) "may significantly contribute to unreasonable risk," and 17 worker COUs do not contribute to unreasonable risk. For each COU, EPA provides a "central tendency" and "high-end" exposure estimate; 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…EPA preferred to provide the 50th percentile of the distribution. However, if the full distribution was unknown, EPA used either the mean, 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 risk evaluation, EPA provided high-end results at the 95th percentile. If the 95th percentile was not reasonably available, the Agency 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.[216]

For the Disposal COU, EPA's high-end margin of exposure (MOE) for workers at acute, intermediate and chronic durations are all less than 10 – well below EPA's "benchmark MOE" of 30, and therefore indicating a high level of risk. EPA, however, did not identify Disposal as a COU contributing to unreasonable risk for workers. For this COU, EPA disregarded the high-end estimates, saying that

> EPA considers central tendency values of exposure to be most representative of worker exposures…The high-end estimates are more likely to occur under the more conservative combination of [model] parameters.[217]

EPA does not provide evidence to support the notion that its high-end estimate is unrealistic; rather this statement indicates that the estimate represents unusual or uncertain circumstances that correspond to a high-end estimate. Further, EPA's statement that the central tendency estimates are "most representative" is simply a reiteration of the definition of central tendency and not a rationale for disregarding risks to workers with exposures that are greater-than-typical.

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[218] 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 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.[219]

The practice of utilizing high-end exposure estimates is scientifically well-supported and is consistent with both the requirements of TSCA[220] and previous TSCA risk evaluations. This

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[216] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 77.
[217] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), pp. 158-159.
[218] 15 U.S.C. § 2605(b)(4)(A).
[219] 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.
[220] 15 U.S.C. § 2605(b)(4)(A).

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.[221] 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 the Disposal COU. EPA's conclusion regarding the worker exposure estimates for this COU states:

> EPA has concluded that the weight of scientific evidence for this assessment provides moderate confidence in the estimate of exposures in consideration of the strengths and limitations of reasonably available data.[222]

EPA then describes the strengths of its occupational exposure assessment:

> A strength of the modeling assessment includes the consideration of variable model input parameters as opposed to using a single static value. Parameter distributions increase the variability of modeled exposures and the likelihood that the exposure estimates are more representative of the true distribution. An additional strength is that all data that EPA used to inform the modeling parameter distributions have overall data quality ratings of either high or medium.[223]

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 true distribution of each of the model input parameters.[224]

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.[225]

EPA's conclusions regarding the exposure estimates for the Disposal COU do not indicate any concerns about the high-end exposure estimates. EPA does not provide evidence in the DEHP

[221] 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
[222] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 96.
[223] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 99.
[224] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 100.
[225] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 159.

Draft Risk Evaluation for its claims that the high-end estimates are not representative of exposures for at least some disposal workers. EPA further does not present evidence that central tendency estimates will not underestimate exposures and risks for significant proportions of workers in this 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.

b. EPA improperly determined that consumer exposure to DEHP in furniture does not pose an unreasonable risk to infants and toddlers by disregarding high-intensity exposure and risk estimates.

EPA determined that no consumer COUs, out of 16 evaluated, pose an unreasonable risk. However, it reached this conclusion by applying 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 were below the benchmark of 30 for the high-intensity use scenario, EPA reevaluated the approaches and inputs used and determined if refinement of those was needed. In addition, EPA considered 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. [226]

EPA should not disregard elements of its exposure assessment based on risk characterization results. TSCA requires EPA to use the "best available science"[227] considering "reasonably available"[228].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 furniture COU.

EPA's risk characterization found that aggregate high-intensity acute exposures to DEHP in furniture pose a risk to infants, with an MOE of 30 that is equal to EPA's benchmark MOE.

[226] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 180.
[227] 15 U.S.C. § 2625(h).
[228] 15 U.S.C. § 2625(k).

After calculating the MOE in the risk characterization section, EPA then dismissed the high-intensity scenario for only this COU in the unreasonable risk determination section, saying that:

> The high-intensity was chosen for all COUs, except for Consumer use – furnishing, cleaning, treatment/care products – fabric, textile, and leather products; furniture and furnishings. For this COU, although dermal contact with synthetic leather furniture may be possible for infants and toddlers, it is expected to be minimal. Infants are not likely to be set on furniture for extended periods of time (*i.e.,* 2–8 hours) for safety reasons, and toddlers are unlikely to stay seated for the 4-hour exposure duration used in the medium-intensity use dermal assessment.[229]

EPA does not present evidence to justify its assertions that infants and toddlers are unlikely to be in contact with leather furniture for multiple hours in a day; further, the contact with the furniture need not be continuous, and multiple hours of contact in a day could reasonably occur on an occasional basis, which could result in acute (24-hour) exposures of concern. Infants and toddlers may stay in place on furniture for extended durations in certain circumstances. For example, during a single day a toddler may be seated or laying on a synthetic leather couch to watch television, view videos or play games on an iPad, sit with a parent who is reading a book to them, and take a nap. EPA should not disregard its high-intensity exposure and risk estimates and should find unreasonable risk for this COU.

