August 04, 2025

Comments from Scientists, Academics, and Clinicians on the Draft Non-cancer Human Health Hazard Assessment for Diisobutyl Phthalate (DIBP) 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 Diisobutyl Phthalate (DIBP), 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 process for designating 24 mg/kg-day as the point of departure (POD) for characterizing non-cancer risks of DIBP, based on benchmark dose modeling of a single study. Although this value is a viable option for POD, there are better choices for POD from the scientifically rigorous updated application of a meta-regression model developed by the National Academies of Sciences, Engineering, and Medicine (NASEM). In addition, EPA's process for determining the POD is critically deficient in multiple respects. Our detailed comments address the following issues:

1. **EPA has not made a chemical-specific protocol for the DIBP hazard assessment available to the public or the SACC.**
2. **EPA inappropriately excluded large numbers of relevant health-effects studies of DIBP from consideration.**
    a. **EPA has not conducted a comprehensive literature search since 2019.**
    b. **EPA excluded relevant DIBP 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 DIBP derived from the updated NASEM meta-regression model from consideration.**
4. **EPA should delete the options for a DIBP point of departure that inappropriately rely on NOAELs and instead include approaches using benchmark dose estimates provided by the updated NASEM meta-regression model.**

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

Sincerely,

[1] 15 USC §2625(h).

Daniel Axelrad, MPP
Independent Consultant
Washington, DC

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

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

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

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

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

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

Ronald H White, MST
Principal
RHWhite Environmental Health Consulting

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

Sharyle Patton
Director
Health and Environment Program - Commonweal

Daniel Ruiz, PhD

Postdoctoral Fellow
Emory University School of Medicine, Department of Human Genetics

Courtney Carignan, PhD
Associate Professor
Michigan State University

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

Robert M. Gould, MD*
President
San Francisco Bay Physicians for Social Responsibility

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

Linda S. Birnbaum, PhD
Scientist Emeritus
NIEHS

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

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

Christopher LeBoa, PhD
Post-doctoral scholar
UC Berkeley

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

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

James Seward, MD, MPP

Clinical Professor of Medicine
UCSF

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

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

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

Sara Carpenter, MD, MSPH, DCM
Retired

Detailed Comments:

1. **EPA has not made a chemical-specific protocol for the DIBP 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 DIBP draft non-cancer hazard assessment references a "Draft Systematic Review Protocol for Diisobutyl Phthalate" in multiple places.[2] The protocol, however, is not available in EPA's DIBP 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 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

[2] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisobutyl Phthalate (DIBP), pp. 9, 10, 11, 15, 16.
[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.

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 DIBP 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 DIBP systematic review protocol that is not yet publicly available.

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

2. EPA inappropriately excluded large numbers of relevant health-effects studies of DIBP 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 DIBP 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 40 new epidemiologic studies (24 developmental and 16 reproductive) that evaluated the association between urinary DIBP and its metabolite (MIBP) and reproductive and developmental outcomes.[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.

For identifying relevant toxicology studies of DIBP, EPA's review considered only those toxicology studies "published between 2017 to 2019,"[10] although EPA also says that it considered studies published from 2014 to 2019.[11] EPA says it identified 2 relevant studies published in 2017-2019,[12] but one of them (Gray et al.) was actually published in 2021, so EPA's process is not clear. Further it is unclear whether the 2 identified studies represents all relevant DIBP toxicology studies from EPA's search, as EPA applied a process to narrow the number of studies it considered (see comment below). It appears that EPA did not attempt to determine whether additional relevant toxicology studies were published after 2019. After including studies identified by previous other assessments of DIBP toxicity, EPA considered 13 studies in its hazard and dose-response assessment:

---

[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 Diisobutyl Phthalate (DIBP), p. 10.
[8] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisobutyl Phthalate (DIBP), p. 19.
[9] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisobutyl Phthalate (DIBP), p. 23.
[10] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisobutyl Phthalate (DIBP), p. 16.
[11] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisobutyl Phthalate (DIBP), Figure 1-1.
[12] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisobutyl Phthalate (DIBP), p. 16.

