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Non-cancer Human Health Hazard Assessment for Diisobutyl Phthalate (DIBP)

Technical Support Document for the Risk Evaluation

CASRN: 84-69-5

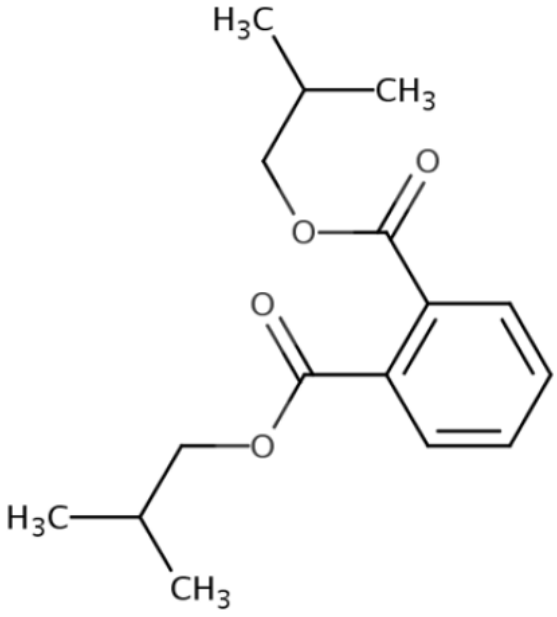

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDIX TABLES

KEY ABBREVIATIONS AND ACRONYMS

ADME	Absorption, distribution, metabolism, and excretion
BMD	Benchmark dose
BMDL	Benchmark dose lower bound
BMR	Benchmark response
CASRN	Chemical abstracts service registry number
CPSC	Consumer Product Safety Commission (U.S.)
BBP	Butyl-benzyl-phthalate
DBP	Dibutyl phthalate
DEHP	Di-ethylhexyl phthalate
DIBP	Diisobutyl phthalate
DINP	Di-isononyl phthalate
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency (U.S.)
GD	Gestational day
HEC	Human equivalent concentration
HED	Human equivalent dose
LOAEL	Lowest-observable-adverse-effect level
LOEL	Lowest-observable-effect level
MOA	Mode of action
MOE	Margin of exposure
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEL	No-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
OPPT	Office of Pollution Prevention and Toxics
PBPK	Physiologically based pharmacokinetic
PECO	Population, exposure, comparator, and outcome
PESS	Potentially exposed or susceptible subpopulations
PND	Postnatal day
POD	Point of departure
RPF	Relative Potency Factor
SACC	Science Advisory Committee on Chemicals
SD	Sprague-Dawley
TSCA	Toxic Substances Control Act
UF	Uncertainty factor
U.S.	United States

SUMMARY

This technical support document is in support of the TSCA *Risk Evaluation for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025n). This document describes the use of available information to identify the non-cancer hazards associated with exposure to DIBP and the points of departure (PODs) to be used to estimate risks from DIBP exposures in the risk evaluation of DIBP. Environmental Protection Agency (EPA, or the Agency) summarizes the cancer and genotoxicity hazards associated with exposure to DIBP in the *Cancer Human Health Hazard Assessment for Di(2-ethylhexyl) Phthalate (DEHP), Dibutyl Phthalate (DBP), Diisobutyl Phthalate (DIBP), Butyl Benzyl Phthalate (BBP), and Dicyclohexyl Phthalate (DCHP)* (U.S. EPA, 2025a).

EPA identified effects on the developing male reproductive system as the most sensitive and robust non-cancer hazard associated with oral exposure to DIBP in experimental animal models (Section 3.1). Existing assessments of DIBP also identified effects on the developing male reproductive system as the most sensitive and robust non-cancer effect following oral exposure to DIBP. Existing assessments included those by the U.S. Consumer Product Safety Commission (U.S. CPSC, 2014, 2011), Health Canada (ECCC/HC, 2020; EC/HC, 2015b), European Chemicals Agency (2017a, b), and the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS, 2008a), as well as a systematic review by Yost et al., (2019), which drew conclusions consistent with those of the aforementioned regulatory bodies. EPA also considered epidemiologic evidence qualitatively as part of hazard identification and characterization. However, epidemiologic evidence for DIBP was not considered further for dose response analysis due to limitations and uncertainties in exposure characterization (discussed further in Section 1.1). Use of epidemiologic evidence qualitatively is consistent with phthalates assessment by Health Canada, U.S. CPSC, NICNAS, and ECHA.

As discussed further in Section 3.1.2, EPA identified 13 oral exposure studies (11 of rats, 2 of mice) that have investigated the developmental and reproductive effects of DIBP following gestational and/or perinatal exposure to DIBP (Gray et al., 2021; Pan et al., 2017; Saillenfait et al., 2017; Wang et al., 2017; Sedha et al., 2015; Furr et al., 2014; Hannas et al., 2012; Hannas et al., 2011; Howdeshell et al., 2008; Saillenfait et al., 2008; BASF, 2007; Borch et al., 2006; Saillenfait et al., 2006). No one- or two-generation reproduction studies of DIBP are available for any route of exposure. Across available studies, the most sensitive developmental effects identified by EPA include effects on the developing male reproductive system consistent with a disruption of androgen action and the development of phthalate syndrome. EPA has selected a POD of 24 mg/kg-day (human equivalent dose [HED] of 5.7 mg/kg-day) based on phthalate syndrome-related effects on the developing male reproductive system (*i.e.,* decreased fetal testicular testosterone) to estimate non-cancer risks from oral exposure to DIBP for acute, intermediate, and chronic durations of exposure in the risk evaluation of DIBP. The selected POD was derived from benchmark dose (BMD) modeling of *ex vivo* fetal testicular testosterone data and supports a 95 percent lower confidence limit on the BMD associated with a benchmark response (BMR) of 5 percent ($BMDL_5$) of 24 mg/kg-day (Gray et al., 2021).

The Agency performed ¾ body weight scaling to yield the HED and applied the animal to human extrapolation factor (*i.e.,* interspecies extrapolation; UF_A) of 3× and a within human variability extrapolation factor (*i.e.,* intraspecies extrapolation; UF_H) of 10×. Thus, a total uncertainty factor (UF) of 30× was applied for use as the benchmark margin of exposure (MOE). Based on the strengths, limitations, and uncertainties discussed Section 4.3, EPA reviewed the weight of scientific evidence and has robust overall confidence in the selected POD based on decreased fetal testicular testosterone for use in characterizing risk from exposure to DIBP for acute, intermediate, and chronic exposure scenarios. The applicability and relevance of this POD for all exposure durations (acute, intermediate, and chronic) is described in the introduction to Section 4 and additionally in Section 4.2 and Appendix B. For

purposes of assessing non-cancer risks, the selected POD is considered most applicable to women of reproductive age, pregnant women, and male infants. Use of this POD to assess risk for other age groups (*e.g.*, older children, adult males, and the elderly) is considered to be conservative and appropriate for a screening level assessment for these other age groups.

No data are available for the dermal or inhalation routes that are suitable for deriving route-specific PODs. Therefore, EPA is using the acute/intermediate/chronic oral POD to evaluate risks from dermal and inhalation exposure to DIBP. For the dermal route, differences in absorption are being accounted for in dermal exposure estimates in the risk evaluation for DIBP. For the inhalation route, EPA extrapolated the oral HED to an inhalation human equivalent concentration (HEC) per EPA's *Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry* (U.S. EPA, 1994) using the updated human body weight and breathing rate relevant to continuous exposure of an individual at rest provided in EPA's *Exposure factors handbook: 2011 edition* (U.S. EPA, 2011b). Table ES-1 and Section 6 summarize EPA's selection of the oral HED and inhalation HEC values used to estimate non-cancer risk from acute/intermediate/chronic exposure to DIBP in the risk evaluation of DIBP.

This non-cancer human health hazard assessment for DIBP was released for public comment and was peer-reviewed by the Science Advisory Committee on Chemicals (SACC) during the August 4-8, 2025 SACC Meeting (U.S. EPA, 2025o). Following SACC peer-review and public comment, this technical support document was revised to incorporate recommendations from the SACC and the public.

Table ES-1. Non-cancer HED and HEC Used to Estimate Risks

Exposure Scenario	**Target Organ System**	**Species**	**Duration**	**POD (mg/kg-day)**	**Effect**	**HED (mg/kg-day)**	**HEC (mg/m^3) [ppm]**	**Benchmark MOE**	**Reference** (TSCA Study Quality Evaluation)
Acute, intermediate, chronic	Developmental toxicity	Rat	4 days during gestation (GDs 14-18)	$BMDL_5$= 24	↓ *ex vivo* fetal testicular testosterone production	5.7	30.9 [2.71]	UF_A= 3[a] UF_H=10 *Total UF=30*	(Gray et al., 2021) (High)

Abbreviations: HEC = human equivalent concentration; HED = human equivalent dose; MOE = margin of exposure; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor

[a] EPA used allometric body weight scaling to the three-quarters power to derive the HED. Consistent with EPA Guidance (U.S. EPA, 2011c), the UF_A was reduced from 10 to 3.

1 INTRODUCTION

In December 2019, EPA designated diisobutyl phthalate (DIBP) (CASRN 85-69-5) as a high-priority substance for risk evaluation following the prioritization process as required by Section 6(b) of the Toxic Substances Control Act (TSCA) and implementing regulations (40 CFR part 702). The Agency published the draft and final scope documents for DIBP in 2020 (U.S. EPA, 2020a, b). Following publication of the final scope document, one of the next steps in the TSCA risk evaluation process is to identify and characterize the human health hazards of DIBP and conduct a dose-response assessment to determine the toxicity values to be used to estimate risks from DIBP exposures. This technical support document summarizes the non-cancer human health hazards associated with exposure to DIBP and provides the selected non-cancer toxicity values to be used to estimate risks from DIBP exposures. Cancer human health hazards associated with exposure to DIBP are summarized in EPA's *Cancer Human Health Hazard Assessment for Di(2-ethylhexyl) Phthalate (DEHP), Dibutyl Phthalate (DBP), Diisobutyl Phthalate (DIBP), Butyl Benzyl Phthalate (BBP), and Dicyclohexyl Phthalate (DCHP)* (U.S. EPA, 2025a).

