May 9, 2025

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

Submitted online via Regulations.gov to docket EPA-HQ-OPPT-2018-0504-0119

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 Dicyclohexyl Phthalate, (hereafter referred to as the *DCHP 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] DCHP 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 health hazards of DCHP exposure.[3]

In the DCHP Draft Risk Evaluation, EPA has **failed to incorporate the best available science and makes a number of scientifically-unsupported assumptions**. For many 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 DCHP 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 systematic review methods that lacked transparency, and inappropriately excluded relevant health-effects studies from the hazard assessment without scientific justification. EPA's Science Advisory Committee on Chemicals (SACC) recently criticized EPA's decision to disregard epidemiology studies in the dose-response assessment in the DINP Draft Risk Evaluation.[5] In addition, EPA has not

[1] 15 USC §2625(h).
[2] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 9.
[3] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 9.
[4] 15 U.S.C. § 2625(h).
[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.

conducted a comprehensive literature search for DCHP since 2019, and as a result, is missing reasonably available scientific information, including newer evidence finding that liver toxicity is a hazard of DCHP.[6] 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.[7] The SACC also provided over 200 recommendations to EPA on improving its systematic review methods in 2022,[8] 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 DCHP.

The DCHP Draft Risk Evaluation also relies on dose-response and risk characterization methods that violate TSCA's "best available science" requirement. EPA did not use the benchmark dose (BMD) for reduced fetal testosterone – estimated in EPA's draft TSCA cumulative risk assessment of 6 phthalates, using a NASEM-developed model – for estimating non-cancer risks of DCHP, and instead inappropriately used a dose level that EPA incorrectly called a no-observed-adverse-effect level (NOAEL) when it is actually a lowest-observed-adverse-effect level (LOAEL). It then applied the scientifically deficient margin of exposure approach for risk characterization. We used the BMD and applied methods developed by the World Health Organization (WHO) to quantify the risk of male reproductive effects from chronic DCHP exposure, and found that EPA's current approach results in acceptance of exposures producing an unacceptable upper bound risk greater than 5% (1-in-20).

Another critical concern with the DCHP 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 DCHP, including exposures through food and food packaging. Given that food is the primary route of exposure to many phthalates in children and adults,[9] 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.[10]

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[6] Aydemir D, Aydogan-Ahbab M, Barlas N, Ulusu NN. Effects of the *in-utero* dicyclohexyl phthalate and di- *n*-hexyl phthalate administration on the oxidative stress-induced histopathological changes in the rat liver tissue correlated with serum biochemistry and hematological parameters. Front. Endocrinol (Lausanne). 2023 May 19;14:1128202. doi: 10.3389/fendo.2023.1128202.

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

[8] 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.

[9] 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.

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

EPA also failed to adequately identify potentially exposed or susceptible subpopulations (PESS) and calculate risks posed to these groups, as required under TSCA.[11] In the DCHP Draft Risk Evaluation, EPA failed to consider 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 increase susceptibility to harm from DCHP 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 DCHP 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 Dicyclohexyl Phthalate (DCHP) Draft Risk Evaluation address the following issues:

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

2. **EPA's non-cancer dose-response assessment for DCHP is not consistent with the best available science.**
    a. **EPA improperly excluded human epidemiology studies from dose-response assessment.**
    b. **EPA failed to make appropriate use of benchmark dose modeling to specify a non-cancer point of departure for risk characterization.**
    c. **EPA should apply best available methods to generate quantitative estimates of non-cancer risks for varying levels of exposure to DCHP.**

3. **EPA should take an established scientific approach to addressing the data gap on DCHP carcinogenicity and not use an unvalidated and inappropriate framework to draw conclusions about cancer hazards.**

4. **EPA did not apply the best available science to identify and evaluate relevant and useful health effects studies for DCHP.**
    a. **EPA did not conduct a comprehensive and up-to-date literature search.**
    b. **EPA relied on assessments conducted by Health Canada to exclude studies, without supporting justification and inconsistent with the best available science.**

[11] 15 U.S.C. §§ 2602(12).

c. **EPA used deficient inclusion and exclusion criteria for health effects evidence that inappropriately excluded important toxicity endpoints.**
d. **EPA inappropriately excluded at least 37 PECO-relevant health effects studies from evidence integration.**
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 DCHP 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.**

5. **EPA should re-evaluate its conclusion that DCHP liver effects are not adverse in light of new data.**

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

7. **EPA's approach systematically underestimates DCHP exposure and risk**
    a. **EPA failed to conduct a background exposure assessment, underestimating risk to potentially exposed or susceptible subpopulations.**
    b. **EPA considered aggregate exposure to only a limited extent.**

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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Detailed Comments:

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

In the DCHP Draft Risk Evaluation, EPA determined that 9 occupational conditions of use (COUs) contribute to unreasonable risk, and the remaining 15 worker COUs do not contribute to unreasonable risk. EPA used high-end exposure and risk estimates for 5 of the COUs determined to contribute to unreasonable risk, and used only central tendency estimates combined with a relative potency factor (RPF) analysis for female workers of reproductive age for the remaining 4 COUs. For the majority of COUs not contributing to unreasonable risk, EPA improperly based its determination on only central tendency estimates of exposure and risk and disregarded high-end estimates. 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, 1224 1992). For risk evaluation, EPA provided high-end results at the 95th percentile. If the 95th percentile was not reasonably available, EPA used a different percentile greater than or equal to the 90th percentile but less than or equal to the 99th percentile, depending on the statistics available for the distribution. If the full distribution is not known and the preferred statistics are not reasonably available, EPA estimated a maximum or bounding estimate in lieu of the high-end.[12]

EPA's exposure assessment (Tables 4-3 and 4-4) and risk characterization (Table 4-14) provide both central tendency and high-end estimates for each COU, but for most COUs, EPA used only central tendency values in determining unreasonable risk, without acknowledging that it has therefore disregarded the potential unreasonable risks to workers with exposures greater than the central tendency.

EPA repeatedly states that it is using the central tendency for the unreasonable risk determination because these values are the most representative of worker exposures for the COU. For example:

> Due to this uncertainty in DCHP concentration in workplace dust, central tendency values of exposure are expected to be most reflective of worker exposures within the COUs covered under the "Import and repackaging" OES (i.e., Manufacture COU: Importing; Processing COU: Repackaging [e.g., laboratory chemicals]).[13]

Similar reasoning is provided for other COUs including "Manufacturing," "Incorporation into Adhesives and Sealants," "Incorporation into Paints and Coatings," "Incorporation into other formulations, mixtures, or reaction products not Covered Elsewhere," "PVC Plastics Compounding," "Non-PVC Material Compounding," "PVC plastics converting," "Non-PVC Material Converting," "Application of Adhesives and Sealants – Solids," "Application of Paints and Coatings – Solids," "Use of Laboratory Chemicals," "Fabrication or use of final products or articles," and "Recycling and Waste Handling, Treatment, and Disposal."[14]

> For paints and coatings liquids, in general, central tendency represents the typical exposure of most workers to DCHP through spray application; however, a confluence of a subset of variables (e.g., low ventilation, high-pressure spray, etc.) would result in risk below the benchmark.[15]

> High-end levels of exposure represent scenarios where one or more factors are contributing to unusually elevated exposure levels, whereas central tendency levels of exposure represent more typical levels of exposure for scenarios where there are few

[12] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 58.
[13] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 104.
[14] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 103-115.
[15] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 181.

> factors contributing to increased exposure. There is uncertainty regarding the particular combination of factors that would lead to high-end levels of exposure.[16]

EPA's statements are not a justification for using central tendency estimates and are instead a reiteration of the definition of central tendency. These statements disregard the Agency's obligation under TSCA to determine whether workers with greater-than-typical exposures are experiencing an unreasonable risk.[17] Further, uncertainty is not a defensible basis for disregarding potential risks to more-exposed workers. Finally, this ignores the risks to 50% of the occupational population.

EPA's Science Advisory Committee on Chemicals (SACC) recently commented on the unexpected and unjustified change from EPA's practice in previous TSCA risk evaluations that have been carried through recent evaluations including for 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.[18]

The practice of utilizing high-end exposure estimates is scientifically well-supported and is consistent with both the requirements of TSCA[19] and previous TSCA risk evaluations, and is appropriate for addressing risks to most **of the people being exposed**. This approach is crucial for ensuring that the risk evaluation comprehensively addresses all potential risks, particularly to the most vulnerable and highly exposed groups within the workforce.

