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Comments from Scientists, Academics, and Clinicians on the Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP) Under TSCA

Submitted online via Regulations.gov to docket EPA-HQ-OPPT-2024-0551-0011

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.

We appreciate the opportunity to provide written comments on EPA's Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), conducted under the Toxic Substances Control Act (TSCA), which requires EPA to evaluate chemical risks based on the "best available science."[1]

Our comments are focused on EPA's inappropriate designation of a no-observed-adverse-effect level (NOAEL) of 50 mg/kg-day as the point of departure (POD) for characterizing non-cancer risks of BBP. EPA's selection of this POD is critically deficient in multiple respects, and our detailed comments address the following issues:

1. **EPA has not made a chemical-specific protocol for the BBP hazard assessment available to the public or the SACC.**
2. **EPA inappropriately excluded large numbers of relevant health-effects studies of BBP from consideration.**
    a. **EPA has not conducted a comprehensive literature search since 2019.**
    b. **EPA excluded relevant BBP health effects studies from the hazard assessment without scientific justification.**
    c. **EPA improperly excluded all human epidemiology studies from dose-response assessment.**
3. **EPA inappropriately excluded points of departure for BBP derived from the updated NASEM meta-regression model from consideration.**
4. **EPA inappropriately relied on NOAELs and LOAELs instead of conducting benchmark dose modeling, contrary to existing EPA guidance and NASEM recommendations.**

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

Sincerely,

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[1] 15 USC §2625(h).

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Detailed Comments:

1. **EPA has not made a chemical-specific protocol for the BBP hazard assessment available to the public or the SACC.**

In response to NASEM and SACC comments, EPA has initiated the practice of preparing a chemical-specific systematic review protocol for each TSCA risk evaluation it conducts. A protocol contains critical information detailing how evidence of a chemical's hazards is identified and evaluated, and best practices in systematic review dictate that a protocol be released before an assessment is conducted. EPA has previously released systematic review protocols for other phthalates (DCHP, DBP, DEHP) at the same time it released its draft risk evaluations for public comment and SACC review. The BBP draft non-cancer hazard assessment references a "Draft Systematic Review Protocol for Butyl Benzyl Phthalate" in multiple places.[2] The protocol, however, is not available in EPA's BBP or SACC dockets. EPA should be publishing a chemical-specific systematic review protocol for public comment before completing each draft risk evaluation, as recommended by the Institute of Medicine and the NASEM as a best practice for systematic review.[3,4]

The phthalate risk evaluation protocols that are available to the public were critically deficient, with inappropriate procedures for evidence identification and other crucial aspects of the risk

[2] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), pp. 11, 12, 17, 18.
[3] Institute of Medicine (2011). Finding what works in health care: Standards for systematic reviews.
[4] National Research Council (2014). Review of EPA's Integrated Risk Information System (IRIS) process.

evaluation, and were also incomplete, failing to address other key aspects. Despite their flaws, EPA's draft phthalate protocols did provide important information about EPA's process for narrowing the relevant health effects literature to a small subset of studies that were considered for non-cancer POD selection. For example, the DBP protocol indicates that EPA excluded 218 PECO-relevant epidemiology studies[5] and 228 PECO-relevant toxicology studies[6] from consideration, without valid scientific justification. From the prior protocols, we infer that EPA's BBP hazard assessment similarly excluded a large proportion of PECO-relevant health effects studies from consideration; actual numbers and procedures are likely stated in the draft BBP systematic review protocol that is not yet publicly available.

EPA should immediately release a systematic review protocol for BBP. The SACC should not complete its response to charge question 5.e. regarding the BBP point of departure until it has received a BBP systematic review protocol from EPA.

2. EPA inappropriately excluded large numbers of relevant health-effects studies of BBP from consideration.

a. EPA has not conducted a comprehensive literature search since 2019.

EPA last conducted a search of the literature for studies relevant to the BBP hazard assessment in 2019.[7] EPA considered only those epidemiology studies "published between 2018 and 2019."[8] A large number of epidemiology studies were published in this brief window:

> EPA identified 24 new developmental and 16 new reproductive epidemiology studies published between 2018 to 2019.[9]

This suggests it is highly likely that even more epidemiology studies have been published since 2019. Any such studies were not considered by EPA.