Over the past several decades, the human health effects of DIBP have been reviewed by several regulatory and authoritative agencies, including: the U.S. Consumer Product Safety Commission (U.S. CPSC); Health Canada; the European Chemicals Agency (ECHA); the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS); and The National Academies of Sciences, Engineering, and Medicine (NASEM). EPA relied on information published in these assessments as a starting point for its human health hazard assessment of DIBP. Additionally, EPA considered literature published since the most recent existing assessments of DIBP to determine if newer information might support the identification of new human health hazards or lower PODs for use in estimating human risk. EPA's process for considering and incorporating DIBP literature is described in the *Systematic Review Protocol for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025q). EPA's approach and methodology for identifying and using human epidemiologic data and experimental laboratory animal data is described in Sections 1.1 and 1.2.

1.1 Human Epidemiologic Data: Approach and Conclusions

To identify and integrate human epidemiologic data into the DIBP Risk Evaluation, EPA first reviewed existing assessments of DIBP conducted by regulatory and authoritative agencies, as well as several systematic reviews of epidemiologic studies of DIBP published by Radke et al., in the open literature. Although the authors (*i.e.*, Radke et al.) are affiliated with the U.S. EPA's Center for Public Health and Environmental Assessment, the reviews do not reflect EPA policy. Existing epidemiologic assessments reviewed by EPA are listed below. As described further in Appendix A, most of these assessments have been subjected to peer-review and/or public comment periods and have employed formal systematic review protocols of varying structure and scope. The assessments and open literature used as a baseline in this risk evaluation are listed below.

- *Supporting documentation: Evaluation of epidemiologic studies on phthalate compounds and their metabolites for hormonal effects, growth and development and reproductive parameters* (Health Canada, 2018b);
- *Supporting documentation: Evaluation of epidemiologic studies on phthalate compounds and their metabolites for effects on behaviour and neurodevelopment, allergies, cardiovascular function, oxidative stress, breast cancer, obesity, and metabolic disorders* (Health Canada, 2018a);
- *Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals (*NASEM, 2017*);*

- *Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence* (Radke et al., 2018);
- *Phthalate exposure and female reproductive and developmental outcomes: A systematic review of the human epidemiological evidence* (Radke et al., 2019b);
- *Phthalate exposure and metabolic effects: A systematic review of the human epidemiological evidence* (Radke et al., 2019a); and
- *Phthalate exposure and neurodevelopment: A systematic review and meta-analysis of human epidemiological evidence* (Radke et al., 2020a).

In developing the epidemiology human health hazard assessment for DIBP, EPA conducted literature searches and updates at two different timepoints, including 2018–2019 and 2025. These literature updates are described further below.

Next, EPA sought to identify population, exposure, comparator, and outcome (PECO)-relevant literature published since the most recent existing assessment(s) of DIBP by applying a literature inclusion cutoff date. For DIBP, the applied cutoff date was based on existing assessments of epidemiologic studies of phthalates by Health Canada (2018a, b), which included literature up to January 2018. The Health Canada (2018a, b) epidemiologic evaluations were considered the most appropriate existing assessments for setting a literature inclusion cutoff date because those assessments provided a robust and the most recent evaluation of human epidemiologic data for DIBP. Health Canada evaluated epidemiologic study quality using the Downs and Black method (Downs and Black, 1998) and reviewed the database of epidemiologic studies for consistency, temporality, exposure-response, strength of association, and database quality to determine the level of evidence for association between urinary DIBP metabolites and health outcomes. PECO-relevant literature published between 2018 to 2019 was identified through the literature search conducted by EPA in 2019, as well as references published between 2018 to 2023 that were submitted with public comments to the DIBP Docket (https://www.regulations.gov/docket/EPA-HQ-OPPT-2018-0434), and these studies were evaluated for data quality and extracted consistent with EPA's *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (U.S. EPA, 2021). Data quality evaluations for studies reviewed by EPA are provided in the *Data Quality Evaluation Information for Human Health Hazard Epidemiology for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025e).

As described further in the *Systematic Review Protocol for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025q), EPA considers phthalate metabolite concentrations in urine to be an appropriate proxy of exposure from all sources—including exposure through ingestion, dermal absorption, and inhalation. As described in the *Application of US EPA IRIS systematic review methods to the health effects of phthalates: Lessons learned and path forward* (Radke et al., 2020b), the "problem with measuring phthalate metabolites in blood and other tissues is the potential for contamination from outside sources" (Calafat et al., 2015). Phthalate diesters present from exogenous contamination can be metabolized to the monoester metabolites by enzymes present in blood and other tissues, but not urine." Therefore, EPA has focused its epidemiologic evaluation on urinary biomonitoring data; epidemiologic studies that examined DIBP metabolites in matrices other than urine were considered supplemental and not evaluated for data quality.

EPA used epidemiologic studies of DIBP qualitatively. This is consistent with Health Canada, U.S. CPSC, and ECHA. 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 (Shin et al., 2019; Aylward et al., 2016). Conclusions from Health Canada (2018a, b), NASEM (2017) and systematic review articles by Radke et al. (2020a; 2019b; 2019a; 2018) regarding the level of evidence for association between urinary DIBP metabolites and each health outcome were reviewed by EPA and used as a starting point for its human health hazard assessment. The Agency also evaluated and summarized epidemiologic studies identified by EPA's systematic review process (as described in the *Systematic Review Protocol for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025q)) to use qualitatively during evidence integration to inform hazard identification and the weight of scientific evidence (Shin et al., 2019; Aylward et al., 2016).

Following release of the draft non-cancer human health hazard assessment of DIBP in December 2024, EPA updated the literature considered as part of the DIBP human health hazard assessment. As described further in the DIBP Systematic Review Protocol (U.S. EPA, 2025p), studies submitted to the docket by the SACC and by public commenters were screened for PECO-relevance and, if relevant, were included in this non-cancer human health hazard assessment. Overall, EPA did not identify any epidemiological studies suitable for quantitative dose-response analysis.

1.2 Laboratory Animal Data: Summary of Existing Assessments, Approach, and Methodology

1.2.1 Summary of Existing Assessments

The human health hazards of DIBP have been evaluated in existing assessments by the U.S. CPSC (2014, 2011), Health Canada (ECCC/HC, 2020; EC/HC, 2015b), ECHA (2017a, b), and Australia NICNAS (2016, 2008a, b). These assessments have consistently identified toxicity to the developing male reproductive system as the most sensitive and robust outcome for use in estimating human risk from exposure to DIBP. The PODs from these assessments are shown in Table 1-1.

Additionally, a recent systematic review of animal toxicology studies of DIBP was published by Yost et al. (2019) in the open literature. Although the authors (*i.e.*, Yost et al.) are affiliated with the U.S. EPA's Center for Public Health and Environmental Assessment, the review does not reflect EPA policy. Consistent with existing assessments of DIBP by regulatory bodies, Yost et al. (2019) concluded that there was: *robust* evidence that DIBP causes male reproductive toxicity and *robust* evidence that DIBP causes developmental toxicity. Yost et al. (2019) also concluded that there was *slight* evidence for female reproductive toxicity and effects on the liver, and *indeterminant* evidence for effects on kidney. However, for these hazards, evidence was "limited by the small number of studies, experimental designs that were suboptimal for evaluating outcomes, and study evaluation concerns such as incomplete reporting of methods and results."

Table 1-1. Summary of DIBP Non-cancer PODs Selected for Use by other Regulatory Organizations

Brief Study Description	NOAEL/ LOAEL (mg/kg-day)	Critical Effect	U.S. CPSC (2014)	ECCC/HC (2020)	NICNAS (2008a)	ECHA (2012a, b)	ECHA (2017a, b)
Pregnant Sprague-Dawley rats (20-22 pregnant rats/dose) gavaged with 0, 250, 500, 750, 1000 mg/kg-day DIBP on GD 6-20 (non-guideline study) (Saillenfait et al., 2006)	250/ 500	↓ fetal body weight (both sexes); ↑ incidence of cryptorchidism			✓		
Pregnant Sprague-Dawley rats (11-14 dams/dose) gavaged with 0, 125, 250, 500, 625 mg/kg-day of DIBP on GD 12-21 (non-guideline study) (Saillenfait et al., 2008)	125/ 250	↓ AGD, NR, testicular pathology (degeneration of seminiferous tubules) and oligo-/azoospermia in epididymis)	✓	✓			
	None/ 125	Testicular pathology (degeneration of seminiferous tubules) and oligo-/azoospermia in epididymis)				✓[a]	
Pregnant rats (6-8/group) exposed to 0, 20, 200, 2000, or 10,000 ppm DBP via diet from GD15 – PND21 (equivalent to 0, 1.5, 14, 148, 712 mg/kg-day [males]; 0, 3, 29, 291, 1372 mg/kg-day [females]). F1 evaluated at PND14, PND21, & PNW 8-11 (non-guideline study) (Lee et al., 2004)[b]	None/ 2.5[b]	Reduced spermatocyte development (PND 21) and mammary gland changes (vacuolar degeneration, alveolar hypertrophy) in adult male offspring[b]					✓[c]

Brief Study Description	NOAEL/ LOAEL (mg/kg-day)	Critical Effect	U.S. CPSC (2014)	ECCC/HC (2020)	NICNAS (2008a)	ECHA (2012a, b)	ECHA (2017a, b)

[a] ECHA (2012a, b) considered the study by Saillenfait et al. to support a LOAEL of 125 mg/kg-day based on increased incidence of testicular pathology.

[b] ECHA (2017a, b) concluded "Few reproductive toxicity studies have been published on [DIBP] compared to DEHP and DBP. No two-generation studies are available and the substance has not been tested at doses <100 mg/kg bw/d. Current data suggest that DIBP could have similar effects to DBP, if studied at lower dose levels. If the potency difference between DIBP and DBP, as a very rough estimate of the observed effects in Saillenfait et al. (2008) (type of effects seen at 500 and 625 mg/kg bw-day, corresponding to a difference of 25%), is extrapolated from the high dose area to the lower dose area, an estimated LOAEL for DIBP would be 25% higher than the current LOAEL for DBP (2 mg/kg bw-day). Available information is shown in Table B7. A LOAEL for DIBP of 2.5 mg/kg bw-day is selected for use in the current combined risk assessment."