> EPA identified 13 oral exposure studies (11 of rats, 2 of mice) that have investigated the effects of DIBP on the developing male reproductive system.[13]

Gray et al. 2021 was the only toxicology study included in the DIBP hazard assessment that was published after 2017.

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

EPA's DIBP 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 as the most sensitive effects associated with oral exposure to DIBP in experimental animal models in existing assessments of DIBP… as well as prior systematic reviews…EPA identified no new information through systematic review that would change this conclusion. Therefore, EPA focused its non-cancer hazard characterization on the developing male reproductive system.[14]

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 DIBP systematic review protocol that is not yet publicly available.

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 DIBP toxicology studies, based on publication date (2014-2019 only) and dose-response data (value of the lowest-observed-effect level (LOEL)).

As noted above EPA reports that 13 studies that remained after applying this process. 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 DIBP systematic review protocol that is not yet publicly available.

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

[13] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisobutyl Phthalate (DIBP), p. 26.
[14] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisobutyl Phthalate (DIBP), p. 19.

EPA has not yet released any evaluation of the quality of the DIBP 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."[15]

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 DIBP 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 considering DIBP in isolation and failing to account for confounding effects from co-exposure to mixtures of multiple phthalates.[16]

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.[17] 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.[18]

EPA's broad exclusion of DIBP 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 DIBP 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

[15] U.S. EPA (2025). Data Quality Evaluation Information for Human Health Hazard Epidemiology for Dibutyl Phthalate (DBP).
[16] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisobutyl Phthalate (DIBP), p. 10.
[17] 15 USC §2625(h).
[18] 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).[19]

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.[20]

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 DIBP.

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

[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. 91.

[20] 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 DIBP from dose-response analysis, EPA has violated TSCA's requirement to use the best available science.[21] EPA cannot broadly exclude epidemiologic studies from dose-response assessment in the DIBP 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 DIBP 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 (including 3 studies of DIBP) 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 DIBP at the 5% response level are not available from the updated meta-regression model.[22]

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 (36 mg/kg-d) and $BMDL_5$ (23 mg/kg-d) with the updated meta-regression linear quadratic model using Metafor Version 2.0.0.[23] Second, EPA was able to estimate the BMD_5 (28 mg/kg-d) and $BMDL_5$ (20 mg/kg-d) with the updated meta-regression linear model (rather than linear quadratic model) using Metafor Version 4.6.0.[24,25] 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. The updated NASEM meta-regression model therefore provides a $BMDL_5$ of either 23 mg/kg-d or 20 mg/kg-d. These $BMDL_5$ values were derived using a rigorous statistical model derived by the NASEM. EPA's selected POD of 24 mg/kg-d – the $BMDL_5$ from Gray et al.[26] – is roughly comparable and nearly as protective. However, the BMDL values from the NASEM model have

[21] 15 USC §2625(h).
[22] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisobutyl Phthalate (DIBP), p. 39.
[23] 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 4-12.
[24] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisobutyl Phthalate (DIBP), Table 4-3.
[25] 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 4-12.
[26] U.S. EPA (2024). Draft Non-cancer Human Health Hazard Assessment for Diisobutyl Phthalate (DIBP), Table ES-1.

the advantages of being more rigorous in integrating the data from Gray et al. and 2 other studies, and providing a slightly more health-protective value.

4. **EPA should delete the options for a DIBP point of departure that inappropriately rely on NOAELs and instead include approaches using benchmark dose estimates provided by the updated NASEM meta-regression model.**

EPA presents 3 options for deriving a non-cancer POD for DIBP and selected as POD the $BMDL_5$ of 24 mg/kg-d derived from the Gray et al. study as discussed above (Option 3). EPA correctly rejected the use of a NOAEL (Option 1); this option should be replaced with the meta-regression BMDL outputs for DIBP as described above.

As Option 2, EPA presented a combination of the NOAEL with the DIBP RPF. Although Option 2 is critically flawed in its consideration of a NOAEL rather than BMDL, the element of this option involving use of the RPF warrants further consideration in a more scientifically rigorous application that uses the DBP $BMDL_5$ instead of the DBP NOAEL.