EPA considered only those toxicology studies "published between 2014 to 2019."[10] EPA says it identified 10 relevant studies published in this 5-year window, but it is unclear whether this represents all BBP toxicology studies from 2014-2019, as EPA applied a process to narrow the number of studies it considered (see comment below). Given there were at least 10 relevant toxicology studies published from 2014-2019, it is highly likely that more relevant studies were published since 2019. Any such studies were not considered by EPA.

b. EPA excluded relevant BBP health effects studies from the hazard assessment without scientific justification.

[5] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), p. 24.
[6] U.S. EPA (2025). Draft Systematic Review Protocol for Dibutyl Phthalate (DBP), Figure 4-6.
[7] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), p. 12.
[8] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), p. 32.
[9] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), p. 32.
[10] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), p. 28.

EPA's BBP hazard assessment excluded all studies of endpoints other than male reproductive effects. EPA says:

> the effects on the developing male reproductive system has consistently been identified in existing assessments of BBP as the most sensitive effects associated with oral exposure to BBP in experimental animal models…EPA identified no new information through systematic review that would change this conclusion. Therefore, EPA focused its non-cancer hazard characterization on developing male reproductive toxicity.[11]

EPA did not provide any explanation of how it decided not to evaluate studies of other endpoints. EPA did not disclose how many health effects studies of endpoints other than male reproductive effects it identified as PECO-relevant but then excluded from consideration. Based on the contents of protocols for other phthalates that are available, this information is likely stated in the draft BBP systematic review protocol that is not yet publicly available. EPA does mention animal studies of other endpoints published between 2014-2019 that it identified (3 reproductive/developmental studies, 3 neurotoxicity studies, 1 immunotoxicity study, 2 renal toxicity studies, 1 hepatic toxicity study),[12] but it is unclear whether this represents all identified toxicology studies of other endpoints published during that 5-year window, and it is unclear how many studies published prior to 2014 were identified and then disregarded.

Even within the narrowed scope of male reproductive effects, EPA did not consider all relevant studies. Figure 1-1 of the draft hazard assessment indicates that EPA applied a process to narrow the body of PECO-relevant BBP toxicology studies, based on publication date (2014-2019 only) and dose-response data (value of the lowest-observed-effect level (LOEL)).

EPA does report the number of studies that remained after applying this process:

> EPA identified 14 oral exposure studies (all of rats) that have investigated the effects of BBP on the developing male reproductive system.[13]

However, EPA does not report the number of studies that were considered in the process or the number that were excluded based on publication date or LOEL. Based on the contents of protocols for other phthalates that are available, this information is likely stated in the draft BBP systematic review protocol that is not yet publicly available.

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

[11] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), p. 27.
[12] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), pp. 18-19.
[13] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), p. 34.

EPA has not yet released any evaluation of the quality of the BBP epidemiology studies considered in the assessment. EPA's epidemiology study quality evaluations for other phthalates have rated the vast majority of studies as "High" or "Medium."[14]

EPA has disregarded the results of its systematic review procedures, in which the quality of each study is evaluated individually, by excluding all epidemiology studies from its BBP 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, primarily due to uncertainty associated with exposure characterization. Primary sources of uncertainty include the source(s) of exposure; timing of exposure assessment that may not be reflective of exposure during outcome measurements; and use of spot-urine samples, which due to rapid elimination kinetics may not be representative of average urinary concentrations that are collected over a longer term or calculated using pooled samples. The majority of epidemiological studies introduced additional uncertainty by not considering BBP in isolation and failing to account for confounding effects from co-exposure to mixtures of multiple phthalates.[15]

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.[16] The preamble to EPA's 2024 final framework rule for conducting risk evaluations re-stated EPA's commitment to systematic review:

> EPA believes that integrating appropriate and applicable systematic review methods into the TSCA risk evaluations is critical to meeting the scientific standards as described in TSCA section 26(h) and (i)…. The principles of systematic review are well-established and include "transparent and explicitly documented methods, consistent and critical evaluation of all relevant literature, application of a standardized approach for grading the strength of evidence, and clear and consistent summative language" (Ref. 26). EPA has finalized the requirement to use and document systematic review methods to assess reasonably available information.[17]