1.2.2 Approach to Identifying and Integrating Laboratory Animal Data

Figure 1-1 provides an overview of EPA's approach to identifying and integrating laboratory animal data into the DIBP Risk Evaluation. EPA first reviewed existing assessments of DIBP conducted by various regulatory and authoritative agencies. Existing assessments reviewed by EPA are listed below. The purpose of this review was to identify sensitive and human relevant hazard outcomes associated with exposure to DIBP, and while these authoritative sources identified a broader pool of studies to inform hazard identification, EPA only selected those studies used quantitatively for dose-response analysis in prior assessments for further consideration in estimating human risk. As described further in Appendix A, most of these assessments have been subjected to external peer-review and/or public comment periods but have not employed formal systematic review protocols.

- *Toxicity review of diisobutyl phthalate (DiBP, CASRN 84-69-5)* (U.S. CPSC, 2011);
- *Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives (with appendices)* (U.S. CPSC, 2014);
- *State of the science report: Phthalate substance grouping: Medium-chain phthalate esters: Chemical Abstracts Service Registry Numbers: 84-61-7; 84-64-0; 84-69-5; 523-31-9; 5334-09-8;16883-83-3; 27215-22-1; 27987-25-3; 68515-40-2; 71888-89-6* (EC/HC, 2015b);
- *Screening assessment - Phthalate substance grouping* (ECCC/HC, 2020);
- *Existing chemical hazard assessment report: Diisobutyl phthalate* (NICNAS, 2008a);
- *Phthalates hazard compendium: A summary of physicochemical and human health hazard data for 24 ortho-phthalate chemicals* (NICNAS, 2008b);
- C4-6 side chain transitional phthalates: Human health tier II assessment (NICNAS, 2016);
- *Committee for Risk Assessment (RAC) Opinion on an Annex XV dossier proposing restrictions on four phthalates* (ECHA, 2012b);
- *Committee for Risk Assessment (RAC) Committee for Socio-economic Analysis (SEAC): Background document to the Opinion on the Annex XV dossier proposing restrictions on four phthalates* (ECHA, 2012a);
- *Opinion on an Annex XV dossier proposing restrictions on four phthalates (DEHP, BBP, DBP, DIBP)* (ECHA, 2017b);
- *Annex to the Background document to the Opinion on the Annex XV dossier proposing restrictions on four phthalates (DEHP, BBP, DBP, DIBP)* (ECHA, 2017a);
- *Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals* (NASEM, 2017); and
- *Hazards of diisobutyl phthalate (DIBP) exposure: A systematic review of animal toxicology studies* (Yost et al., 2019).

In developing the human health hazard assessment for DIBP, EPA conducted literature searches and updates at three different timepoints, including 2017–2019, 2022, and 2025. These literature updates are described further below.

EPA sought to identify PECO-relevant literature published since the most recent existing assessment(s) of DIBP by applying a literature inclusion cutoff date. Along with existing assessments, EPA used the systematic review in the open literature by Yost et al. (2019) as the starting point for this document (publicly available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8596331/). The systematic review by Yost et al. employed a systematic review protocol and included scientific literature up to July 2017. Further, Yost et al. (2019) considered a range of human health hazards (*e.g.*, developmental toxicity, male and female reproductive toxicity, liver and kidney toxicity, and cancer) across all durations (*i.e.*, acute, intermediate, subchronic, chronic) and routes of exposure (*i.e.*, oral, dermal, inhalation).

Likewise, Yost et. al reached similar conclusions related to the human health hazards of DIBP, as other assessments by U.S. CPSC, Health Canada, NICNAS, ECHA, and NASEM. Therefore, EPA considered literature published between 2017 to 2019 further as shown in Figure 1-1. For the DIBP human health hazard assessment, EPA also considered literature related to effects on the developing male reproductive system identified through development of EPA's *Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act* (U.S. EPA, 2023a), which included a literature search in 2022. EPA first screened titles and abstracts and then full texts for relevancy using PECO screening criteria described in the *Systematic Review Protocol for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025q). Next, for PECO-relevant studies, EPA reviewed and extracted key study information from those studies including: PECO relevance; species tested; exposure route, method, and duration of exposure; number of dose groups; target organ/systems evaluated; information related to potentially exposed or susceptible subpopulations (PESS); and the study-wide lowest-observable-effect level (LOEL) (Figure 1-1).

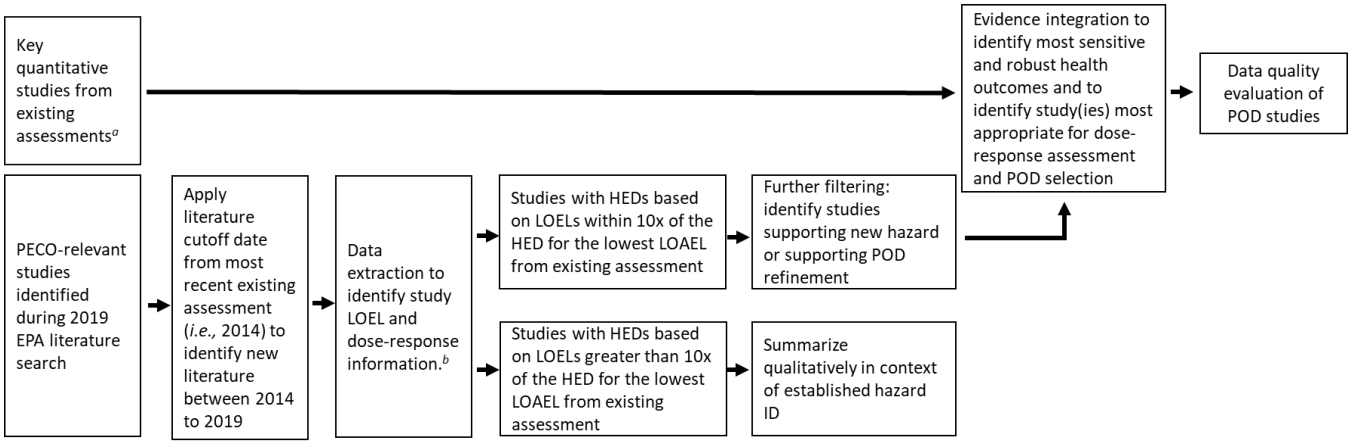

Figure 1-1. Overview of DIBP Human Health Hazard Assessment Approach

[a] Any study that was considered for dose-response assessment, not necessarily limited to the study used for POD selection.
[b] Extracted information includes PECO relevance, species, exposure route and type, study duration, number of dose groups, target organ/systems evaluated, study-wide LOEL, and PESS categories.

Information for DIBP, which was identified during the 2014 to 2019 and 2022 literature searches described above and which reflects reasonably available information since the most recent existing assessment (Yost et al., 2019) was limited to two oral exposure studies. No studies were reasonably available for other exposure routes (*i.e.,* dermal or inhalation). Study LOELs were converted to an HED by allometric scaling across species using the ¾ power of body weight ($BW^{3/4}$) for oral data, which is the approach recommended by U.S. EPA when physiologically based pharmacokinetic models (PBPK) or other information to support a chemical-specific quantitative extrapolation is absent (U.S. EPA, 2011c). EPA's use of allometric body weight scaling is described further in Appendix C. Studies with HEDs within an order of magnitude of the lowest LOAEL-based HED identified across existing assessments were considered sensitive and potentially relevant for POD selection. These studies were further reviewed by EPA to determine if they support a different human health hazard or potentially lower POD than those identified in existing assessments of DIBP. Mechanistic studies and studies with HEDs more than an order of magnitude above the HEDs associated with the lowest LOAELs from previous assessments were integrated into the hazard identification and characterization process but did not undergo TSCA study quality evaluations. Instead, as discussed further in the Systematic Review protocol for DIBP (U.S. EPA, 2025q), these studies were evaluated in a manner consistent with the

Office of Pesticide Programs *Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Hazard Assessment* (U.S. EPA, 2012).

Following release of the draft non-cancer human health hazard assessment of DIBP in December 2024, EPA updated the literature considered as part of the DIBP human health hazard assessment. As described further in the DIBP Systematic Review Protocol (U.S. EPA, 2025p), studies submitted to the docket by the SACC and by public commenters were screened for PECO-relevance and, if relevant, were included in this non-cancer human health hazard assessment. Overall, EPA did not identify any additional studies that support selection of a lower POD for DIBP.

Data quality evaluations for DIBP animal toxicity studies are provided in the *Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025d). Notably, Yost et al. (2019) included data quality evaluations, which are documented and publicly available in the Health Assessment Workspace Collaborative (HAWC) (https://hawc.epa.gov/assessment/497/). As described further in the *Systematic Review Protocol for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025q), EPA relied on the data quality evaluations completed by Yost et al. (2019), which were imported from HAWC to Distiller and are included in the *Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025d). Further, as described in the *Systematic Review Protocol for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025q), OPPT harmonized its draft TSCA systematic review protocol for human health animal toxicology and epidemiologic study data quality evaluations with the process described in the IRIS Systematic Review Handbook (U.S. EPA, 2022). Therefore, the data quality evaluations completed by Yost et al. (2019) are reflective of the harmonized TSCA data quality evaluation process.

1.2.3 Literature Identified and Hazards of Focus for DIBP

In its review of literature published between 2017 to 2019 for information on sensitive human health hazards not previously identified in existing assessments, including information that may indicate a more sensitive POD, EPA identified one PECO-relevant study that provided information pertaining to one primary hazard outcome (*i.e.*, reproductive/developmental toxicity) (Pan et al., 2017). EPA also identified one additional PECO-relevant study (*i.e.*, (Gray et al., 2021)) during its 2022 search in support of the *Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act* (U.S. EPA, 2023a). No PECO-relevant studies were identified from the 2025 literature update. These studies of DIBP are discussed further in Section 3.1.2. Based on information provided in existing assessments of DIBP for developmental and reproductive effects in combination with information identified by EPA, the Agency focused its non-cancer human health hazard assessment on developmental and reproductive toxicity (Section 3.1).