[229] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 251.

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

In the *Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP)*, EPA selected increased male reproductive tract malformations for estimation of risks from chronic oral exposures. The draft TSCA risk evaluation calculates a "margin of exposure" (MOE) for each exposure scenario, which is the ratio of the point of departure (POD) to the exposure level. For the DEHP malformations, the *DEHP Draft Risk Evaluation* concludes that an MOE of 30 or more indicates that "risk is not considered to be of concern and mitigation is not needed."[230]

EPA's approach to risk characterization does not actually estimate risks of adverse effects in the population with chronic exposure to DEHP, 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),[231] 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.[232,233,234,235,236]

We applied the IPCS approach for "quantal-deterministic" endpoints and the "approximate probabilistic" calculation (see IPCS report Fig 3.5, panel C)[237] to estimate risks of malformations from chronic oral exposure to DEHP. The analysis involved the following steps:

1. Derivation of IPCS POD and corresponding uncertainty adjustments
2. Application of interspecies adjustments
3. Application of intraspecies adjustments

[230] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 138.

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

[232] 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

[233] 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

[234] 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

[235] 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

[236] 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

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

4. Calculation of HD_M^I - the human dose (HD) of DEHP associated with a particular magnitude of effect M at a particular population incidence I.

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.

We demonstrate each of these steps starting with the EPA-determined no-observed-adverse-effect level (NOAEL) (i.e. the chronic oral POD in applied dose units) to derive a set of oral HD_M^I values for different levels of population incidence. Use of a benchmark dose (BMD) is preferred as the starting point for application of the WHO/IPCS framework, but EPA did not conduct BMD modeling for the male reproductive tract malformations endpoint or other candidate PODs.

We also conducted a second application of the IPCS framework using a LOAEL for female reproductive effects. This alternate analysis is presented below following the results for the application to male reproductive tract malformations.

STEP 1: Derivation of IPCS POD and corresponding uncertainty adjustments

The IPCS methodology requires the use of an ED_{50} (median effective dose) value as the POD for quantal-deterministic endpoints. Since an ED_{50} is not available from the EPA risk evaluation, we began with EPA's NOAEL, which 4.8 mg/kg-day, and applied adjustments provided by the IPCS methodology. Uncertainty in the NOAEL estimate is unquantified, which is represented by a P95/P50 value of 1.

To estimate an ED_{50} from a NOAEL for a quantal-deterministic developmental toxicity endpoint, the IPCS framework multiplies the NOAEL by 2/9 (central estimate, or P50) with uncertainty (P95/P50) equal to 5.0.[238] The adjustment from the NOAEL to ED_{50} to derive the IPCS POD is entered in the IPCS approximate probabilistic calculation template as follows:

[238] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.1.

Determination of point of departure (POD) and its uncertainty[a] for probabilistic dose-response analysis of chronic oral exposure to DEHP: increased male reproductive tract malformations		
Aspect	**P50**	**P95/P50**
NOAEL	4.8 mg/kg-d	1[b]
NOAEL-to-ED_{50} adjustment	0.22[c]	5[c]
IPCS POD = ED_{50}	**21.6 mg/kg-d[d]**	**5[e]**

[a] Uncertainty is expressed as the ratio of the 95th percentile (P95) to the 50th percentile (P50)
[b] No estimate of uncertainty for the NOAEL is available, so P95/P50 = 1
[c] IPCS Table 4.1: quantal (deterministic) - developmental effects
[d] IPCS POD = (4.8 mg/kg-d) / 0.22 = 12.6 mg/kg-d
[e] (Composite P95/P50) = $10^{[(\log 1)^2 + (\log 5)^2]^{0.5}} = 5$

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)[239] using IPCS formulas 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.[240] We incorporated these IPCS recommendations, which are entered In the IPCS approximate probabilistic calculation template as follows:

[239] U.S. EPA (2024). Draft Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), Appendix D.
[240] 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 DEHP: increased male reproductive tract malformations		
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**
10%[a]	3.49	2.24
5%[a]	4.98	2.82
1.25%[b]	8.92	4.10
1%[a]	9.69	4.32
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 the developmental effect of male reproductive tract malformations. 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 DEHP: increased male reproductive tract malformations (Incidence = 5%)		
Aspect	**P50**	**P95/P50**
NOAEL	4.8 mg/kg-d	1
NOAEL-to-ED_{50} adjustment	0.22	5
IPCS POD = ED_{50}	**21.6 mg/kg-d**	**5**
$AF_{Interspecies-BS}$	5.64	1.26
$AF_{Interspecies-TK/TD}$	1	3
$AF_{Intra-I=5\%}$	4.98	2.82
HD_M^I	0.77 mg/kg-d[a]	9.2[b]
	P05	**P95**
HD_M^I [(c)]	**0.08 mg/kg-d**	7.1 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) = $10^{[(\log 5)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 2.82)^2]^{0.5}} = 9.2$
[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 DEHP: increased male reproductive tract malformations (Incidence = 1%)		
Aspect	**P50**	**P95/P50**
NOAEL	4.8 mg/kg-d	1
NOAEL-to-ED_{50} adjustment	0.22	5
IPCS POD = ED_{50}	**21.6 mg/kg-d**	**5**
$AF_{Interspecies-BS}$	5.64	1.26
$AF_{Interspecies-TK/TD}$	1	3
$AF_{Intra-I=1\%}$	9.69	4.32
HD_M^I	0.40 mg/kg-d[a]	11.6[b]
	P05	**P95**
HD_M^I [(c)]	**0.03 mg/kg-d**	4.6 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) = $10^{[(\log 5)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 4.32)^2]^{0.5}} = 11.6$
[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.[241]
>
> 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.[242]

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).[243]

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).

[241] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 140.
[242] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 140.
[243] 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 DEHP: increased male reproductive tract malformations	
Incidence (I)	**HD_M[I] lower -confidence limit (P05)**
10%	0.13 mg/kg-day
5%	0.08 mg/kg-day
1.25%	0.04 mg/kg-day
1%	0.03 mg/kg-day
0.5%	0.02 mg/kg-day
0.1% (1-in-1,000)	0.012 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 DEHP male reproductive tract malformation from chronic exposures, using the Blystone et al. NOAEL of 4.8 mg/kg-d, we find that:

- 0.13 mg/kg-day is the lower bound (95% confidence) chronic human dose at which increased male reproductive tract malformations are expected in 10% of the exposed population;
- 0.08 mg/kg-day is the lower bound (95% confidence) chronic human dose at which increased male reproductive tract malformations are expected in 5% of the exposed population;
- 0.03 mg/kg-day is the lower bound (95% confidence) chronic human dose at which increased male reproductive tract malformations are expected in 1% of the exposed population;
- 0.012 mg/kg-day is the lower bound (95% confidence) chronic human dose at which increased male reproductive tract malformations are expected in 0.1% of the exposed population;
- 0.005 mg/kg-day is the lower bound (95% confidence) chronic human dose at which increased male reproductive tract malformations are expected in 0.01% 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 1.1 mg/kg-day (the HED for the NOAEL of 4.8 mg/kg-d) and a benchmark MOE of 30, meaning that EPA

concludes "risk is not considered to be of concern and mitigation is not needed"[244] for any DEHP exposure below 0.04 mg/kg-day (1.1 mg/kg-day / 30 = 0.04 mg/kg-day). Our analysis finds that an exposure of 0.04 mg/kg-day is the lower-bound dose for the 1.25% (1-in-80) 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.[245]

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 Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP)*. 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.[246,247,248] 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.

Alternate analysis with LOAEL for female reproductive effects

In contrast to EPA's selection of the Blystone et al. NOAEL of 4.8 mg/kg-d as POD, the Agency for Toxic Substances and Disease Registry (ATSDR) published an assessment of DEHP in 2022[249] that used a LOAEL of 0.04 mg/kg-d for female reproductive effects in mice from a study by Zhang et al.[250] as the POD. We therefore also applied the IPCS framework using the Zhang et al. LOAEL.

For this alternate analysis, the value of the IPCS POD is changed due to the difference in starting value (0.04 mg/kg-d) and the addition of an adjustment factor for extrapolation from a LOAEL to a NOAEL. These revised steps to derive the IPCS POD are entered in the IPCS approximate probabilistic calculation template as follows:

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[244] U.S. EPA (2025). Draft Risk Evaluation for Diethylhexyl Phthalate (DEHP), p. 138.

[245] U.S. EPA (2024). Unreasonable Risk Determination of the Draft Risk Evaluation for Formaldehyde, p. 13.

[246] 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

[247] 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

[248] 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

[249] ATSDR (2022). Toxicological Profile for Di(2-Ethylhexyl)Phthalate (DEHP), p. A-13.

[250] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), Table 1-2.