EPA's broad exclusion of BBP 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. Judging by procedures applied for other phthalates, EPA evaluated the quality of individual studies, following systematic review methods outlined in the draft BBP protocol that is not publicly available. It then effectively ignored its systematic review process and excluded all epidemiology studies from dose-response assessment with an argument that

[14] U.S. EPA (2025). Data Quality Evaluation Information for Human Health Hazard Epidemiology for Dibutyl Phthalate (DBP).
[15] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), p. 13.
[16] 15 USC §2625(h).
[17] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA). 89 FR 37028.

demonstrates a bias against environmental epidemiology, rather than a thoughtful approach to evidence evaluation that is consistent with best practices in systematic review.

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

> Several recent human epidemiology studies of DINP non-cancer effects, including developmental effects were excluded from the dose-response assessment. These studies were excluded because of uncertainty about exposure. However, the studies focused on measurement of urinary biomarkers of phthalates, including metabolites of DINP. While there are technical issues when using urinary biomarkers for determination of exposure, this is a common approach and the gold standard for phthalates to understand the association between the chemicals and outcomes relevant in people. EPA individually assessed the merits of 53 epidemiology studies of DINP, published from 2018 to 2021, applying a pre-specified set of study quality domains and metrics that closely mirrors the approach used by EPA's IRIS program, which has been favorably reviewed by the NASEM. EPA's overall quality determination was "Medium" or "High" for 46 of these epidemiology studies. Each study was individually assessed for its exposure measurement methods (Domain 2) and treatment of potential confounding (Domain 4).[18]

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.[19]

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

Moreover, EPA's explanation considers only alleged limitations of the BBP 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

[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. 91.

[19] 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.

to the extent this occurs, it is likely to result in imprecision in effect estimates, rather than overstatement of effects. In general, the uncertainties in exposure characterization may result in exposure misclassification, but that does not mean the studies are not useful or informative and potentially strong candidates for determination of the point of departure (POD).

By excluding relevant epidemiology studies of BBP from dose-response analysis, EPA has violated TSCA's requirement to use the best available science.[20] EPA cannot broadly exclude epidemiologic studies from dose-response assessment in the BBP hazard assessment, and must consider each relevant study on an individual basis as a candidate for POD derivation.

3. EPA inappropriately excluded points of departure for BBP derived from the updated NASEM meta-regression model from consideration.

EPA updated a meta-regression model developed by the NASEM, using data from 14 studies of reduced fetal testosterone for 6 anti-androgenic phthalates to derive relative potency factors (RPFs) for cumulative risk assessment and to inform selection of PODs for the individual phthalate risk evaluations. EPA says that benchmark dose (BMD) results for BBP are not available from the updated meta-regression model:

> Although BBP effects on *ex vivo* fetal testicular testosterone production has been used in prior assessments for BMD modeling and effect level estimates (NASEM, 2017), updated meta-analysis modeling data by the EPA could not derive a BMD_5 (Table 4-5).[21]

EPA's statement is incorrect. Although it is true that the updated meta-regression linear quadratic model using the most current version of the statistical software package (Metafor Version 4.6.0) did not estimate a BMD_5 or its lower confidence limit ($BMDL_5$), EPA has still has at least two BMD/BMDL options from the updated meta-regression. First, EPA was able to estimate the BMD_5 (31 mg/kg-d) and $BMDL_5$ (17 mg/kg-d) with the updated meta-regression linear quadratic model using Metafor Version 2.0.0.[22] Second, EPA was able to estimate the BMD_5 (22 mg/kg-d) and $BMDL_5$ (17 mg/kg-d) with the updated meta-regression linear model (rather than linear quadratic model) using Metafor Version 4.6.0.[23,24] Using either set of results is scientifically appropriate given that Metafor Version 4.6.0 did not provide BMD/BMDL estimates using the linear quadratic model. In either instance, the updated NASEM meta-regression model provides a $BMDL_5$ of 17 mg/kg-d. The $BMDL_5$ is derived using the best available science – a rigorous statistical model derived by the NASEM, compared with a simplistic NOAEL – and is also far more health protective, with a value equal to 1/3 of the NOAEL.