EPA's application of the central tendency estimates instead of high-end exposure estimates in the DCHP Draft Risk Evaluation effectively disregards potential unreasonable risks to 50% of workers for the majority of COUs evaluated. This raises significant concerns about the adequacy and methods of the risk evaluation. The justification provided by the EPA for excluding high-end exposure estimates lacks supporting evidence. For example, the EPA asserts that high-end estimates are representative of exposure scenarios where one or more factors contribute to elevated exposure levels and suggests that central tendency estimates are more reflective of worker exposures.[20] However, EPA presents no evidence to support the notion that high-end exposures are an overestimation or that such exposure scenarios are unlikely to occur. Moreover, EPA's sole reliance on central tendency estimates likely underestimates exposures in scenarios that do not conform to this median.

More critically, the use of central tendency estimates fails to consider the risk to individuals exposed at levels above this median, disregarding the potential for health risks to half of the exposed population. This approach does not align with EPA's mission of protecting the public

[16] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 111.
[17] 15 U.S.C. § 2605(b)(4)(A).
[18] 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.
[19] 15 U.S.C. § 2605(b)(4)(A).
[20] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 111.

and is in direct violation of TSCA's mandate to identify and protect potentially exposed or susceptible subgroups (PESS), characterized by greater exposure levels than the general population.[21]

Applying only central tendency estimates for the risk evaluation also means that EPA will potentially overlook significant risks, particularly for workers engaged in high-exposure tasks or those exposed to multiple chemical and non-chemical stressors. Special consideration should be given to more vulnerable workers, including women of reproductive age and other PESS, who might face heightened risks even at lower levels of exposure. The inclusion of Table 4-22, which presents risk estimates for female workers of reproductive age using the RPF analysis, is a meaningful step towards evaluating increased risks among PESS. However, EPA continued to rely *only* on central tendency estimates to inform unreasonable risk for this PESS group.

To adhere to the requirements of TSCA and to ensure robust protection for all workers, the EPA 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.[22] 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 level of concern, particularly those currently deemed as less certain or not contributing to unreasonable risk.[23]

Given the EPA's existing high-end worker exposure estimates presented in the DCHP Draft Risk Evaluation, the Agency's unreasonable risk determination has disregarded significant worker risks for multiple COUs. According to the text and Table 4-14, high-end risk estimates are at levels indicating unreasonable risk for the following occupational exposure scenarios:

- Manufacturing – importing;
- Processing – incorporation into article – plasticizer in plastics product manufacturing and rubber product manufacturing;
- Processing – repackaging (e.g., laboratory chemicals);
- Processing – recycling;
- Industrial use – adhesives and sealants – solids (e.g., computer and electronic product manufacturing; transportation equipment manufacturing);
- Industrial use – other articles with routine direct contact during normal use including rubber articles; plastic articles (hard) – solids (e.g., transportation equipment manufacturing);
- Commercial use – adhesives and sealants;
- Commercial use – building/construction materials not covered elsewhere;
- Commercial use – laboratory chemicals – solids;
- Commercial use – other articles with routine direct contact during normal use including rubber articles; plastic articles (hard);
- Disposal.

[21] 15 U.S.C. § 2605(b)(4)(A).
[22] 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
[23] 15 U.S.C. §2602(12).

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 4-14) high risks for several scenarios. For example, the discussion of PVC Plastics Compounding in EPA's Draft Environmental Release and Occupational Exposure Assessment for DCHP makes no mention of any excessive uncertainties that undermine confidence in the high-end exposure estimate, and its weight of the scientific evidence conclusion finds that the estimates are plausible:

> Based on this information, EPA concluded that the weight of scientific evidence for this assessment is moderate, and the assessment provides a plausible estimate of releases, considering the strengths and limitations of the reasonably available data.[24]

In fact, EPA concluded that the weight of the scientific evidence for **all** occupational exposures scenarios was "moderate" and the estimates were "plausible."[25] If EPA's exposure assessors had any concerns about the representativeness of either the central tendency or high-end exposure estimates, those would have been stated in the Draft Environmental Release and Occupational Exposure Assessment. Further, no significant concerns regarding the estimates are stated in the Occupational Exposures section of the DCHP Draft Risk Evaluation (Section 4.1.1). Instead, this section describes the strengths of the assessment as:

> The exposure scenarios and exposure factors underlying the inhalation and dermal assessment are supported by moderate to robust evidence. Occupational inhalation exposure scenarios were informed by moderate or robust sources of surrogate monitoring data or GSs/ESDs used to model the inhalation exposure concentration. Exposure factors for occupational inhalation exposure include duration of exposure, body weight, and breathing rate, which were informed by moderate to robust data sources.
>
> A strength of the modeling assessment includes the consideration of variable model input parameters as opposed to using a single static value. Parameter variation increases the likelihood that the true occupational inhalation exposures fall within the range of modeled estimates. 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 from EPA's systematic review process. Strengths associated with dermal exposure assessment are described in Table 4-5.[26]

The concluding text regarding limitations, assumptions, and uncertainties in the Occupational Exposures section of the DCHP Draft Risk Evaluation notes uncertainties in the available data but does not mention any concerns regarding the representativeness of the high-end exposure estimates.

Instead, the questions regarding the representativeness of some estimates are raised only in the Risk Characterization and Unreasonable Risk Determination sections of the Draft DCHP Risk

[24] U.S. EPA (2024). Draft Environmental Release and Occupational Exposure Assessment for Dicyclohexyl Phthalate (DCHP), p. 134.
[25] U.S. EPA (2024). Draft Environmental Release and Occupational Exposure Assessment for Dicyclohexyl Phthalate (DCHP), Table 4-1.
[26] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 79.

Evaluation – sections that can be drafted only after risks have been calculated using the central tendency and high-end exposure estimates. The placement of the statements raising doubts about the high-end exposure estimates seems to indicate that EPA developed these concerns only after finding that the high-end exposures led to risk estimates that represent unreasonable risks.

EPA does not provide evidence in the DCHP Draft Risk Evaluation for its claims that the high-end estimates are not representative of exposures for at least some workers. EPA further does not present evidence justifying the use of central tendency estimates to characterize exposures and risks to all workers in each COU. If EPA did 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.

Ignoring calculated risk at the final stage of the draft risk evaluation based on flawed, scientifically inappropriate, and unsupported rationales undermines the integrity of the risk estimates. Thus, without justification, EPA is disregarding high-end estimates solely to avoid determining a contribution to unreasonable risk for each occupational COU. EPA must adopt a more transparent, consistent, and accountable approach to risk assessment. Uncertainties identified by EPA must be addressed early in the exposure assessment; all reasonably foreseeable exposures, including high-end exposures for each occupational exposure scenario and COU must be accounted for; and the unreasonable risk determination must not disregard half of its exposure estimates, including high-end exposure estimates developed in the exposure assessment component of conducting a risk evaluation.

In addition, EPA's unscientific and nontransparent attempts to justify disregarding the high-end estimates, including repeated mentions of uncertainties and lack of data, indicate that EPA failed in its obligation to ensure that it obtained the necessary data needed to conduct a defensible risk evaluation. EPA did not utilize its authority under TSCA to obtain data during or after the process that designated DCHP as a high priority for risk evaluation. Given the potentially significant data gaps, EPA's high-end exposure estimates make appropriate use of the reasonably available data and should be used as the basis for the unreasonable risk determination.

2. EPA's non-cancer dose-response assessment for DCHP is not consistent with the best available science.

a. EPA improperly excluded human epidemiology studies from dose-response assessment.

In the DCHP draft hazard assessment, EPA identified 24 human epidemiology studies of DCHP non-cancer effects published from 2011 to 2019.[27] EPA excluded all of these studies from its dose-response analysis, without any consideration of the strengths and weaknesses of each individual study:

> EPA did not use epidemiology studies quantitatively for dose-response assessment due to uncertainty associated with the source(s) of exposure, timing of exposure assessment that

[27] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), Figure 4-5.