Determination of point of departure (POD) and its uncertainty[a] for probabilistic dose-response analysis of chronic oral exposure to DEHP: female reproductive effects		
Aspect	**P50**	**P95/P50**
LOAEL	0.04 mg-kg-day	1[b]
$AF_{LOAEL\text{-}to\text{-}NOAEL}$[c]	3	3
$AF_{NOAEL\text{-}to\text{-}ED50}$[d]	0.22	5
IPCS POD = ED_{50}	**0.06 mg/kg-day[e]**	**7.02[f]**

[a] Uncertainty is expressed as the ratio of the 95th percentile (P95) to the 50th percentile (P50)
[b] No estimate of uncertainty for the NOAEL is available, so P95/P50 = 1
[c] P50 value of 3 for the LOAEL adjustment factor is applied. ATSDR applied a LOAEL-to-NOAEL uncertainty factor of 10 (ATSDR p. A-15); use of this value for the P50 value would be appropriate and consistent with the IPCS adjustment factor (per Chiu et al. (2018), Table 4) and would result in lower HD_M^I estimates.
[d] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.1
[e] IPCS POD = (0.04 mg/kg-d) / (3 x 0.22) = 0.06 mg/kg-d
[f] (Composite P95/P50) = $10^{[(\log 1)^2 + (\log 3)^2 + (\log 5)^2]^{0.5}} = 7.02$

An additional difference for this alternate analysis is in the $AF_{Interspecies\text{-}BS}$, since the Zhang et al. LOAEL is obtained from a study in mice whereas the Blystone et al. NOAEL was obtained from a study in rats. We applied EPA's assumptions for human body weight (80 kg) and mouse body weight (0.025 kg)[251] using IPCS formulas to derive the appropriate central tendency (P50) factor and its uncertainty (P95/P50).

Interspecies adjustments for probabilistic dose-response analysis of chronic oral exposure to DEHP: female reproductive effects		
Aspect	**P50**	**P95/P50**
$AF_{Interspecies\text{-}BS}$	11.26[a]	1.38[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 mice (0.025 kg).

[251] U.S. EPA (2024). Draft Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), Appendix D.

No changes to the $AF_{Intraspecies}$ factors presented above are necessary for this alternate analysis.

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 $AF_{Intraspecies}$.

Calculation of HD_M^I for chronic oral exposure to DEHP: female reproductive effects (Incidence = 5%)		
Aspect	**P50**	**P95/P50**
LOAEL	0.04 mg-kg-day	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$	3	3
$AF_{NOAEL\text{-}to\text{-}ED50}$	0.22	5
IPCS POD = ED_{50}	**0.06 mg/kg-day**	**7.02**
$AF_{Interspecies\text{-}BS}$	11.26	1.38
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intra\text{-}I=5\%}$	4.98	2.82
HD_M^I	0.0011 mg/kg-d[a]	12.02[b]
	P05	**P95**
$HD_M^{I\,(c)}$	**0.0001 mg/kg-d**	0.013 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 7.02)^2 + (\log 1.38)^2 + (\log 3)^2 + (\log 2.82)^2]^{0.5}} = 12.02$
[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 DEHP: female reproductive effects (Incidence = 1%)		
Aspect	**P50**	**P95/P50**
LOAEL	0.04 mg-kg-day	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$	3	3
$AF_{NOAEL\text{-}to\text{-}ED50}$	0.22	5
IPCS POD = ED_{50}	**0.06 mg/kg-day**	**7.02**
$AF_{Interspecies\text{-}BS}$	11.26	1.38
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intra\text{-}I=1\%}$	9.69	4.32
HD_M^I	0.00055 mg/kg-d[a]	14.77[b]
	P05	**P95**
HD_M^I [(c)]	**0.00004 mg/kg-d**	0.008 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 7.02)^2 + (\log 1.38)^2 + (\log 3)^2 + (\log 4.32)^2]^{0.5}} = 14.77$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Based on application of the WHO/IPCS methodology to DEHP female reproductive effects from chronic exposures, using the Zhang et al. LOAEL of 0.04 mg/kg-d, we find that:

- 0.0001 mg/kg-day is the lower bound (95% confidence) chronic human dose at which increased female reproductive effects are expected in 5% of the exposed population;
- 0.00004 mg/kg-day is the lower bound (95% confidence) chronic human dose at which increased female reproductive effects are expected in 1% of the exposed population.

EPA should apply the WHO framework to multiple male and female reproductive endpoints of DEHP (including but not limited to those included in Table 4-3 of the DEHP draft non-cancer hazard assessment), using BMDLs instead of the NOAELs/LOAELs as the starting point, and should also apply the framework to other non-cancer endpoints of DEHP with BMD-derived PODs for comparison.