Further, EPA reviewed and supports the conclusions of the systematic review and hazard identification for DIBP published by Yost et al. (2019). EPA did not identify any literature that would change the conclusions of Yost et al. (2019) pertaining to *slight* evidence for female reproductive effects and liver effects and *indeterminant* evidence for kidney effects. Therefore, EPA did not further characterize these non-cancer hazards in this assessment or carry them forward to dose-response assessment in Section 4.

Genotoxicity and carcinogenicity data for DIBP are summarized in EPA's *Cancer Human Health Hazard Assessment for Di(2-ethylhexyl) Phthalate (DEHP), Dibutyl Phthalate (DBP), Diisobutyl Phthalate (DIBP), Butyl Benzyl Phthalate (BBP), and Dicyclohexyl Phthalate (DCHP)* (U.S. EPA, 2025a).

2 TOXICOKINETICS

2.1 Oral Route

No *in vivo* studies of experimental animal models are available that have evaluated the absorption, distribution, metabolism, and excretion (ADME) properties of DIBP for the oral exposure route.

One intentional human dosing study is available that investigates urinary elimination of DIBP (Koch et al., 2012). In this study, an individual volunteer (36-year-old male, 87 kg) was administered a single oral dose of 60 µg/kg deuterium-labelled DIBP (5.001 mg total), and urine samples were collected up to 48 hours following dosing (Koch et al., 2012). Three urinary metabolites of DIBP were detected: Monoisobutyl phthalate (MIBP); 2OH-MIBP; and 3OH-MIBP. MIBP was the primary urinary metabolite of DIBP (70 to 71 percent of excreted DIBP over 24 to 48 hours), while 2OH-MIBP (approximately 19 percent of excreted DIBP over 24 to 48 hours) and 3OH-MIBP (0.7 percent of excreted DIBP over 24 to 48 hours) were minor urinary metabolites. After 24 hours, 90.27 percent of the administered dose was recovered in urine, indicating DIBP is absorbed across the gastrointestinal tract and urine is the primary elimination route. After 48 hours, 90.84 percent was recovered. Peak urinary metabolite concentrations occurred 2.83 hours post-dosing. Urinary elimination half-lives were similar for MIBP (3.9 hours), 2OH-MIBP (4.2 hours) and 3OH-MIBP (4.1 hours), indicating rapid absorption and urinary elimination. Fecal and biliary excretion were not investigated in this study.

MIBP has been measured in human milk in the United States (Hartle et al., 2018), Korea (Kim et al., 2020; Kim et al., 2018; Kim et al., 2015), Italy (Del Bubba et al., 2018; Latini et al., 2009), Germany (Fromme et al., 2011), Taiwan (Lin et al., 2011), Switzerland (Schlumpf et al., 2010), and Sweden (Hogberg et al., 2008), indicating that absorbed DIBP can partition into human milk. Furthermore, because human biomonitoring data reflects recent aggregate exposure, it cannot quantitatively be attributed to a specific route although it is assumed to predominately come from oral exposure; however, exposure from the dermal and inhalation routes may also contribute.

For the DIBP risk evaluation, EPA will assume 100 percent oral absorption of DIBP. Notably, other regulatory agencies have also assumed 100 percent oral absorption of DIBP (ECCC/HC, 2020; ECHA, 2017a, b; EC/HC, 2015b; U.S. CPSC, 2014, 2011).

2.2 Inhalation Route

No controlled human exposure studies or *in vivo* animal studies are available that evaluate the ADME properties of DIBP for the inhalation route. EPA will assume 100 percent absorption via inhalation for the DIBP risk evaluation. Notably, ECHA (2017a, b) has also assumed 100 percent absorption via the inhalation route for DIBP.

2.3 Dermal Route

No *in vitro* or controlled human exposure studies are available that evaluate the ADME of DIBP for the dermal route.

EPA identified one *in vivo* ADME study is available that indicates dermally absorbed DIBP is widely distributed to tissues in rats (Elsisi et al., 1989). Skin on the backs of male Fischer 344 (F344) rats was shaved one hour before DIBP administration (rats with visual signs of abrasions were eliminated from the study). Neat carbon-14 labelled DIBP (^{14}C-DIBP) in an ethanol vehicle (30 to 40 mg/kg) was

applied to a circular area of the skin 1.3 centimeters in diameter, which represents a dose of 5 to 8 mg/cm^2. Ethanol was allowed to evaporate and then the application site was covered with a perforated circular plastic cup. Rats were then housed in metabolic cages for 7 days during which time urine and feces were collected every 24 hours. Following 7 days of dermal exposure to ^{14}C-DIBP, Elsisi et al. measured low levels of radioactivity associated with ^{14}C-DIBP in adipose tissue (0.11 percent of applied dose), muscle (0.22 percent of applied dose), skin (0.2 percent of applied dose) and other tissues (less than 0.5 percent of applied dose found in the brain, lung, liver, spleen, small intestine, kidney, testis, spinal cord, and blood). Thirty-five percent of the applied dose was recovered from the skin at the application site, while six percent was recovered from the plastic cap. Total recovery of the applied dose was 93 percent. After 24 hours of exposure, approximately 6 percent of the applied dose was recovered in urine, while approximately 1 percent was recovered in feces. After seven days, approximately a total of 51 percent of the applied dose was excreted in urine and feces.

Given the limited amount of dermal absorption data available for DIBP, EPA also considered use of DBP (isomer of DIBP) dermal absorption data to determine the absorptive flux for DIBP through read-across. As discussed in the *Human Health Hazard Assessment of DBP* (U.S. EPA, 2025i), EPA used dermal absorption data from Beydon et al. (2010) to estimate dermal absorption of DBP. Briefly, Beydon et al. (2010) evaluated percutaneous absorption and metabolism of DBP by skin esterases in skin samples from humans, rats, rabbits, guinea-pigs, and mice. DBP was hydrolyzed by carboxylesterases in the skin of all species evaluated; therefore, carboxylesterase activity was measured in addition to skin thickness and flux to determine the relationship between DBP absorption flux and enzymatic activity across species. Beydon et al. (2010) reported differences in skin thickness across species, as well as fluxes. DBP fluxes for rats were 40 to 90 times higher for rats than humans (24.0 ± 5.2 μg/cm^2/hr [Hairy rats] and 48.9 ± 17.7 μg/cm^2/hr [Hairless rats] compared to 0.59 ± 0.25 μg/cm^2/hr [human skin]), which is a similar finding to the aforementioned results of Scott et al. (1987). Of the species examined in Beydon et al. (2010), guinea-pig skin had the most comparable DBP flux to human skin. Nevertheless, DBP flux of guinea pig skin was approximately ten times higher than the DBP flux of human skin (Humans: 0.59 ± 0.25 μg/cm^2/hr; Guinea pigs: 5.39 ± 0.88 μg/cm^2/hr). Human and guinea-pig skin thickness (1.38 ± 0.17 mm, 1.31 ± 0.05 mm) and epidermis and dermis carboxylesterase activities were comparable.

As described further in the *Consumer and Indoor Exposure Assessment for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025b) and the *Environmental Release and Occupational Exposure Assessment for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025f), EPA used DBP dermal absorption data from the Beydon et al. (2010) study to estimate dermal absorption of liquid formulations of DIBP because this study was determined to be the most suitable dermal absorption study (*i.e.,* used metabolically active human skin). Using Beydon et al. (2010), EPA derived an estimate of the steady-state flux of neat DBP of 5.9×10^{-4} mg/cm^2/h., which will be applied to the DIBP dermal absorption approach.

3 NON-CANCER HAZARD IDENTIFICATION

3.1 Effects on the Developing Male Reproductive System

As discussed in Section 1.2, 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 (ECCC/HC, 2020; ECHA, 2017a, b; NASEM, 2017; EC/HC, 2015b; U.S. CPSC, 2014; ECHA, 2012a, b; U.S. CPSC, 2011; NICNAS, 2008a) as well as prior systematic reviews (Yost et al., 2019). EPA identified no information through systematic review that would change this conclusion. Therefore, EPA focused its non-cancer hazard characterization on the developing male reproductive system. Evidence from epidemiological and laboratory animal studies for developmental and reproductive outcomes is summarized in Sections 3.1.1 and 3.1.2, respectively.

3.1.1 Summary of Available Epidemiological Studies

3.1.1.1 Previous Epidemiology Assessment (Conducted in 2019 or Earlier)

EPA reviewed and summarized conclusions from previous assessments conducted by Health Canada (2018b) and NASEM (2017), as well as systematic review articles by Radke et al. (2019b; 2018), that investigated the association between exposure to DIBP and its metabolites and male and female developmental and reproductive outcomes. As can be seen from Table 3-1, epidemiologic assessments by Health Canada (2018b), NASEM (2017), and systematic review articles by Radke et al. (2019b; 2018) varied in scope and considered different developmental and reproductive outcomes. Further, these assessments used different approaches to evaluate epidemiologic studies for data quality and risk of bias in determining the level of confidence in the association between phthalate exposure and evaluated health outcomes (Table 3-1). Section 3.1.1.1.1, Section 3.1.1.1.2, and Section 3.1.1.1.3 provide further details on previous assessments of DIBP by Health Canada (2018b), Radke et al., (2019b; 2018) and NASEM (2017), respectively, including conclusions related to exposure to DIBP and health outcomes. Additionally, EPA also evaluated epidemiologic studies published after the Health Canada (2018b) assessment as part of its literature search (*i.e.*, published between 2018 and 2019) to determine if newer epidemiologic studies would change the conclusions of existing epidemiologic assessments or provide useful information for evaluating exposure-response relationship (Section 3.1.1.2).