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[20] 15 USC §2625(h).
[21] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), p. 60.
[22] U.S. EPA (2024). Draft Meta-analysis and Benchmark Dose Modeling of Fetal Testicular Testosterone for Di(2-ethylhexyl) Phthalate (DEHP), Dibutyl Phthalate (DBP), Butyl Benzyl Phthalate (BBP), Diisobutyl Phthalate (DIBP), and Dicyclohexyl Phthalate (DCHP), Table 4-16.
[23] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), Table 4-5.
[24] U.S. EPA (2024). Draft Meta-analysis and Benchmark Dose Modeling of Fetal Testicular Testosterone for Di(2-ethylhexyl) Phthalate (DEHP), Dibutyl Phthalate (DBP), Butyl Benzyl Phthalate (BBP), Diisobutyl Phthalate (DIBP), and Dicyclohexyl Phthalate (DCHP), Table 4-16.

4. **EPA inappropriately relied on NOAELs and LOAELs instead of conducting benchmark dose modeling, contrary to existing EPA guidance and NASEM recommendations.**

EPA considered 14 animal studies of BBP male reproductive toxicity published up to 2021 in its dose-response analysis.[25] For most of these studies, EPA considered only the NOAEL or lowest-observed-adverse-effect level (LOAEL) as candidate PODs. From this set of studies EPA selected a NOAEL of 50 mg/kg-d from a study by Tyl et al. as the POD. In making this selection, EPA discounted the meta-regression BMDLs of 17 mg/kg-d (see comment above), as well as the NOAEL of 11 mg/kg-d from a 2021 study by Gray et al. and the NOAEL of 20 mg/kg-d from a study by Ahmad et al.[26]

EPA's explanation for disregarding the Gray et al. NOAEL is not valid, disregarding the broader knowledge of the adverse outcome pathway for phthalates:

> Gray et al. (2021) reported testicular mRNA expression changes in pertinent steroidogenic genes…These mRNA changes suggested a no-observed-effect-level of 11 mg/kg-day (Table 4-1); however, these gene effects are not considered adverse in isolation.[27]

EPA's draft hazard documents for other phthalates (e.g. DCHP, DEHP) clearly and correctly identify decreased steroidogenic gene expression as a key event in the phthalate syndrome mode of action.[28] This endpoint is clearly adverse, contrary to EPA's assertion in the BBP hazard assessment, based on EPA's own characterization of phthalate syndrome elsewhere.

Instead of selecting any NOAEL or LOAEL as the POD, EPA should follow its own well-established guidance[29] and recommendations of the NASEM and SACC by conducting BMD modeling for all studies and endpoints listed in Table 4-1, many of which could conceivably yield a BMDL below EPA's chosen POD of 50 mg/kg-d, and considering the results alongside the meta-regression BMDL of 17 mg/kg-d. EPA should also conduct BMD modeling for other candidate studies and endpoints – not restricted to male reproductive effects – and then use the lowest overall BMDL, or a set of BMDLs (representing different studies, endpoints and organ systems) as the POD for risk characterization of BBP. This is the approach taken in multiple

[25] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), Table 4-1.
[26] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), Table 4-1.
[27] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Butyl Benzyl Phthalate (BBP), p. 55.
[28] U.S. EPA (2024). Draft Non-Cancer Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP), Figure 3-1.
[29] U.S. EPA (2012). Benchmark Dose Technical Guidance.

previous TSCA risk evaluations, such as those for trichloroethylene,[30] 1,4-dioxane,[31] n-methylpyrrolidone,[32] and 1,3-butadiene.[33]

EPA's dose-response assessment for DEHP is not consistent with the best available science, as stated in EPA guidance[34] and reports from the NASEM.[35,36] EPA's 2012 Benchmark Dose Technical Guidance is unequivocal in describing the limitations of NOAEL/LOAELs and in stating a strong preference for BMDLs rather than NOAEL/LOAELs.