> may not be reflective of exposure during outcome measurements, and use of spot-urine samples, which may not be representative of average urinary concentrations that are collected over a longer term due to rapid elimination kinetics and are calculated using pooled samples. The majority of epidemiological studies introduced additional uncertainty by considering DCHP in isolation and failing to account for confounding effects from co-exposure to mixtures of multiple phthalates.[28]

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.[29] The preamble to EPA's recent final framework rule for conducting risk evaluations re-stated EPA's commitment to systematic review:

> EPA believes that integrating appropriate and applicable systematic review methods into the TSCA risk evaluations is critical to meeting the scientific standards as described in TSCA section 26(h) and (i)…. The principles of systematic review are well-established and include "transparent and explicitly documented methods, consistent and critical evaluation of all relevant literature, application of a standardized approach for grading the strength of evidence, and clear and consistent summative language" (Ref. 26). EPA has finalized the requirement to use and document systematic review methods to assess reasonably available information.[30]

EPA's broad exclusion of DCHP 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 flawed systematic review methods outlined in the DCHP 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

[28] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP), p. 9.
[29] 15 USC §2625(h).
[30] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA). 89 FR 37028.

> 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).[31]

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.[32]

As pointed out by the SACC, the issues that EPA raises in an attempt to disqualify the entire set of epidemiology studies are accounted for in the systematic review process using pre-specified procedures to assess the quality of each study, including domains for exposure assessment and potential confounding. In the DINP hazard assessment, EPA's own study quality assessments indicated that the excluded studies were consistent with existing standards for use of studies in dose-response assessment. In the DCHP hazard assessment, EPA inappropriately and without valid justification decided to not even assess study quality for 22 out of the 24 identified epidemiological studies,[33] thereby eliminating them from further consideration (see further comment below).

Moreover, EPA's explanation considers only alleged limitations of the DCHP 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. 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 DCHP from study quality evaluation and dose-response analysis, EPA has violated TSCA's requirement to use the best available science.[34] EPA cannot broadly exclude epidemiologic studies from dose-response assessment in the DCHP Draft Risk Evaluation, and must consider each relevant study on an individual basis as a candidate for POD derivation.

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[31] 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.
[32] 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.
[33] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), p. 22.
[34] 15 USC §2625(h).

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

EPA's dose-response analysis of DCHP reproductive and developmental toxicity relies on no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs), instead of benchmark dose (BMD) analysis as recommended in well-established EPA guidance.[35] EPA did derive a benchmark dose lower confidence limit (BMDL) for decreased fetal testosterone using an update of the meta-regression approach developed by the NASEM and applied to multiple studies of multiple phthalates, but then inappropriately selected a NOAEL from a single study as the POD for risk characterization rather using the BMDL for DCHP. EPA has therefore not used the best available science to select the POD or to estimate risk.

The update of the NASEM meta-regression used data from 14 studies of reduced fetal testosterone for 6 anti-androgenic phthalates, and is used to derive relative potency factors (RPFs) in the draft phthalates cumulative risk assessment.[36] The meta-regression estimates the dose of DCHP resulting in a 5% decrease in fetal testosterone with a BMD of 8.4 mg/kg-day and a BMDL of 6.0 mg/kg-day. EPA chose not to use the BMDL as the POD, stating that:

> There is some uncertainty associated with the BMDL estimate…only one data point below a dose of 100 mg/kg-day was available for inclusion in the meta-analysis (*i.e.,* at 33 mg/kg-day, where a 25 percent decreased in testosterone was observed) and the estimated BMD_5 (8.4 mg/kg-day) and $BMDL_5$ (6.0 mg/kg-day) values for DCHP are both well below the lowest dose tested. Consistent with EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012), the lack of data to inform the low-end of the dose-response curve reduces EPA's confidence in using the $BMDL_5$ of 6.0 mg/kg-day for risk characterization.[37]

EPA's claim that the DCHP BMDL is too low to be trusted is scientifically inappropriate, for multiple reasons.

First, as summarized by EPA, studies of DCHP male reproductive toxicity demonstrate reproductive toxicity at levels very close to the BMD and BMDL:

> Across available studies, effects on the developing male reproductive system are observed at doses ranging from 10 to 33 mg/kg-day.[38]

[35] U.S. EPA (2012). Benchmark Dose Technical Guidance.
[36] U.S. EPA (2024). 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.
[37] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP), p. 35.
[38] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP), p. 35.

This range identified by EPA is only slightly greater than the BMD and BMDL of 8.4 and 6.0 mg/kg-day. Included in the range are 5 studies with NOAELs or LOAELS of 20 mg/kg-day or less.[39]

Second, EPA's disregards the many factors that should give it increased confidence in the DCHP BMDL. Most importantly, it is derived from a meta-regression approach developed and published specifically for anti-androgenic phthalates by the nation's authoritative scientific body, the NASEM. The meta-regression applies rigorous statistical techniques to an extensive data set assembled from 14 different published studies (including 2 High Confidence studies of DCHP), in contrast to the simple techniques used to derive a NOAEL from a single study. In addition, the ratio of the BMD to BMDL is relatively small (8.4 /6.0 = 1.4), indicating low statistical uncertainty in the estimated BMDL. Further, the analysis in EPA's draft phthalates CRA document provides significant support to the BMDL, increasing confidence. Specifically, dibutyl phthalate (DBP) is designated as the index chemical for the CRA, with an BMDL of 9 mg/kg-day, and the RPF for DCHP is 1.66.[40] Combining the DBP BMDL and the DCHP RPF produces an implicit DCHP BMDL of 5.4 mg/kg-day (9 mg/kg-day / 1.66 = 5.4 mg/kg-day) for the CRA, very similar to the directly-estimated DCHP BMDL of 6.0 mg/kg-day and thus providing increased confidence in this value.

Third, using the meta-regression BMD/BMDL to derive RPFs for the phthalates cumulative risk assessment but not for single-chemical phthalates risk evaluations produces inconsistent results. Specifically, DCHP is found to produce much higher margins of exposure (MOEs) when using the NOAEL than the MOEs calculated using the RPFs; specifically, for 4 worker conditions of use, EPA says:

> At the central tendency in the individual analysis, these COUs have acute inhalation and acute aggregate risk estimates for female workers of reproductive age that initially do not appear to significantly contribute to unreasonable risk because they are slightly above the benchmark of 30 (*i.e.,* MOEs of 36 for acute inhalation and 35 for acute aggregate exposure). However, at the central tendency using the draft RPF analysis, those same four COUs have acute inhalation and acute aggregate risk estimates for DCHP exposure expressed in index chemical equivalents that are well below the benchmark for female workers of reproductive age (*i.e.,* MOEs of 19.1 for acute inhalation and 18.5 for aggregate exposure)… most of the difference between the MOEs calculated using the individual analysis and the MOEs calculated using the draft RPF analysis is due to scaling DCHP to the index chemical and not to the additional, non-attributable cumulative risk from NHANES.[41]

[39] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP), Table 4-1.
[40] U.S. EPA (2024). 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), Tables 2-2 and 2.4.
[41] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), pp. 179-180.

The difference in MOEs between the "individual analysis" of DCHP and the MOEs for DCHP from the RPF analysis is simply an artifact of EPA's unjustified use of the NOAEL rather than BMDL for estimating risks of DCHP alone in the individual analysis.

Fourth, EPA's use of 10 mg/kg-day as the POD is highly inconsistent with its appropriate and scientifically-justified rationale for use of a 5% benchmark response (BMR) for reduced fetal testosterone rather than a higher effect level.[42] The NOAEL of 10 mg/kg-day represents a dose at which a greater than 5% reduction in fetal testosterone occurs; therefore using this value as the POD contradicts the selection of a 5% BMR. Further, EPA has incorrectly called the dose of 10 mg/kg-day a NOAEL rather than a LOAEL, as it dismisses multiple early biological changes observed at that dose that are part of phthalate syndrome:

> Statistically significant effects at 10 mg/kg-day are limited to fetal Leydig cell effects, decreased expression of genes and proteins involved in steroidogenesis, and decreased protein expression of INSL3 (all of which are not considered adverse in isolation). The remaining effects listed reached statistical significance at higher doses.[43]

EPA's draft hazard document elsewhere clearly and correctly identifies fetal Leydig cell effects, decreased steroidogenesis gene and protein expression, and decreased INSL3 all as key events in the phthalate syndrome mode of action.[44] Since these effects are all statistically significant at the dose of 10 mg/kg-day, this dose is clearly a LOAEL rather than a NOAEL. If EPA proceeds with using 10 mg/kg-day as the POD for DCHP, it must apply a LOAEL-to-NOAEL adjustment factor to the benchmark MOE for risk characterization.