Table 3-1. Summary of Scope and Methods Used in Previous Assessments to Evaluate the Association Between DIBP Exposure and Male Reproductive Outcomes

Previous Assessment	Outcomes Evaluated	Method Used for Study Quality Evaluation
Health Canada (2018b)	**Hormonal effects:** • Sex hormone levels (*e.g.*, testosterone) **Growth & Development:** • AGD • Birth measures • Male infant genitalia (*e.g.*, hypospadias/cryptorchidism) • Placental development and gene expression	Downs and Black (Downs and Black, 1998)

Previous Assessment	Outcomes Evaluated	Method Used for Study Quality Evaluation
	• Preterm birth and gestational age • Postnatal growth • DNA methylation **Reproductive:** • Altered male puberty • Gynecomastia • Changes in semen parameters • Sexual dysfunction (males) • Sex ratio	
Radke et al. (2018)	• AGD • Hypospadias/cryptorchidism • Pubertal development • Semen parameters • Time to pregnancy • Testosterone • Timing of pubertal development	Approach included study sensitivity as well as risk of bias assessment consistent with the study evaluation methods described in (U.S. EPA, 2022)
Radke et al. (2019b)	• Pubertal development • Time to pregnancy (Fecundity) • Preterm birth • Spontaneous abortion	ROBINS-I (Sterne et al., 2016)
NASEM (2017)	• AGD • Hypospadias (incidence, prevalence, and severity/grade) • Testosterone concentrations (measured at gestation or delivery)	OHAT (based on GRADE) (NTP, 2015)
Abbreviations: AGD = anogenital distance; ROBINS-I= Risk of Bias in Non-randomized Studies of Interventions; OHAT = National Toxicology Program's Office of Health Assessment and Translation; GRADE = Grading of Recommendations, Assessment, Development and Evaluation		

3.1.1.1.1 Health Canada (2018b)

Health Canada evaluated studies that looked at individual phthalates (or their metabolites) and health outcomes and did not consider studies that only looked at summed exposure to multiple phthalates due to the challenging nature of interpreting results for the sum of several phthalates. The outcomes that were evaluated are listed in Table 3-1. To evaluate the quality of individual studies and risk of bias, Health Canada (2018b) used the Downs and Black evaluation criteria (Downs and Black, 1998), which is based on the quality of the epidemiology studies and the strength and consistency of the relationship between a phthalate and each health outcome. The level of evidence for association of a phthalate and each health outcome was established based on the quality of the epidemiology studies and the strength and consistency of the association.

Health Canada (2018b) evaluated several studies that investigated the association between urinary metabolites of DIBP and several developmental and reproductive outcomes. Health Canada concluded

that there was some limited evidence of association[1] for DIBP and several outcomes, including changes in serum levels of sex hormones (*e.g.,* follicle stimulating hormone, luteinizing hormone, testosterone), increased sperm DNA damage and apoptosis, and changes in infant sex ratio at birth. For other health outcomes, Health Canada concluded there was inadequate evidence of association[1] (*i.e.,* for changes in thyroid and other miscellaneous hormones, changes in semen parameters, pregnancy complication and loss, sexual dysfunction in males and females, and age at menopause). In addition, there was no evidence of association[1] based on lack of changes in AGD, birth weight, birth length, head circumference, femur length, preterm birth, gestational age, altered male puberty, gynecomastia, time to pregnancy, uterine leiomyoma, and polycystic ovary syndrome, or that the level of evidence of association could not be established due to limitations in the available studies (*i.e.,* for changes in placental development, postnatal growth, altered female puberty, altered fertility).

3.1.1.1.2 Radke et al. (2019b; 2018)

Radke et al. conducted systematic reviews of male (Radke et al., 2018) and female (Radke et al., 2019b) developmental and reproductive outcomes. These systematic review articles are considered herein. Radke et al. (2018) evaluated the associations between DIBP or its metabolite (MIBP) and male reproductive outcomes, including AGD and hypospadias/cryptorchidism following *in utero* exposures; pubertal development following *in utero* or childhood exposures, and semen parameters, time to pregnancy (following male exposure), and testosterone following adult exposures. Male reproductive outcomes and level of confidence in the associations is listed in Table 3-2.

Table 3-2. Summary of Epidemiologic Evidence of Male Reproductive Effects Associated with Exposure to DIBP

Timing of Exposure	Outcome	Level of Confidence in Association
In utero	Anogenital distance	Slight
	Hypospadias/cryptorchidism	Slight
In utero or childhood	Pubertal development	Indeterminate
Adult	Semen parameters	Slight
	Time to pregnancy	Slight
	Testosterone	Moderate
Male Reproductive Outcomes Overall		Moderate

[a] Table from Figure 3 in Radke et al. (2018).

[1] Health Canada defines *limited evidence* as "evidence is suggestive of an association between exposure to a phthalate or its metabolite and a health outcome; however, chance, bias or confounding could not be ruled out with reasonable confidence." Health Canada defines *inadequate evidence* as "the available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association." Health Canada defines *no evidence of association* as "the available studies are mutually consistent in not showing an association between the phthalate of interest and the health outcome measured."

Data quality evaluation criteria and methodology used by Radke et al. (2018) were qualitatively similar to those used by NASEM (2017) (*i.e.*, OHAT methods) and Health Canada (2018b). Similar to NASEM (2017) and Health Canada (2018b), most studies reviewed by Radke et al. (2018) relied on phthalate metabolite biomarkers for exposure evaluation. Therefore, different criteria were developed for short-chain (DIBP, DEP, DBP, BBP) and long-chain (DEHP, DINP) phthalates due to better reliability of single measures for short-chain phthalates. Radke et al. (2018) used data quality evaluations to inform overall study confidence classifications, and ultimately evidence conclusions of "Robust," "Moderate," "Slight," "Indeterminate," or "Compelling evidence of no effect." "Robust" and "Moderate" evidence of an association is distinguished by the amount and caliber of data that can be used to rule out other possible causes for the findings. "Slight" and "Indeterminate" describe evidence for which uncertainties prevent drawing a causal conclusion in either direction.

Similar to the conclusions of Health Canada, Radke et al. (2019b; 2018) found moderate evidence of an association[2] between exposure to DIBP and decreased testosterone levels in males, while evidence of an association between exposure to DIBP and other male and female reproductive outcomes was found to the slight (*i.e.*, for decreased AGD, hypospadias and/or cryptorchidism, changes in semen parameters, time to pregnancy [based on male exposure to DIBP]) or indeterminant (*i.e.*, for male and female pubertal development, spontaneous abortion, time to pregnancy [based on female exposure to DIBP]).

3.1.1.1.3 NASEM (2017)

NASEM (2017) included a systematic review of the epidemiological evidence of the associations between exposure to various phthalates or their monoester or oxidative metabolites including DIBP, and the following male reproductive outcomes 1) AGD measurements, 2) incidence, prevalence, and severity/grade of hypospadias, and 3) testosterone concentrations measured at gestation or delivery. In contrast to Health Canada (2018b), and Radke et al. (2018), NASEM (2017) relied on methodological guidance from the National Toxicology Program's Office of Health Assessment and Translation (OHAT) to assign confidence ratings and determine the certainty of the evidence to ultimately draw hazard conclusions (NTP, 2015).

NASEM (2017) concluded that there was inadequate evidence to establish an association between prenatal exposure to DIBP and hypospadias due to the limited number of studies and dissimilar matrices utilized to evaluate them (urine and amniotic fluid). NASEM also concluded that there is inadequate evidence to determine whether fetal exposure to DIBP is associated with a decrease in fetal testosterone in males, given the various matrices used to measure testosterone (amniotic fluid, maternal serum, or cord blood), the differences in timing of exposure (during pregnancy or at delivery), and the limited number of studies. This conclusion is slightly different from those of Health Canada (2018b) and Radke et al. (2019b; 2018), because they are looking at different life stages, each of which found limited and moderate evidence, respectively, of an association between exposure to DIBP and decreased testosterone levels in males. Radke et al. (2018) and Health Canada (2018b) considered the association between exposure to DIBP and testosterone in children and adults while NASEM looked at fetal life stages.

NASEM also concluded that there was an inadequate level of evidence to determine an association between DIBP (MIBP) and AGD, although there was moderate confidence in the evidence of

[2] Radke et al. (2019b; 2018) define *Robust* and *Moderate* evidence descriptors as "evidence that supports a hazard, differentiated by the quantity and quality of information available to rule out alternative explanations for the results." Slight and indeterminant evidence descriptors are defined as "evidence that could support a hazard or could support the absence of a hazard. These categories are generally limited in terms of quantity or confidence level of studies and serve to encourage additional research across the exposure range experienced by humans."

association based on three prospective cohort studies. However, NASEM also conducted a meta-analysis of three studies (Jensen et al., 2016; Swan et al., 2015; Swan, 2008) and found that the available studies do not support the association between DIBP exposure and decreased AGD (% change [95% CI] = -2.23 [-5.15, 0.70] [p = 0.13]). The AGD effect estimates in the NASEM (2017) meta-analyses are slope estimates based on the assumption that exposure and effect have a monotonic dose-response relationship. This conclusion is similar to the conclusions of Radke et al. (2018), who found slight evidence of an association between DIBP exposure and decreased AGD.

3.1.1.1.4 Summary of the Existing Assessments of Male Reproductive Effects

Each of the three assessments discussed above provided qualitative support as part of the weight of scientific evidence for the association between DIBP exposure and male reproductive outcomes. The existing assessments and review article came to similar conclusion on the effect of exposure to DIBP and male reproductive outcomes. Radke et al. (2018) concluded that there was a slight level of confidence in the association between exposure to DIBP and AGD, while Health Canada (2018b) and NASEM (2017) found inadequate evidence of an association. Further, Radke et al. (2018) found that there was moderate evidence for the association between testosterone and exposure to DIBP, while Health Canada (2018b) found that total testosterone (TT) and free testosterone (fT) had negative associations (*i.e.*, increase exposure to DIBP with decrease testosterone) in peripubertal or adolescent boys (6-12, 8-14 or 12-20 years) per IQR increase with exposure to DIBP and its metabolite MIBP, and negative associations for total testosterone in adult males 17 to 52 years. Radke et al. (2018), also found a slight level of confidence in the association between exposure to DIBP and cryptorchidism/hypospadias, but this association was not consistent with the findings of Health Canada (2018b) or NASEM (2017). The scope and purpose of the assessments by Health Canada (2018b), systematic review articles by Radke et al. (2018), and the report by NASEM (2017) differ and may be related to differences in quality evaluation and confidence conclusions drawn. Health Canada (2018b) was the most comprehensive review, and considered prenatal and perinatal exposures, as well as peripubertal exposures and multiple different outcomes. NASEM (2017) evaluated fewer epidemiological outcomes than Health Canada (2018b) and systematic review articles by Radke et al. (2018), but also conducted a second systematic review of the animal literature, which will be discussed further in Section 4. The results of the animal and epidemiological systematic reviews were considered together by NASEM (2017) to draw hazard conclusions. Each of the existing assessments covered above considered a different number of epidemiological outcomes and used different data quality evaluation methods for risk of bias. Despite these differences, and regardless of the limitations of the epidemiological data, each assessment provides qualitative support as part of the weight of scientific evidence.