In the draft cumulative risk assessment (CRA) for phthalates, EPA designated dibutyl phthalate (DBP) as the index chemical, with a $BMDL_5$ of 9 mg/kg-d derived from the updated application of the NASEM meta-regression model.[27] From the same meta-regression model, EPA calculated a DIBP relative potency factor (RPF) of 0.53.[28] EPA should combine these two values to derive a $BMDL_5$ for DIBP, as a replacement for EPA's current Option 2:

$$\text{DIBP } BMDL_5 = \text{DBP } BMDL_5 / \text{DIBP RPF}$$
$$\text{DIBP } BMDL_5 = 9 \text{ mg/kg-d} / 0.53$$
$$\text{DIBP } BMDL_5 = 17 \text{ mg/kg-d}$$

This value should be regarded as the best available science because it is determined entirely from outputs of the scientifically rigorous NASEM meta-regression model, integrating data from multiple studies of reduced fetal testicular testosterone for multiple phthalates in the same model, and does not make use of a scientifically deficient NOAEL.

EPA therefore has 3 viable options for the POD, all of which use BMD modeling rather than a NOAEL:

- New Option 1 – $BMDL_5$ of 23 mg/kg-d or 20 mg/kg-d estimated directly by NASEM meta-regression model integrating data from multiple studies.

[27] U.S. EPA (2025). Revised Draft Technical Support Document for the Cumulative Risk Analysis of Di(2-ethylhexyl) Phthalate (DEHP), Dibutyl Phthalate (DBP), Butyl Benzyl Phthalate (BBP), Diisobutyl Phthalate (DIBP), Dicyclohexyl Phthalate (DCHP), and Diisononyl Phthalate (DINP) Under the Toxic Substances Control Act (TSCA), p. 27.

[28] U.S. EPA (2025). Revised Draft Technical Support Document for the Cumulative Risk Analysis of Di(2-ethylhexyl) Phthalate (DEHP), Dibutyl Phthalate (DBP), Butyl Benzyl Phthalate (BBP), Diisobutyl Phthalate (DIBP), Dicyclohexyl Phthalate (DCHP), and Diisononyl Phthalate (DINP) Under the Toxic Substances Control Act (TSCA), p. 27.

- New Option 2 – $BMDL_5$ of 17 mg/kg-d estimated from NASEM meta-regression outputs for DBP $BMDL_5$ and DIBP RPF, integrating data from multiple studies.
- Option 3 - $BMDL_5$ of 24 mg/kg-d derived from Gray et al. 2021.

New Option 2 is the best choice, because it uses data that derived from the same model and the $BMDL_5$ and RPF are being used in EPA's phthalates CRA. This approach is consistent with the CRA while using the most rigorous modeling approach that represents the best available science. New Option 1 also warrants consideration because it is based on the meta-regression model and uses outputs that are directly for DIBP. Option 3 is a viable option, however it is not the best choice because it relies on data from a single study rather than the more rigorous modeling that underlies Options 1 and 2, and is a somewhat less health-protective value.

EPA's Options 1 (NOAEL) and 2 (RPF-adjusted NOAEL) should be discarded. These options are critically deficient because they are based on NOAELs when strong candidate PODs based on BMD modeling are available. These approaches are not consistent with the best available science, as stated in EPA guidance[29] and reports from the NASEM.[30,31] 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

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

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%.[32]

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.[33]
>
> 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.[34]
>
> 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.[35]
>
> 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.[36]

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.[37]

[32] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 4.
[33] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 6.
[34] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 12.
[35] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 30.
[36] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 40.
[37] U.S. EPA (2020). Risk Evaluation for n-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP), p. 262.

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.[38]
>
> Basis of the POD: A modeled BMDL is preferred over a NOAEL, which is in turn preferred over a LOAEL.[39]

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.[40]

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.[41]

To be consistent with the best available science, EPA should not give any further consideration to any candidate DIBP POD that is based on a NOAEL, and it should replace the 2 current NOAEL-based options with approaches based on BMDL values provided by the updated application of the NASEM meta-regression model.

[38] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, p. 8-1.
[39] U.S. EPA (2022). ORD Staff Handbook for Developing IRIS Assessments, p. 8-18.
[40] NASEM (2017). Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals, p. 158.
[41] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 129.