Fifth, using a NOAEL as the POD rather than a benchmark dose (BMD) is not consistent with the best available science, as stated in EPA guidance[45] and reports from the NASEM.[46,47] EPA's reference to its 2012 *Benchmark Dose Technical Guidance* to justify its decision to use a NOAEL instead of BMDL as the point of departure disregards the broader message of that well-established guidance, which is unequivocal in describing the limitations of NOAELs and in stating a strong preference for BMDLs rather than NOAELs.

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

[42] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP), Appendix E.
[43] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP), Table ES-1 (note c).
[44] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP), Figure 3-1.
[45] U.S. EPA (2012). Benchmark Dose Technical Guidance.
[46] NASEM (2017). Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals, p. 158.
[47] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 129.

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%.[48]

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.[49]

> 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.[50]

[48] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 4.
[49] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 6.
[50] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 12.

> 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.[51]
>
> 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.[52]

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.[53]

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.[54]
>
> Basis of the POD: A modeled BMDL is preferred over a NOAEL, which is in turn preferred over a LOAEL.[55]

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.[56]

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[51] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 30.
[52] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 40.
[53] U.S. EPA (2020). Risk Evaluation for n-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP), p. 262.
[54] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, p. 8-1.
[55] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, p. 8-18.
[56] NASEM (2017). Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals, p. 158.

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.[57]

In addition to use of the dose it calls a NOAEL as the POD, EPA all disregarded all of the above guidance in its overall approach to dose-response assessment for DCHP. Its selection of 10 mg/kg-day as the POD is based on a summary of dose-response data for10 study/endpoint combinations, all of which are NOAELs or LOAELs.[58] In other words, after setting aside the BMDL from the CRA meta-regression for scientifically indefensible reasons, EPA failed to apply BMD modeling at all in its process of selecting a POD.

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.[59]

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 DCHP 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:

[57] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 129.
[58] Hazard Assessment for Dicyclohexyl Phthalate (DCHP), Table 4-1.
[59] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 15.

> 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.[60]
>
> EPA should apply benchmark dose modeling to derive chronic non-cancer points of departure and select the one that is most sensitive (lowest).[61]

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.[62]
>
> EPA will document that the risk evaluation is consistent with the best available science.[63]

EPA's dose-response analysis for DCHP 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.[64]

EPA should use the $BMDL_5$ for DCHP derived from application of the NASEM meta-regression model as the POD in the final DCHP risk evaluation.

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

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

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

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[60] 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.
[61] 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.
[62] 15 U.S.C. § 2625(h).
[63] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA). 89 FR 37028, May 3, 2024, § 702.37(a)(2).
[64] Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA),40 CFR § 702.37.

The MOE approach is a scientifically deficient method for characterizing risk and is inconsistent with TSCA's requirements to use the "best available science"[65] and to ensure protection of "potentially exposed and susceptible subpopulations" (PESS).[66]

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."[67]

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.[68,69]

The National Academies[70] and the World Health Organization[71] (WHO) have outlined more robust methods for risk estimation that more accurately account for variability in the human population and have been demonstrated in published case studies.[72,73,74,75] We applied the WHO methodology to the DCHP endpoint of reduced fetal testosterone, using the BMD and BMDL values derived by EPA through application of the NASEM meta-regression model,[76] to estimate risk-specific doses for several levels of incidence (e.g. 1%, 0.1%, etc.).

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

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[65] 15 U.S.C. §2625 (h).
[66] 15 U.S.C. §2602 (12).
[67] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 102.
[68] 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.
[69] 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.
[70] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, Chapter 5.
[71] 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.
[72] 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.
[73] 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.
[74] 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.
[75] 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.
[76] U.S. EPA (2024). Draft Technical Support Document for the Cumulative Risk Analysis of Di(2-ethylhexyl) Phthalate (DEHP), Dibutyl Phthalate (DBP), Butyl Benzyl Phthalate (BBP), Diisobutyl Phthalate (DIBP), Dicyclohexyl Phthalate (DCHP), and Diisononyl Phthalate (DINP) Under the Toxic Substances Control Act (TSCA), Table 2-2.

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

The implications of these risk values can be understood by comparison with the exposure levels considered by EPA to represent negligible risk. EPA's assessment uses a POD of 2.4 mg/kg-day (HED) and a benchmark MOE of 30,[77] meaning that EPA concludes "risk is not considered to be of concern and mitigation is not needed"[78] for any exposure below 0.08 mg/kg-day (2.4 mg/kg-day / 30 = 0.08 mg/kg-day). Our analysis indicates that an exposure of 0.08 mg/kg-day exceeds the lower-bound dose for the 5% (1-in-20) 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.[79]

EPA should apply the WHO framework to the DCHP male reproductive toxicity and liver toxicity endpoints, using appropriate BMD estimates. The risk-specific dose estimates can in turn be used to characterize the risks associated with the estimated levels of DCHP exposure.

3. EPA should take an established scientific approach to addressing the data gap on DCHP carcinogenicity and not use an unvalidated and inappropriate framework to draw conclusions about cancer hazards.

Using the Rethinking Chronic Toxicity and Carcinogenicity Assessment for Agrochemicals Project (ReCAAP) weight of evidence framework, EPA has inappropriately preliminarily concluded that "…potential carcinogenicity of DCHP is not a significant remaining source of uncertainty in the quantitative and qualitative risk characterization, despite the lack of

[77] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 101.
[78] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 102.
[79] U.S. EPA (2024). Unreasonable Risk Determination of the Draft Risk Evaluation for Formaldehyde, p. 13.

carcinogenicity bioassays for DCHP."[80] There are several scientific issues with the ReCAAP framework that make it inappropriate to use for this purpose.

First, it is unvalidated. There are no data demonstrating that it accurately identifies whether a chemical is a carcinogen, or the appropriate point of departure (POD) to use in risk assessment. The framework was developed for agrichemicals (DCHP is not an agrichemical), and the OECD case studies using the framework specifically say, "Further discussion is needed to explore the applicability beyond agrichemicals (e.g., industrial chemicals)."[81]

The Hilton, 2022 paper EPA cites for the framework has authors with clear financial conflicts of interest- corporations that sell agrichemicals, including Syngenta, BASF, Bayer, and Corteva.[82] 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.[83] The NASEM has highlighted the "large body of evidence showing that financial COIs lead to systemic biases in research."[84]

There is significant concern for DCHP carcinogenicity because it exhibits at least one of the key characteristics of carcinogens (modulates receptor-mediated effects through modulation of hormones), and because other structurally related phthalates (DEHP, DINP) are carcinogens.[85] EPA should utilize a scientifically established approach to fill the data gap on DCHP carcinogenicity. EPA could require tests such as cancer bioassays, or alternatively use the approach recommended by NASEM to make use of data from short term toxicity tests and structure-activity modeling to estimate carcinogenic potency.[86]

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[80] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 100.
[81] OECD (2024), *Case Study on the Use of Integrated Approaches for Testing and Assessment for Chronic Toxicity and Carcinogenicity of Agrichemicals with Exemplar Case Studies – Ninth Review Cycle (2023)*, OECD Series on Testing and Assessment, No. 402, OECD Publishing, Paris.
[82] Hilton, GM; Adcock, C; Akerman, G; Baldassari, J; Battalora, M; Casey, W; Clippinger, AJ; Cope, R; Goetz, A; Hayes, AW; Papineni, S; Peffer, RC; Ramsingh, D; Williamson Riffle, B; Sanches da Rocha, M; Ryan, N; Scollon, E; Visconti, N; Wolf, DC; Yan, Z; Lowit, A. (2022). Rethinking chronic toxicity and carcinogenicity assessment for agrochemicals project (ReCAAP): A reporting framework to support a weight of evidence safety assessment without long-term rodent bioassays. Regul Toxicol Pharmacol 131: 105160. http://dx.doi.org/10.1016/j.yrtph.2022.105160
[83] 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.
[84] National Academies of Sciences, Engineering, and Medicine (2023). Sponsor Influences on the Quality and Independence of Health Research: Proceedings of a Workshop, p. 9.
[85] Krewski, D., Bird, M., Al-Zoughool, M., Birkett, N., Billard, M., Milton, B., Rice, J. M., Grosse, Y., Cogliano, V. J., Hill, M. A., Baan, Robert. A., Little, J., & Zielinski, J. M. (2019). Key characteristics of 86 agents known to cause cancer in humans. *Journal of Toxicology and Environmental Health, Part B*, *22*(7–8), 244–263. https://doi.org/10.1080/10937404.2019.1643536
[86] National Research Council. (2009). *Science and Decisions: Advancing Risk Assessment*. National Academies Press. https://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment

4. EPA did not apply the best available science to identify and evaluate relevant and useful health effects studies for DCHP.