3.1.1.2 EPA Summary of Studies (2018 to 2019)

EPA also evaluated epidemiologic studies published after the Health Canada (2018b) assessment as part of its literature search (*i.e.*, published between 2018 and 2019). EPA identified 40 epidemiologic studies (24 developmental and 16 reproductive) that evaluated the association between urinary DIBP and its metabolite (MIBP) and reproductive and developmental outcomes. Studies reporting a significant association are discussed further below.

Further information (*i.e.*, data quality evaluations and data extractions) on the studies identified by EPA can be found in:

- *Data Quality Evaluation Information for Human Health Hazard Epidemiology for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025e), and

- *Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025c).

In text below, EPA discussed the evaluation of the studies by outcome that contribute to the weight of scientific evidence.

Developmental Outcomes for Males

Twenty-four studies were evaluated for the association between DIBP and developmental outcomes including birth measures, size trajectory, fetal loss, pubertal development, and gestational duration. Of those studies, 1 was high confidence, 17 were of medium confidence and 6 were of low confidence. There were only four studies with significant results, one high confidence study (Harley et al., 2019), one medium confidence study (Burns et al., 2022) and two low confidence study (Durmaz et al., 2018; Yang et al., 2018). The remaining 20 studies evaluating developmental outcomes in males did not show any significant results and are not discussed further in this document. However, further information for these 20 studies can be found in the *Data Quality Evaluation Information for Human Health Hazard Epidemiology for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025e) and *Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025c).

In the evaluation of pubertal development and DIBP exposure, one high confidence (Harley et al., 2019) and one medium confidence (Burns et al., 2022) study examined the relationship between exposure to MIBP and pubertal onset and both reported increasing developmental delay in association with MIBP exposure. The high confidence study (Harley et al., 2019) examined the relationship between prenatal MIBP exposure and pubertal timing (thelarche, pubarche, menarche, gonadarche) among 159 boys and 179 girls enrolled in the CHAMACOS Study and found significant positive association between prenatal MIBP exposure (measured via maternal urinary MIBP) and age at thelarche among girls in exposure quartile 2 vs. quartile 1 [6.5 month mean shift in age at thelarche, 95% CI (1.0, 12.3)]. However, no significant associations were found for Q2 or Q4 vs. Q1, and no significant associations were found for other pubertal timing outcomes among girls or boys. The medium confidence study (Burns et al., 2022) examined the association between prepubertal MIBP exposure (assessed via urinary MIBP concentrations) in relation to age at pubertal onset among 304 boys enrolled in the Russia Children's Study. Puberal onset outcomes were defined as testicular volume greater than 3 mL, Tanner Genitalia Stage greater than or equal to 2, and Tanner Pubarche Stage greater than or equal to 2. Significant positive associations were found for all three outcomes. Significant mean delays in testicular growth were found across all quartiles, as compared to Q1 [Q2 vs Q1: 8.5 months, 95% CI (3.7, 13.5); Q3 vs Q1: 6.4, 95% CI (1.1, 11.7); Q4 vs Q1: 5.7 (0.2, 11.1). Significant mean delays reaching a Tanner Genital Stage ≥ 2 were found for Q2 and Q3 vs Q1 [Q2 vs Q1: 6.4 months, 95% CI (0.2, 12.6); Q3 vs Q1: 7.2 (0.5, 13.8)] but not for Q4 vs Q1. Significant mean delays in reaching Pubarche Stage ≥ 2c were found for Q3 and Q4 vs Q1 [Q3 vs Q1: 10.2 months, 95% CI (2.9, 17.5); Q4 vs Q1: 12.8, 95% CI (5.3, 20.3)], but not for Q2 vs Q1. Trend tests were only significant for increasing quartiles of MIBP exposure for Pubarche Stage greater than or equal to 2c.

Other Developmental Outcomes

Other developmental outcomes such as body mass index (BMI) trajectories were also assessed. One medium confidence study (Heggeseth et al., 2019) and two low confidence study (Durmaz et al., 2018; Yang et al., 2018) examined BMI trajectories in relation to MIBP exposure. Heggeseth et al. (2019) (medium confidence) used growth mixture models and functional principal components analysis to assess whether prenatal phthalate exposure helped explain variation in size trajectory among 162 boys and 173 girls enrolled in Center for the Health Assessment of Mothers and Children of Salinas

(CHAMACOS) Study. The study, although no effect estimates were provided, found that urinary concentrations of MIBP at greater than or equal to 1.7 ng/mL explains variation in BMI in boys. One low confidence study (Yang et al., 2018) examining BMI trajectories in relation to MIBP exposure among 239 children from Mexico City enrolled in the Early Life in Mexico to Environmental Toxicants (ELEMENT) found, without reporting effect estimates, that exposure to the first tertile of MIBP predicted the lowest BMI trajectory in infancy and early childhood but crossed over to predict the highest BMI by age 14. The other low confidence study (Durmaz et al., 2018) examined the relationship between MIBP exposure and BMI and weight in 29 girls between the ages of 4 years and 8 years with premature thelarche, from Antalya City, Turkey and found significant positive associations for both weight (Spearman correlation coefficient: 0.742, $p < 0.01$) and BMI (Spearman correlation coefficient: 0.574, $p = 0.002$).

Reproductive Outcomes for Males

Five medium confidence studies evaluated the association between DIBP exposure and male reproductive outcomes; however, only one (Wenzel et al., 2018) found significant results. Epidemiologic literature that identified male reproductive effects associated with DIBP exposure found one medium confidence study (Wenzel et al., 2018) of infants in Charleston, South Carolina that reported a significant positive association between maternal urinary concentrations of MIBP and anoscrotal distance in white infants only [Beta (95% CI) per unit increase in MIBP for anoscrotal distance = 1.68 (0.09, 3.27)]. No other significant results were reported for other anthropometric measurements or when results were not stratified by race/ethnicity. Studies on other male reproductive effects such as anthropometric measures of male reproductive organs, sperm parameters, prostate and male reproductive hormones found no significant associations. However, further information for these 5 studies can be found in the *Data Quality Evaluation Information for Human Health Hazard Epidemiology for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025e) and *Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025c).

Reproductive Outcomes for Females

Eleven studies (1 high confidence, 9 medium confidence, 1 uninformative) evaluated the association between DIBP exposure and female reproductive outcomes. Of those studies, two medium confidence studies (Chin et al., 2019; Machtinger et al., 2018) and one low confidence study(Durmaz et al., 2018) had significant results. The remaining eight studies evaluating reproductive outcomes in females did not show any significant results and are not discussed further in this document. However, further information for these 9 studies can be found in the *Data Quality Evaluation Information for Human Health Hazard Epidemiology for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025e) and *Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for Diisobutyl Phthalate (DIBP)* (U.S. EPA, 2025c).

Female reproductive effects associated with DIBP exposure were identified in two medium confidence studies (Chin et al., 2019; Machtinger et al., 2018) and one low confidence study (Durmaz et al., 2018). Chin et al. (2019) (medium confidence study) investigated North Carolina women without known fertility issues and reported significantly increased odds of a shorter time between ovulation and implantation [OR (95% CI) for early implantation = 2.09 (95% CI=1.18, 3.69)]. The other medium confidence study (Machtinger et al., 2018) examined women undergoing *in vitro* fertilization (IVF) in Israel and reported a significantly reduced mean number of total oocytes in tertile 2 compared to tertile 1 of urinary MIBP in women undergoing a fresh IVF cycle [Mean difference (95%) CI for tertile 2 = 8.7 (7.9, 9.6)]. This study further reported a significantly reduced mean number of mature oocytes in both tertiles 2 and 3 compared to tertile 1 of MIBP exposure [Mean difference (95% CI) for tertile 2 = 6.7

(6.0, 7.5); Mean (95% CI) for tertile 3 = 8.0 (7.2, 8.8)]. The mean number of fertilized oocytes was also significantly reduced in tertile 2 compared to tertile 1 of MIBP exposure [Mean difference (95% CI) for tertile 2 = 4.6 (4.0, 5.3)]. Women with higher MIBP exposure also had a significantly reduced mean number of top-quality embryos. This study also reported significantly reduced mean number of top-quality embryos [Mean difference (95% CI) for tertile 2 = 2.0 (1.7, 2.5); Mean (95% CI) for tertile 3 = 2.2 (1.8, 2.7)]. The low confidence study (Durmaz et al., 2018) conducted in Turkey reported a significant unadjusted positive correlation between urinary MIBP concentrations and basal follicle stimulating hormone (FSH) in girls with premature thelarche [Spearman correlation coefficient between MIBP and basal FSH = 0.323, p-value = 0.045]. Other studies that examined female reproductive measures, such as anthropometric measures of female reproductive organs or fibroids, and association with DIBP exposure found no significant association.

Conclusion

In conclusion, Health Canada (2018b) and NASEM (2017) found inadequate evidence of association between DIBP and AGD while systematic review articles published by Radke et al. (2018) found slight evidence of association with AGD. Moreover, studies identified by EPA from 2018 to 2019 do not alter the previous conclusions from Health Canada (2018b) and NASEM (2017), and systematic review articles published by Radke et al. (2018). Although there is slight evidence of an association between DIBP and AGD, the results for testosterone were measured at different life stages (*i.e.*, fetal/infants to adults) and causality could not be established, thus the overall evidence does not support an association between DIBP and AGD or testosterone.