The BMD guidance represents the best available science, and it clearly states the significant limitations of NOAELs and LOAELs:

> The NOAEL is actually of little practical utility in describing toxicological dose-response relationships; it does not represent a biological threshold and cannot establish that lower exposure levels are necessarily without risk. Specific limitations of the NOAEL/LOAEL approach are well known and have been discussed extensively (Crump 1984; Gaylor 1983; Kimmel and Gaylor 1988; Leisenring and Ryan 1992; U.S. EPA 1995a):
>
> - The NOAEL/LOAEL is highly dependent on sample size. The ability of a bioassay to distinguish a treatment response from a control response decreases as sample size decreases, so the NOAEL for a compound (and thus the POD, when based on a NOAEL) will tend to be higher in studies with smaller numbers of animals per dose group.
> - More generally, the NOAEL/LOAEL approach does not account for the variability and uncertainty in the experimental results that are due to characteristics of the study design such as dose selection, dose spacing, and sample size.
> - NOAELs/LOAELs do not correspond to consistent response levels for comparisons across studies/chemicals/endpoints, and the observed response level at the NOAEL or LOAEL is not considered in the derivation of RfDs/RfCs.
> - Other dose-response information from the experiment, such as the shape of the dose-response curve (e.g., how steep or shallow the slope is at the BMD, providing some indication of how near the POD might be to an inferred threshold), is not taken into account…
> - While the NOAEL has typically been interpreted as a threshold (no-effect level), simulation studies (e.g., Leisenring and Ryan 1992; study designs involving 10, 20, or 50 replicates per dose group) and re-analyses of developmental toxicity bioassay data (Gaylor 1992; Allen et al. 1994a; studies involving approximately 20 litters per dose group) have demonstrated that the rate of response above control at doses fitting the

[30] U.S. EPA (2020). Risk Evaluation for Trichloroethylene, Tables 3-8 to 3-14.
[31] U.S. EPA (2020). Final Risk Evaluation for 1,4-Dioxane, Table 3-9.
[32] U.S. EPA (2020). Risk Evaluation for n-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP), Table 3-11.
[33] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene, Table 4-1.
[34] U.S. EPA (2012). Benchmark Dose Technical Guidance.
[35] NASEM (2017). Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals, p. 158.
[36] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 129.

> criteria for NOAELs, for a range of study designs, is about 5–20% on average, not 0%.[37]

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.[38]
>
> 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.[39]
>
> 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.[40]
>
> 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.[41]

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.[42]

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

[37] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 4.
[38] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 6.
[39] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 12.
[40] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 30.
[41] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 40.
[42] U.S. EPA (2020). Risk Evaluation for n-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP), p. 262.

> no-observed adverse-effect level/ lowest-observed-adverse-effect level (NOAEL/LOAEL) approach.[43]
>
> Basis of the POD: A modeled BMDL is preferred over a NOAEL, which is in turn preferred over a LOAEL.[44]

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.[45]

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.[46]

EPA disregarded all of the above guidance in its overall approach to dose-response assessment for BBP. Its selection of 50 mg/kg-day as the POD is based on a summary of dose-response data from 14 studies, most of which are characterized only with a NOAEL or LOAEL.[47]

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

[43] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, p. 8-1.
[44] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, p. 8-18.
[45] NASEM (2017). Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals, p. 158.
[46] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 129.
[47] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diethylhexyl Phthalate (DEHP), Table 4-3.

> 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.[48]

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 BBP are very similar to those of its previous risk evaluation of DINP. In its review of that assessment, the SACC commented that much more thorough BMD modeling of multiple studies was necessary to inform selection of the point of departure:

> EPA should use all available dose range studies from which BMD-based POD should be developed, compared with each other to select the lowest BMD-based POD as the basis for the derivation for the HED.[49]

> EPA should apply benchmark dose modeling to derive chronic non-cancer points of departure and select the one that is most sensitive (lowest).[50]

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.[51]

EPA's dose-response analysis for BBP 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.[52]

> EPA will document that the risk evaluation is consistent with the best available science.[53]

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[48] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 15.

[49] 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.

[50] 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.

[51] 15 U.S.C. § 2625(h).

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

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

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