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.[87,88,89] EPA's assessment of DCHP is 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 would have identified and included all relevant health effects studies. This indicates critical deficiencies in the EPA systematic review protocol and the DCHP Draft Risk Evaluation.

To identify epidemiology studies of DCHP, EPA relied on a Health Canada assessment completed in 2020,[90,91] and a literature search that was conducted in 2019 and has not been updated since. As stated in EPA's systematic review protocol for DINP:

> The search for peer-reviewed and gray literature relevant references was completed in September and May 2019, respectively.[92]

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

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

> Previous phthalates risk assessments have been conducted by authoritative sources including Health Canada and the EPA IRIS program. OPPT used these previous assessments to facilitate efficient and scientific risk evaluation. Therefore, data quality evaluation and extraction were conducted only for references published after the literature search end date of the most recent authoritative assessment.
>
> The most recent authoritative assessment was published by Health Canada in 2020 and included literature published up to 2018 (Health Canada, 2020). Therefore, data quality evaluation and extraction were conducted for references published from the beginning of

[87] National Research Council (2011). Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.
[88] 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.
[89] 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.
[90] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), p. 21.
[91] Health Canada (2020). Screening assessment - Phthalate substance grouping.
[92] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), p. 9.

> 2018 through the end date of the OPPT literature search, as well as for references that were published from the beginning of 2018 through the end of 2023 that were sent with public comments in phthalates dockets. Data quality evaluation and extraction was not conducted for any references published before 2018.[93]

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

- Studies published prior to 2018 – are included in EPA's assessment only if they were included in the assessment conducted by Health Canada. The Health Canada document is not a systematic review or and it does not appear to have been peer reviewed. EPA did not assess the quality of the studies identified by Health Canada. EPA did not assess the quality of these studies or extract their data.
- 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 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 relied entirely on the Health Canada assessment and did not apply its own search, inclusion/exclusion and study evaluation procedures. For later studies (after September 2019), EPA did not conduct a search but included only those studies that were submitted by the public to EPA. This is not a clear, comprehensive or consistent approach to identifying the epidemiological evidence relevant to assessing the health effects of DCHP. A further concern is that these inconsistent procedures for identifying epidemiological evidence were ultimately relevant only to the identification of DCHP hazards, since EPA subsequently excluded **all** epidemiological studies from consideration for dose-response assessment, without consideration of the merits of individual studies (see comment 2a above).

For identifying toxicology studies, EPA applied a similar process:

> Previous phthalates risk assessments have been conducted by authoritative sources including Health Canada (EC/HC) (EC/HC, 2015b). OPPT used the previous Health Canada assessment as the key starting point to facilitate an efficient and scientific risk evaluation. Based on this existing assessment, a total of 1 key study (Hoshino et al., 2005) was considered for point of departure (POD) refinement… The remaining references…that met the PECO screening criteria and underwent further filtering were those published after the EC/HC 2015 assessment up until the literature search conducted by OPPT for the DCHP risk evaluation, which covered the years 2014 – 2019… Additionally, an assessor identified reference published after 2019 (Gray et al., 2021) was

[93] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), p. 21.

prioritized for systematic review to support the meta-analysis and benchmark dose modeling of fetal testicular toxicity [94]

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

- Studies published up to 2014 – included only if they were included in the previous assessment by Health Canada. Only one study is included in this subset. The DCHP draft protocol indicates that 13 other pre-2014 toxicology studies identified by Health Canada were excluded from the risk evaluation;[95] it is unclear why EPA did not include these studies. Additionally, EPA did not consider any studies published before 2014 if they were not discovered by or not included in the Health Canada assessment for any reason.
- Relevant studies published from 2014 to September 2019 – EPA conducted its own search of the literature and applied its own inclusion/exclusion criteria.
- Studies published after September 2019 – were not considered at all, with the exception of a 2021 study by Grey et al. The process by which this study was included is not clearly stated by EPA.

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

A glaring consequence of EPA's haphazard approach to identifying relevant health effects studies is the omission of an important study of liver toxicity published by Aydemir et al. in 2023 (see comment 4 below for further discussion).[96] This is just one example; there are likely other relevant health effects studies of DCHP that are missing from EPA's assessment.

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. Post-2019 epidemiology studies were considered if they were submitted to the docket, but EPA makes no mention of whether it considered post-2019

[94] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), pp. 22-23.
[95] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), Figure 4-6.
[96] Aydemir D, Aydogan-Ahbab M, Barlas N, Ulusu NN. Effects of the *in-utero* dicyclohexyl phthalate and di- *n*-hexyl phthalate administration on the oxidative stress-induced histopathological changes in the rat liver tissue correlated with serum biochemistry and hematological parameters. Front. Endocrinol (Lausanne). 2023 May 19;14:1128202. doi: 10.3389/fendo.2023.1128202.

toxicology studies submitted to the docket. It appears that any toxicological findings on DCHP published in the past 5 years were simply not considered by EPA, with the exception of the study by Grey et al., 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.[97] 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 DCHP Draft Risk Evaluation.

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

EPA reviewed Health Canada assessments of DCHP toxicology and epidemiology studies as part of conducting the DCHP Draft Risk Evaluation. Epidemiology studies published before 2019 and toxicology studies published before 2014 were included in the TSCA risk evaluation only if they were included in the Health Canada assessments. Studies published before these dates that were not identified in searches conducted by Health Canada or were excluded from these previous assessments for any reason were not considered at all by EPA.

In principle, the use of previous assessments can be a useful part of conducting a TSCA risk evaluation, but the previous assessments must be carefully evaluated against a pre-specified set of criteria to determine whether they are of sufficient quality, and 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.[98]

However, it appears that the two Health Canada assessments were not systematic reviews, and it is unclear if they were peer reviewed. EPA also does not provide adequate justification for its use of previous DCHP 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.[99] AMSTAR 2 was also applied by the NASEM in multiple prior

[97] 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.
[98] 15 U.S.C. § 2625(h).
[99] NASEM (2023). Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests.

reports on environmental health assessment.[100,101,102] 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.[103]

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

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

PECO statements play a critical role in conducting a systematic review as they provide criteria for screening the literature search results to identify which studies are relevant (included in the risk evaluation) and not relevant (excluded from further consideration). The PECO statement for DCHP 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 DCHP 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.[104] (emphasis added)

[100] NASEM (2019). Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene.
[101] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations.
[102] NASEM (2022). Guidance on PFAS Exposure, Testing, and Clinical Follow-Up.
[103] 15 U.S.C. § 2625(h).
[104] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, Table_Apx H-47.

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."[105] The 2021 TSCA Draft Systematic Review Protocol provides no further guidance on which outcomes are to be considered apical or organ-level, and which outcomes are to be considered cellular-level.

The NASEM has defined an apical end point as "An observable outcome in a whole organism, such as a clinical sign or pathologic state, that is indicative of a disease state that can result from exposure to a toxicant,"[106] and identified "tumors, birth defects, and neurologic impairments"[107] 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."[108] The definition of adverse effect includes, for example, "a biochemical change;" such effects appear to be excluded from the DINP 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:

[105] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, Table_Apx H-47.
[106] National Research Council (2007). Toxicity Testing in the 21st Century: A Vision and a Strategy, p. 38.
[107] National Research Council (2007). Toxicity Testing in the 21st Century: A Vision and a Strategy, p. 177.
[108] U.S. EPA. IRIS Glossary. https://www.epa.gov/iris/iris-glossary.