Furthermore, EPA concludes that the existing epidemiological studies do not support quantitative exposure-response assessment due to uncertainty associated with exposure characterization of individual phthalates, including source or exposure and timing of exposure as well as co-exposure confounding with other phthalates, discussed in Section 1.1. The epidemiological studies provide qualitative support as part of the weight of scientific evidence.

3.1.2 Summary of Laboratory Animals Studies

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 (Gray et al., 2021; Pan et al., 2017; Saillenfait et al., 2017; Wang et al., 2017; Sedha et al., 2015; Furr et al., 2014; Hannas et al., 2012; Hannas et al., 2011; Howdeshell et al., 2008; Saillenfait et al., 2008; BASF, 2007; Borch et al., 2006; Saillenfait et al., 2006). No studies evaluating the developmental and/or reproductive toxicity of DIBP are available for the inhalation or dermal exposure routes.

Available oral exposure studies of DIBP evaluating developmental and reproductive outcomes are summarized in Table 3-3. Most of the available studies evaluate effects on the developing male reproductive system consistent with a disruption of androgen action following gestational, perinatal, or pre-pubertal oral exposures to DIBP. However, several studies are available that evaluate other developmental outcomes (*e.g.*, post-implantation loss, resorptions, fetal body weight, skeletal variations, *etc.*). Effects on the developing male reproductive system and other developmental and reproductive outcomes are discussed in Sections 3.1.2.1 and 3.1.2.2, respectively.

Table 3-3. Summary of Studies of DIBP Evaluating Developmental and Reproductive Outcomes

Reference	Brief Study Description (TSCA Study Quality Rating)	NOAEL/ LOAEL (mg/kg-day)	Effect at LOAEL	Remarks
(Howdeshell et al., 2008)	Pregnant SD rats (5-8 dams/dose) gavaged with 0, 100, 300, 600, 900 mg/kg-day DIBP on GDs 8-18 (High)	100/300	↓ *ex vivo* testicular testosterone production (40%) on GD 18	Maternal Effects - ↓ Maternal body weight on GD 18 (≥600 mg/kg-day) and weight gain (900) Developmental Effects - ↑ fetal morality (900 mg/kg-day) - ↓ # of live fetuses (900 mg/kg-day) - ↑ total resorptions (900 mg/kg-day)
(Hannas et al., 2011)	Pregnant SD rats (3 dams/dose) gavaged with 0, 100, 300, 600, 900 mg/kg-day DIBP on GDs 14-18 (High)	100/300	↓ *ex vivo* fetal testicular testosterone production (56%) and ↓ expression of steroidogenic genes in fetal testes on GD 18	Maternal Effects - None Developmental Effects - ↓ *ex vivo* fetal testicular testosterone production on GD 18 (≥300 mg/kg-day) - ↓ Fetal testis mRNA levels of *StAR* (≥300 mg/kg-day) and *Cyp11a* on GD 18 (≥100 mg/kg-day) Unaffected Outcomes - Maternal mortality, clinical signs of toxicity, maternal body weight, litter size
(Saillenfait et al., 2008)	Pregnant SD rats (11-14 dams/dose) gavaged with 0, 125, 250, 500, 625 mg/kg-day DIBP on GDs 12-21 (High)	None/125	↑ Testicular pathology (degeneration of seminiferous tubules) and oligo-/azoospermia in epididymis)	Maternal Effects - None Developmental Effects - ↓ Male AGD (absolute) on PND 1 (≥250 mg/kg-day) - ↑ Male NR on PNDs 12-14 and at necropsy on PNW 11-12 or PNW 16-17 (≥250 mg/kg-day) - ↓ Male pup weight on PND 1 and PND 21 (625 mg/kg-day) - ↑ hypospadias (≥500 mg/kg-day), cleft prepuce (625 mg/kg-day), exposed os penis (≥500 mg/kg-day), non-scrotal testes at necropsy (PNW 11-12 or 16-17) (≥500 mg/kg-day) - Delayed PPS (≥500 mg/kg-day) - ↓ male offspring body weight on PNW 11-12 and PNW 16-17 (≥500 mg/kg-day) - ↓ absolute prostate weight on PNW 11-12 (≥250 mg/kg-day) and 16-17 (≥500 mg/kg-day); ↓ absolute testis, epididymis, and SV weight on PND 11-12 and 16-17 (≥500 mg/kg-day) Unaffected Outcomes

Reference	Brief Study Description (TSCA Study Quality Rating)	NOAEL/ LOAEL (mg/kg-day)	Effect at LOAEL	Remarks
				- Maternal weight gain (GD 0-12, GD 12-21, PND 1-21); post-implantation loss; % live pups; pup survival (PND 1-4, PND 4-21); female offspring body weight on PND 4, 7, 14, 21
(Saillenfait et al., 2006)	Pregnant SD rats (20-22 pregnant rats/dose) gavaged with 0, 250, 500, 750, 1000 mg/kg-day DIBP on GDs 6-20 (High)	250/500	↓ fetal body weight (7%) (both sexes); ↑ incidence of undescended testes (unilateral or bilateral) and degree of trans-abdominal testicular migration. ↓ Maternal weight gain	Maternal Effects - ↓ Maternal weight gain on GD 6-9 and GD 15-18 (≥500 mg/kg-day) Developmental Effects - ↑ % Resorptions per litter (≥750 mg/kg-day) - ↑ % Post-implantation losses per litter (≥750 mg/kg-day) - ↓ Number of live fetuses per litter (≥750 mg/kg-day) - ↓ Fetal body weight (↓7%) (both sexes) (≥500 mg/kg-day) - ↑ Total number of fetuses with external, visceral, and skeletal malformations (≥750 mg/kg-day) - ↑ Total number of litters with visceral and skeletal malformations (≥750 mg/kg-day) - ↑ incidence of visceral and skeletal variations, including ectopic testis (≥750 mg/kg-day), increased degree of trans-abdominal testicular migration (≥500) Unaffected Outcomes - Maternal mortality; maternal food consumption; overall maternal weight gain corrected for gravid uterine weight; % dead fetus per litter; sex ratio
(BASF, 2007)	Pregnant Wistar rats (22-23/dose) administered diets containing 0, 1000, 4000, 11,000 ppm DIBP on GDs 6-20 (equivalent to 88, 363, 942 mg/kg-day) Adhered to OECD TG 414; GLP-compliant (High)	363/942	↓ maternal food consumption, ↓ maternal body weight gain, ↓ fetal body weight (5%); skeletal variations	Maternal Effects - ↓ Maternal food consumption (approximately 5% below control across GD 6-20) (942 mg/kg-day) - ↓ Maternal body weight gain (approximately 11% below control across GD 6-20) (942 mg/kg-day) Developmental Effects - ↓ Fetal (both sexes) body weight (approximately 5% below control) (942 mg/kg-day) - ↑ skeletal variations, including incomplete ossification of sternebra and unilateral ossification of sternebra (942 mg/kg-day) Unaffected Outcomes - Maternal mortality; no clinical signs; post-implantation loss; resorptions; # of viable fetuses; sex ratio; external or visceral malformations or variations

Reference	Brief Study Description (TSCA Study Quality Rating)	NOAEL/ LOAEL (mg/kg-day)	Effect at LOAEL	Remarks
(Saillenfait et al., 2017)	Pregnant SD rats (15-20 /dose) gavaged with 0 or 250 mg/kg-day DIBP on GDs 13-19 (High)	None/250	↓ AGD, ↓ testicular testosterone (45%) and, androstenedione (27%) production; altered mRNA expression of steroidogenesis genes in the testes	Maternal Effects - None Developmental Effects - ↓ AGD (normalized to cubic root of body weight) - ↓ (27-45%) *ex vivo* testis testosterone and androstenedione production ↓ gene expression in cholesterol and steroid synthesis in fetal testes (*Hmg-CoAR, Hmg-CoAS, SR-B1, StAR, P450c17, 17β-HSD*) Unaffected Outcomes - Dam body weight gain; gravid uterine weight; post-implantation loss; # live fetuses per litter; sex ratio; fetal body weight
(Wang et al., 2017)	Pregnant ICR Mice (15-18 offspring/dose) fed diets containing 0 or 2.8 g DIBP/kg diet (dry weight) (equivalent to 450 mg/kg-day) from GDs 0-21 (designated TC) or from GDs 0 to PND 21 (designated TT) (Medium)	None/450	↓ absolute testes weight on PND 21; ↓ serum and testes testosterone; ↓ expression of steroidogenic genes in testes; ↓sperm concentration and motility on PND 80	Maternal Effects - None Developmental Effects - ↓ absolute testes weight on PND 21 (TT group only) - ↓ serum and testes testosterone in PND 21 males (TC and TT groups) - ↓ serum and testes testosterone in PND 80 males (TT group only) - ↓ mRNA and protein expression of steroidogenic genes in testes of PND 21 and PND 80 males (*e.g., Cyp17a1*) (TC and TT groups) - ↓ sperm concentration and motility for PND 80 males (TT group only) Unaffected Outcomes - Maternal weight gain; litter size; fetal viability; PND 21 male offspring body weight; offspring liver weight; AGD
(Hannas et al., 2012)	Pregnant SD rats (3/dose) gavaged with 0 or 500 mg/kg-day DIBP on GDs 14-18 (High)	None/500	↓ *ex vivo* fetal testicular testosterone production (~25%) on GD 18	Unaffected Outcomes - Maternal body weight gain, maternal liver weight, # of live fetuses,
	Pregnant SD rats gavaged with 0, 100, 300, 600, 900 mg/kg-day DIBP on GDs 14-18 (High)	100/300 (LOEL)	↓ fetal testicular mRNA levels of steroidogenic genes	- ↓ mRNA expression levels of *StAR, Cyp11a1, Hsd3b, Cyp17a1, Scarb1, Insl3, Cyp11b1* (≥300)