- 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)[109,110,111]
- reduced thyroid hormone levels (2020 TSCA risk evaluation of HBCD; 2021 toxicity assessment of PFBS) [112,113]
- decreased erythrocyte counts and hemoglobin (2020 TSCA risk evaluation of perchloroethylene)[114]
- measures of immune function, such as increases in immunoglobulin E, lymphocytes, natural killer cells, and interlukin-4 levels (2020 TSCA risk evaluation of perchloroethylene)[115]
- 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)[116,117,118,119]
- acetylcholinesterase inhibition (numerous assessments of pesticides, including cumulative risk assessments of organophosphate and carbamate pesticides)[120,121]

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

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

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[109] 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.
[110] 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.
[111] 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.
[112] U.S. EPA (2020). Risk evaluation for cyclic aliphatic bromide cluster (HBCD).
[113] 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.
[114] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[115] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[116] U.S. EPA (2020). Risk Evaluation for Trichloroethylene.
[117] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[118] 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.
[119] 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.
[120] U.S. EPA (2006). Organophosphorus cumulative risk assessment. https://www.regulations.gov/document/EPA-HQ-OPP-2006-0618-0002.
[121] U.S. EPA (2008). Revised N-methyl carbamate cumulative risk assessment. https://www.regulations.gov/document/EPA-HQ-OPP-2008-0347-0029.

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"[122] (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.[123] An important theme of the NASEM 2007 *Toxicity Testing in the 21st Century* report was that toxicity testing should move away from reliance on testing of apical outcomes. Accordingly, EPA's research programs and other U.S. health agencies have invested heavily in this new direction. Government and academic toxicology labs now rarely conduct studies of apical endpoints because the science has shifted towards examining more sensitive endpoints representing upstream biological changes ("key events") that lead to apical outcomes. In addition, a restriction to consider only apical or organ-level studies may bias the evidence base of the TSCA risk evaluations toward inclusion of industry-funded guidelines studies that are generally focused on apical endpoints.

d. EPA inappropriately excluded at least 37 PECO-relevant health effects studies from evidence integration.

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 DCHP 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.[124]

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 PECO-relevant health effects studies of DCHP can be excluded from the risk evaluation, and relevant studies were excluded through procedures lacking scientific justification.

One of these procedures is EPA's "further filtering" of PECO-relevant health effects studies:

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[122] U.S. EPA (2021). Draft systematic review protocol supporting TSCA risk evaluations for chemical substances, p. 345.
[123] 15 U.S.C. § 2625(h).
[124] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), p. 5.

> 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.[125]
>
> 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.[126]
>
> The main purpose of this further filtering step was to allow for the refinement of the references that would be considered for data quality evaluation and extraction.[127]

The protocol does not provide any explanation for why the application of the PECO statement was insufficient for determining studies to include in the DCHP Draft Risk Evaluation or why this "further filtering" process (which was not included in the 2021 TSCA draft systematic review method) was applied. It is also unclear why EPA found it necessary to "streamline" the process further when it was already extremely streamlined, with the most recent comprehensive literature search conducted in September 2019 and EPA's decision to expend very limited effort on pre-2018 epidemiology studies:

> Data quality evaluation and extraction was not conducted for any references published before 2018.[128]

Implementation of the further filtering step is also unclear. EPA provides a further filtering form for toxicology studies that includes a series of questions regarding the methods and outputs of a study. The form concludes with the Yes/No question "Should this reference move on to data extraction and evaluation?"[129] but no instructions are given for how the assessor is to answer this question.

EPA then says that only 5 out of the 20 toxicology studies subjected to the further filtering procedure were included in the risk evaluation.[130] The reasons for exclusion of the remaining 15 DCHP toxicology studies – all of which had previously been identified as PECO-relevant – are not clearly stated.

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[125] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), p. 21.
[126] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), p. 21.
[127] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), p. 24.
[128] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), p. 21.
[129] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), Table 4-1.
[130] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), pp. 22-24.

EPA also used the further filtering step to exclude 22 out of 24 PECO-relevant epidemiology studies from study quality evaluation.[131] For 20 of these studies, the only explanation given by EPA is that they were published before 2018. This is not a valid or scientifically-based justification for exclusion of relevant evidence.

The exclusion of 15 toxicology studies and 22 epidemiology studies, already determined by EPA to be relevant to DCHP, from EPA's hazard assessment contradicts EPA's claim that all relevant studies are considered in the DCHP Draft Risk Evaluation. 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.

A further lack of transparency regarding inclusion of toxicology studies is seen in EPA's study quality evaluations, where 9 studies are included,[132] and the draft hazard assessment's statement that 11 toxicology studies are included,[133] compared to 5 studies as stated in the protocol.[134] EPA must clarify its process for inclusion and exclusion of toxicology studies, including an accurate accounting of the number of studies included and how each of the included studies was identified.

EPA also inappropriately excluded at least one study from further consideration based on a lack of statistical significance. EPA said that the excluded epidemiology study:

> had an OQD of Low due to concerns including potential outcome misclassification and lack of adjustment for potential confounders. The study found a positive but not statistically significant association between MCHP exposure and endometriosis. Due to the reference **not meeting the criteria of statistical significance** data weren't extracted.[135] (emphasis added)

EPA does not include statistical significance in its study quality evaluation criteria. Now, EPA appears to introduce it in the DCHP protocol for this assessment as a new criterion for determining studies that advance to data extraction:

> Epidemiology references with an overall quality determination (OQD) of High, Medium, or Low **that found statistically significant associations** between DCHP and an adverse health outcome underwent data extraction; data were not extracted from Uninformative references.[136] (emphasis added)

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[131] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), p. 22.
[132] U.S. EPA (2024). Draft Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for Dicyclohexyl Phthalate (DCHP).
[133] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP), p. 17.
[134] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), Figure 4-6.
[135] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), pp. 55-56.
[136] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), p. 55.

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.[137]

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.[138] 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.[139]

EPA therefore does not provide a valid justification for excluding this PECO-relevant study, and 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.

In addition, the DCHP protocol states the EPA has continued its inappropriate practice of excluding some studies based on study quality evaluations:

> data were not extracted from Uninformative references.[140]

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, again contradicting EPA's claim that all relevant studies are considered in the risk evaluation.

EPA never explains, in either the draft systematic review protocol or the draft hazard assessment, how an OQD is derived from the study quality metrics. A statement at the end of the data quality evaluation forms for both epidemiology and toxicology studies indicates that EPA uses an automatic calculation of the OQD:

> Specify which OQD you would give this paper (either confirm the auto calculated judgement OR suggest a new one based on your professional judgement?[141]

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[137] U.S. EPA (2024). Draft Systematic Review Protocol for Diisononyl Phthalate (DINP), p. 54.
[138] 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.
[139] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 40. https://doi.org/10.17226/25952.
[140] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), p. 55.
[141] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), pp. 63 and 75.

However, there is no other mention of "auto calculated judgement" in the protocol or hazard assessment. Further, there is no guidance given on when and with what basis an OQD not based on auto-calculation may be assigned. It is therefore unclear the basis on which the disqualifying label of "Uninformative" (or alternately, determinations of High, Medium or Low) is assigned to a study.

These examples demonstrate that EPA has not implemented procedures consistent with its claim that "all references that undergo systematic review are considered for use in the risk evaluation."[142] The TSCA systematic review method needs substantial revisions to correct a process that continues to exclude relevant evidence.

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

The DCHP 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.

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.[143]

The NASEM has highlighted the "large body of evidence showing that financial COIs lead to systemic biases in research"[144] and recommended that "funding sources should be considered in the risk-of-bias assessment conducted for systematic reviews that are part of an IRIS

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[142] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), p. 5.
[143] 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.
[144] NASEM (2023). Sponsor Influences on the Quality and Independence of Health Research: Proceedings of a Workshop, p. 9.

assessment."[145] 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 hazard and risk assessment; 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.[146] This was a specific recommendation in the NASEM report on TSCA systematic review:

> 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).[147]

Importantly, an "uninformative" rating can be based on a "critically deficient" rating for any study quality metric, regardless of the ratings for other metrics. One aspect of the significant problems raised in applying an overall study rating is illustrated by EPA's evaluation of study quality for oral toxicity studies of formaldehyde.

EPA identified gastrointestinal effects as the most sensitive endpoint for oral exposure to formaldehyde. However, EPA classified the chronic oral exposure studies (by Til *et al*. and Tobe *et al*.) for gastrointestinal effects as "Uninformative." After further consideration, EPA decided that these studies actually are informative, and that the Til *et al*. study should be used for dose-response analysis:

> Taken together, the three drinking water studies demonstrate a consistent pattern of gastrointestinal effects at comparable dose levels…While limitations in the two chronic drinking water studies resulted in OPPT data quality ratings of "uninformative for dose response" for the individual studies, the body of evidence across all three studies in

[145] National Research Council (2014). Review of EPA's Integrated Risk Information System (IRIS) Process, p. 79.
[146] 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.
[147] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 36.

> combination increases the overall confidence in both the nature of the effects observed and the levels of formaldehyde exposure associated with those effects.[148]
>
> The three oral studies were selected to inform dose-response because they comprise the best available data on oral exposure to formaldehyde…when considered in conjunction with the other two studies, Til et al. 1989 contributes meaningful information to the WOE and dose-response despite the OPPT data quality rating of "uninformative."[149]

EPA's own analysis of its study quality ratings procedures therefore indicated that an overall study quality rating can be highly misleading and that 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,[150] 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 DCHP 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 DCHP. 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. 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."[151]

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[148] U.S. EPA (2024). Draft Human Health Hazard Assessment for Formaldehyde, pp. 30-31.
[149] U.S. EPA (2024). Draft Human Health Hazard Assessment for Formaldehyde, p. 32.
[150] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 36.
[151] 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.

> 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.[152]

In the DCHP 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.[153] The Draft DCHP Hazard Assessment further confuses matters by using the term "hazard identification"[154] 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.[155] 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 DINP endpoints, including a pre-specified set of descriptors that are considered for each endpoint.

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

Along with the DCHP 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 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.[156,157]

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[152] 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.
[153] U.S. EPA (2024). Draft Systematic Review Protocol for Dicyclohexyl Phthalate (DCHP), pp. 76-84.
[154] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP), p. 16.
[155] 15 U.S.C. § 2625(h).
[156] Institute of Medicine (2011). Finding what works in health care: Standards for systematic reviews.
[157] National Research Council (2014). Review of EPA's Integrated Risk Information System (IRIS) process.

The TSCA program should follow the established procedures of EPA's IRIS program, which makes a draft protocol for each assessment publicly available in advance of its release for public comment. Following the public comment process, the IRIS program then publishes an updated protocol, as needed. For example, for the IRIS assessments of five per- and polyfluoroalkyl substances (PFAS), a draft protocol was made available for public comment for 45 days. The IRIS program then followed up with a revised protocol to address public comments, with documentation of the changes, that was published before the release of the PFAS draft assessments.[158] 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. EPA should also prepare a chemical-specific systematic review protocol for each TSCA risk evaluation it conducts, and these protocols should be complete, stand-alone documents that do not refer to the 2021 Draft TSCA Method for critical elements. The chemical-specific protocols for ongoing and future risk evaluations should also be released for public comment well before the draft risk evaluations are completed to allow for public input, scrutiny, and opportunities for improvement. We urge EPA to consistently adopt the practices of the IRIS program for systematic review protocol development and publication across all EPA programs and offices.

5. EPA should re-evaluate its conclusion that DCHP liver effects are not adverse in light of new data.

EPA concluded that the liver effects observed in oral DCHP studies are generally not indicative of an adverse response.[159] EPA cites lack of data on histopathology and clinical markers in support of its conclusion. Because it did not update its literature search from 2019, EPA did not consider a 2023 study by Aydemir et al. that evaluated both histopathological changes and serum biochemistry to find that DCHP causes liver damage in male and female rats.[160] EPA should include the data in the Aydemir study in its analysis and re-evaluate its conclusion on DCHP and liver toxicity. Additionally, EPA has concluded that liver toxicity is a hazard of other ortho-

[158] 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).
[159] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP). pg. 30.
[160] Aydemir D, Aydogan-Ahbab M, Barlas N, Ulusu NN. Effects of the in-utero dicyclohexyl phthalate and di-n-hexyl phthalate administration on the oxidative stress-induced histopathological changes in the rat liver tissue correlated with serum biochemistry and hematological parameters. Front Endocrinol (Lausanne). 2023;14:1128202. doi:10.3389/fendo.2023.1128202

phthalates including DIDP and DINP; it is consistent that the structurally-related DCHP would exhibit similar toxicity.

6. EPA failed to adequately identify 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 DCHP Draft Risk Evaluation.[161] 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 DCHP exposures.

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

> determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other nonrisk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation.[162]

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.[163]

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.[164] To remedy the problem of inconsistent and incomplete identification of PESS, Rayasam *et al.* recommended that:

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[161] 15 U.S.C. §2605(b)(4)(A).
[162] 15 U.S.C. §2605(b)(4)(A).
[163] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act, § 702.33.
[164] 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

> EPA should prepare a comprehensive methodology to identify PESS and quantify their risks consistently within and across the TSCA risk evaluations.[165]

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

> women of reproductive age, pregnant women, infants, children and adolescents, people who frequently use consumer products and/or articles containing high concentrations of DCHP, people exposed to DCHP in the workplace, people in proximity to releasing facilities, including fenceline communities, and Tribes and subsistence fishers whose diets include large amounts of fish.[166]

The DCHP 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.[167] However, the evaluation is still deficient in identifying PESS, particularly in its failure to include a similar table that identifies PESS on the basis of greater exposure as required by statute.[168] EPA has thus 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 DCHP 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 DCHP.[169]

Further, the DCHP Draft Risk Evaluation does not provide any careful consideration of how its risk estimates should be adjusted to account for risks to susceptible groups, beyond the selection of the POD. While the selection of POD for DCHP may ensure protection for some populations, it cannot guarantee absolute protection, especially for those with greater susceptibility or exposure. The full discussion of this issue is:

Chemicals in the United States. Environmental science & technology, 56(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079.

[165] 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].

[166] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 11.

[167] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP), p. 42, Table 5-1.

[168] 15 U.S.C. §2605(b)(4)(A).

[169] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP), p. 42, Table 5-1.

> EPA used a default value of 10 for human variability (UF_H) to account for increased susceptibility when quantifying risks from exposure to DCHP. 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).[170]

This statement is also a step backward from the acknowledgment in other recent risk evaluations that a 10-fold factor is likely insufficient to account for the extent of human variability in response to hazardous chemical exposures. For example, the final TCEP risk evaluation includes language similar to the quote above, but goes on to elaborate on the uncertainties of the default value, including susceptibility factors not accounted for:

> EPA used a default value of 10 for human variability (UF_H) to account for increased susceptibility when quantifying risks from exposure to TCEP. The Risk Assessment Forum, in *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002b), discusses some of the evidence for choosing the default factor of 10 when data are lacking and describe the types of populations that may be more susceptible, including different lifestages (*e.g.,* of children and elderly). U.S. EPA (2002b), however, did not discuss all the factors presented in [the TCEP risk evaluation]. 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 TCEP risk evaluation. In addition, given that EPA is using a default UF_H in the absence of data regarding whether adverse effects from TCEP exposure differ for certain subpopulations (such as those with genetic polymorphisms or underlying diseases), **it is also not known whether the chosen default UF_H would fully cover pre-existing diseases or disorders**.[171] (emphasis added)

In fact, the WHO and other authoritative bodies have demonstrated that the traditional 10X uncertainty factor is insufficient for fully accounting for risk in sensitive groups and recommend the use larger uncertainty factors.[172,173] Instead of increasing the use of uncertainty factors to account for the wide range of vulnerability and variability in the human population, EPA uses inadequate default uncertainty factors, which will result in an underestimation of risk, particularly for PESS.

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[170] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP), p. 41.
[171] U.S. EPA (2024). Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), pp. 462-463.
[172] 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.
[173] Varshavsky, J. R., Rayasam, S. D. G., Sass, J. B., Axelrad, D. A., Cranor, C. F., Hattis, D., Hauser, R., Koman, P. D., Marquez, E. C., Morello-Frosch, R., Oksas, C., Patton, S., Robinson, J. F., Sathyanarayana, S., Shepard, P. M., & Woodruff, T. J. (2023). Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. Environmental Health, 21(Suppl 1), 133. https://doi.org/10.1186/s12940-022-00940-1.

For the identified PESS, EPA also concluded that, due to a lack of chemical specific data for each PESS, no further adjustment is necessary. 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.[174]

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, and then, as a separate step, consider how to adequately account for the elevated risks for each group, in some cases by using scientifically-supported uncertainty factors. The initial identification of PESS, however, should not be contingent on chemical-specific data. Once the appropriate groups are identified as PESS, EPA should then consider the availability of chemical-specific data. When such data are absent, the application of appropriate adjustment factors (beyond the customary 10x factor for human variability) should be applied to ensure that risks to PESS are not underestimated.[175]

7. EPA's approach systematically underestimates DCHP exposure and risk.

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

Phthalates such as DCHP are ubiquitous contaminants worldwide to which the general population is continuously exposed through multiple pathways, including water, air, and

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[174] 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/.

[175] 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.

inhalation and/or ingestion of household dust.[176] DCHP 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.[177]

EPA failed to account for these multiple sources of exposure in their assessment of unreasonable risk in the DCHP 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 be considered because they constitute "non-TSCA" uses.[178] 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 DCHP 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.[179] 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."[180] The NASEM recommends consideration of background exposures when conducting a risk evaluation for both individual chemicals and categories of chemicals through a cumulative risk assessment,[181] citing that background exposures at "even small doses may have a relevant biological effect."[182]

Given the widespread exposure to DCHP 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 DCHP 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

[176] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 10.
[177] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 9.
[178] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 10.
[179] 15 U.S.C. §2602(4).
[180] 15 U.S.C. § 2625(h).
[181] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, pp. 135, 136, and 214.
[182] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 130.

> 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.[183]

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.[184]

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.[185] EPA's plan to exclude from consideration uses of DCHP 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 DCHP Draft Risk Evaluation so it addresses all sources and pathways of DCHP 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 DCHP 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.[186]

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

The DCHP Draft Risk Evaluation states:

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[183] 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.
[184] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act.
[185] Sulfuryl Fluoride; Proposed Order Granting Objections to Tolerances and Denying Request for Stay, 76 Fed. Reg. 3,422-01 (Jan. 19, 2011).
[186] 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.

> 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 DCHP 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 4.1.5, EPA employed a risk screen approach for the general population exposure assessment. Based on results from the risk screen, no pathways of concern (*i.e.,* ambient air, surface water, drinking water, fish ingestion) to DCHP exposure were identified for the generation population.
>
> 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.[187]

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

By failing to recognize that some individuals may be exposed in multiple ways – that is, experiencing combinations of general population, consumer and worker exposures – EPA is systematically underestimating exposures and risks to some of the most-exposed people in the population. This approach is not consistent with the requirements of TSCA to apply the best available science,[188] and to identify and eliminate unreasonable risks to potentially exposed or susceptible subpopulations,[189] which include groups with higher exposure levels. TSCA also

[187] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 97.
[188] 15 USC §2625(h).
[189] 15 U.S.C. §2605(b)(4)(A).

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."[190] 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 DCHP risk evaluation, the resulting underestimation would then be a consideration that must be incorporated into the unreasonable risk determination.

[190] 15 U.S.C. §2605(a).

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

In the *Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP)*, EPA characterizes risks of effects on the developing male reproductive system. The draft TSCA risk evaluation calculates a "margin of exposure" (MOE) to characterize risk for each exposure scenario, which is the ratio of the point of departure (POD) to the exposure level. For the DCHP, EPA says that an MOE of 30 or more indicates that "risk is not considered to be of concern and mitigation is not needed."[191]

EPA's approach to risk characterization does not actually estimate risks of adverse effects in the population with chronic exposure to DCHP, 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),[192] 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.[193,194,195,196,197]

We applied the IPCS approach for continuous endpoints and the "approximate probabilistic" calculation (see IPCS report Fig 3.5, panel C)[198] to estimate risks of male reproductive effects from chronic oral exposure to DCHP. The analysis involved the following steps:

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

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[191] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 102.

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

[193] 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

[194] 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

[195] 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

[196] 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

[197] 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

[198] 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 DCHP 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.

STEP 1: Determination of IPCS POD and corresponding uncertainty adjustments

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

EPA derived a BMD of 8.4 mg/kg-day and a lower confidence limit (BMDL) of 6.0 mg/kg-day (applied dose) for a 5% reduction in fetal testicular testosterone by incorporating updated data in a meta-regression model developed by the National Academies of Science, Engineering, and Medicine (NASEM).[199] We use these values in applied dose units, as adjustment for allometric scaling to derive a human equivalent dose (HED) is applied separately in the interspecies adjustment step below.

In the IPCS methodology, the BMD of 8.4 mg/kg-day is the central estimate (P50) of the POD, and uncertainty in the POD (P95/P50) is equal to the ratio of BMD / BMDL:

P95/P50 = BMD / BMDL = 8.4 mg/kg-day / 6.0 mg/kg-day = 1.40

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)[200] 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

[199] U.S. EPA (2024). 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.

[200] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP), p. 71.

uncertainty with a P95/P50 factor of 3.[201] We incorporated these IPCS recommendations, which are entered In the IPCS approximate probabilistic calculation template as follows:

Interspecies adjustments for probabilistic dose-response analysis of chronic oral exposure to DCHP: reduced fetal testosterone		
Aspect	**P50**	**P95/P50**
$AF_{Interspecies\text{-}BS}$	5.64[a]	1.26[a]
$AF_{Interspecies\text{-}TK/TD}$	1	3
[a] Calculated from IPCS equation 4-2 using EPA assumptions regarding body weight of humans (80 kg) and rats (0.25 kg).		

Step 3: Application of intraspecies (human variability) adjustments

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

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

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

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

Step 4: Calculation of HD_M^I

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

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

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

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

Calculation of HD_M^I for chronic oral exposure to DCHP: reduced fetal testosterone (Incidence = 5%)		
Aspect	**P50**	**P95/P50**
BMD	8.4 mg/kg-d	1.4
$AF_{Interspecies-BS}$	5.64	1.26
$AF_{Interspecies-TK/TD}$	1	3
$AF_{Intra-I=1\%}$	4.98	2.82
HD_M^I	0.30 mg/kg-d[a]	4.78[b]
	P05	**P95**
HD_M^I [(c)]	**0.063 mg/kg-d**	1.4 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.4)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 2.82)^2]^{0.5}} = 4.78$
[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 DCHP: reduced fetal testosterone (Incidence = 1%)		
Aspect	**P50**	**P95/P50**
BMD	8.4 mg/kg-d	1.4
$AF_{Interspecies-BS}$	5.64	1.26
$AF_{Interspecies-TK/TD}$	1	3
$AF_{Intra-I=1\%}$	9.69	4.32
HD_M^I	0.15 mg/kg-d[a]	6.52[b]
	P05	**P95**
HD_M^I [(c)]	**0.024 mg/kg-d**	1.0 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.4)^2 + (\log 1.26)^2 + (\log 3)^2 + (\log 4.32)^2]^{0.5}} = 6.52$
[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.[202]
>
> 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.[203]

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).[204]

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).

Risk-specific dose estimates for chronic oral exposure to DCHP: reduced fetal testosterone	
Incidence (I)	**HD_M^I lower -confidence limit (P05)**
5%[a]	0.063 mg/kg-day
1%	0.024 mg/kg-day
0.5%	0.016 mg/kg-day
0.1% (1-in-1,000)	0.008 mg/kg-day
0.01% (1-in-10,000)	0.003 mg/kg-day
0.001% (1-in-100,000)	0.001 mg/kg-day

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

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

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

The implications of these risk values can be understood by comparison with the exposure levels considered by EPA to represent negligible risk. EPA's assessment uses a POD of 2.4 mg/kg-day (HED) and a benchmark MOE of 30,[205] meaning that EPA concludes "risk is not considered to be of concern and mitigation is not needed"[206] for any exposure below 0.08 mg/kg-day (2.4 mg/kg-day / 30 = 0.08 mg/kg-day). Our analysis indicates that an exposure of 0.08 mg/kg-day exceeds the lower-bound dose for the 5% (1-in-20) 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.[207]

The estimates of HD_M^I presented here were based entirely on input values and equations available from the WHO/IPCS methodology document and related publications, and from EPA's *Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP)*. 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

[205] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 101.
[206] U.S. EPA (2024). Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP), p. 102.
[207] U.S. EPA (2024). Unreasonable Risk Determination of the Draft Risk Evaluation for Formaldehyde, p. 13.

found in the general population.[208,209,210] 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.

[208] 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

[209] 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

[210] 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