Reference	Brief Study Description (TSCA Study Quality Rating)	NOAEL/ LOAEL (mg/kg-day)	Effect at LOAEL	Remarks
(Borch et al., 2006)	Pregnant Wistar Rats (6/dose) gavaged with 0 or 600 mg/kg-day DIBP on GDs 7-19 or GDs 7-20/21 (High)	None/600	↓ *ex vivo* testes testosterone production (96%), ↓ AGD, ↑ testicular histopathology	Maternal Effects - None Developmental Effects - ↓ Testes testosterone content on GD20/21 (effect on GD 19 not statistically significant) - ↓ *ex vivo* testis testosterone production on GD 20/21, but not GD 19 - ↓ absolute AGD on GD 19 and GD 20/21; ↓ AGD (normalized to cubic root of body weight) on GD 20/21 - ↓ fetal body weight on GD 19 - ↑ testicular pathology (Leydig cell clusters on GD 19 and GD 20/21), Sertoli cell vacuolization MNGs, central localization of gonocytes on GD 20/21) - ↓ immunohistochemistry staining for StAR and P450scc in Leydig cells Unaffected Outcomes - Maternal weight gain during pregnancy; litter size; fetal viability; number of resorptions
(Furr et al., 2014)[a]	Pregnant SD rats (3-5/group) gavaged 0 or 750 mg/kg-day DIBP on GDs 14-18 (Block 2) (High)	None/750	↓ *ex vivo* fetal testicular testosterone production (81%) on GD 18	Unaffected Outcomes - Fetal viability on GD18 - Dam body weight gain
	Pregnant SD rats (3-4/group) gavaged with 0 or 500 mg/kg-day DIBP on GDs 14-18 (Block 14) (High)	None/500	↓ *ex vivo* fetal testicular testosterone production (70%) on GD 18	Unaffected Outcomes - Fetal viability on GD18 - Dam body weight gain
	Pregnant SD rats (2-4/group) gavaged with 0 or 200 mg/kg-day DIBP on GDs 14-18 (Block 30) (High)	None/200	↓ *ex vivo* fetal testicular testosterone production (47%) on GD 18	Unaffected Outcomes - Fetal viability on GD18 - Dam body weight gain
(Sedha et al., 2015)	Uterotrophic Assay	None/250	↓ Body weight gain	- ↓ Body weight gain (≥250 mg/kg-day)

Reference	Brief Study Description (TSCA Study Quality Rating)	NOAEL/ LOAEL (mg/kg-day)	Effect at LOAEL	Remarks
	Young female Wistar rats (20 days old) (≥6 mice/dose) gavaged 0, 250, or 1250 mg/kg-day DIBP for 3 days (Medium)			- Lack of effect on uterus and ovary wet weight indicate DIBP lacks estrogenic potential Unaffected Outcomes - No clinical signs; uterus and ovary wet weight
	Pubertal Assay Young female Wistar rats (20 days old) (≥6 mice/dose) gavaged 0, 250, or 1250 DIBP for 20 days (PND 21-41) (Medium)	None/250	↓ Body weight gain	- ↓ Body weight gain (≥250 mg/kg-day) - Lack of effect on reproductive organ weight and vaginal opening indicate DIBP lacks estrogenic potential Unaffected Outcomes - Absolute and relative uterus, ovary, and vagina weight; vaginal opening
Studies of DIBP Since Yost et al. (2019)				
(Pan et al., 2017)	Young (6-8 week old) male ICR mice (20/dose) fed diets containing 0 or 2.8 g DIBP/kg chow (equivalent received dose of 450 mg/kg-day) for 28 days (Medium)[b]	None/450	Sperm effects, ↓ serum & testes testosterone, ↓ mRNA & protein levels of steroidogenesis genes	- ↓ Epididymal sperm concentration, sperm motility, and progressiveness (450 mg/kg-day) - ↑ Sperm malformation (450 mg/kg-day) -↓ Serum and testis testosterone, ↓ serum follicle stimulating hormone levels (450 mg/kg-day) - ↓ mRNA and protein levels of steroidogenic genes in testes (*e.g., P450cc, StAR, 3β-hsd)* Unaffected Outcomes - Body weight gain; food intake; absolute and relative testes and epididymis weight; serum levels of estradiol and luteinizing hormone
(Gray et al., 2021)[a]	Pregnant SD rats (3-4 dams/dose) were gavaged with 0, 100, 300, 600, or 900 mg/kg-day DIBP on GDs 14-18 (High)	100/300	↓ *ex vivo* testicular testosterone production (34%) on GD 18	- ↓ *ex vivo* testicular testosterone production on GD18; Block 67 (≥300 mg/kg-day) - ↓ mRNA expression of Phase I metabolism genes (*e.g.*, Cyp11b1, Cyp11a1, Cyp17a1, ALDH2) (900 mg/kg-day) - ↓ mRNA expression of lipid signaling and cholesterol metabolism gene (≥900 mg/kg-day) Unaffected Outcomes - Maternal liver weight (Block 19)

Abbreviations: ↓ = statistically significant decrease; ↑ = statistically significant increase; NOAEL = No observed adverse effect level; LOAEL = Lowest observed adverse effect level; GD = Gestational Day; PND = Postnatal Day AGD = Anogenital distance; GLP = Good Laboratory Practice; MNG = multinucleated gonocytes; NR = Nipple

Reference	Brief Study Description (TSCA Study Quality Rating)	NOAEL/ LOAEL (mg/kg-day)	Effect at LOAEL	Remarks
Retention; PPS = preputial separation; SD = Sprague Dawley; SV = Seminal Vesicles; TT = pups exposed both prenatally and postnatally; TC = pups exposed prenatally only [a] These studies were conducted by EPA's Office of Research and Development (ORD). [b] As discussed in the Systematic Review protocol for DIBP (U.S. EPA, 2025q) and consistent with Office of Pesticide Programs *Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Hazard Assessment* (U.S. EPA, 2012), the study was of sufficient quality to be considered qualitatively as part of the weight of scientific evidence and was assigned a quality score of medium.				

3.1.2.1 Developing Male Reproductive System

EPA previously developed a weight of scientific evidence analysis and concluded that oral exposure to DIBP can induce effects on the developing male reproductive system consistent with a disruption of androgen action (see EPA's *Draft Proposed Approach for Cumulative Risk Assessment of High-Priority and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act* (U.S. EPA, 2023a)). Notably, EPA's conclusion was supported by the Science Advisory Committee on Chemicals (SACC) (U.S. EPA, 2023b). A brief summary of the MOA for phthalate syndrome and data available for DIBP supporting this MOA are provided below in Figure 3-1. Readers are directed to see EPA's *Draft Proposed Approach for Cumulative Risk Assessment of High-Priority and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act* (U.S. EPA, 2023a) for a more thorough discussion of DIBP's effects on the developing male reproductive system and EPA's MOA analysis. Effects on the developing male reproductive system are considered further for dose-response assessment in Section 4.

As shown in Figure 3-1, a MOA for phthalate syndrome has been proposed to explain the link between gestational or perinatal exposure to DIBP and effects on the male reproductive system in rats. The MOA has been described in greater detail in EPA's *Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act* (U.S. EPA, 2023a) and is described briefly below.

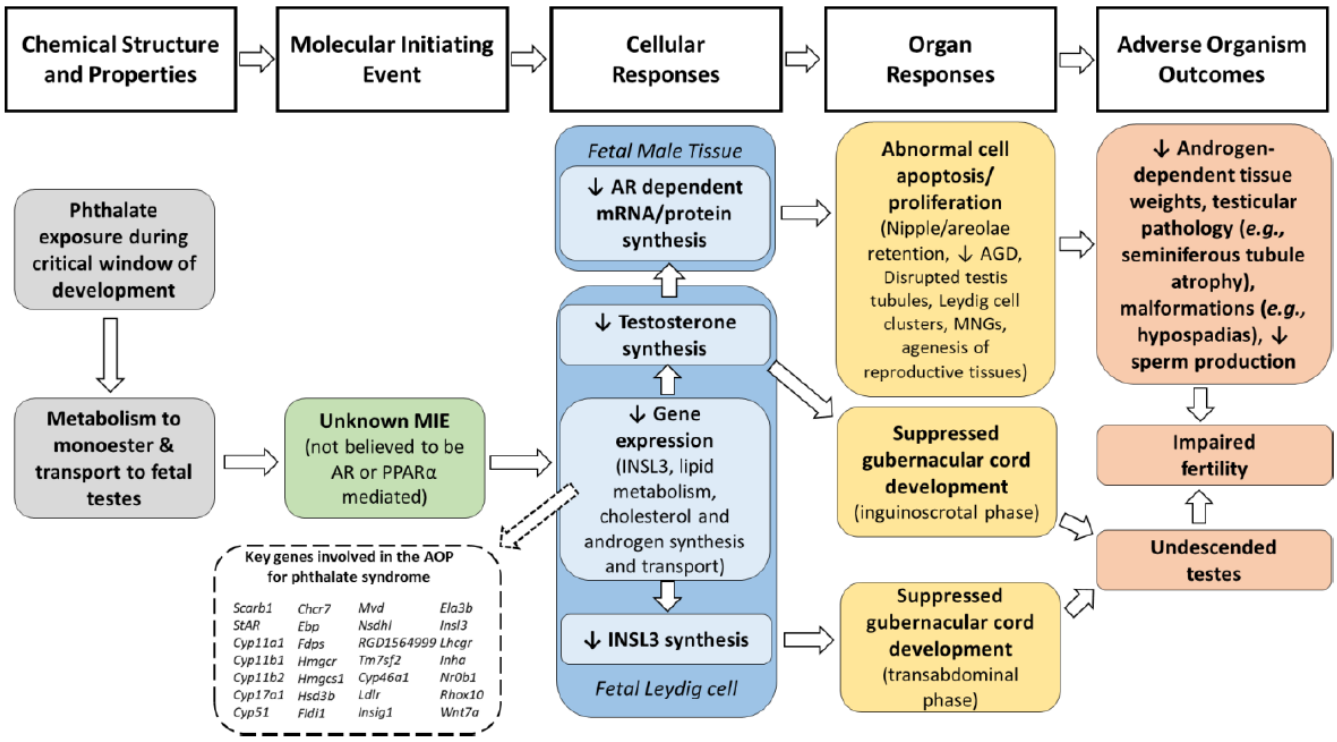

Figure 3-1. Hypothesized Phthalate Syndrome Mode of Action Following Gestational Exposure
Figure taken directly from (U.S. EPA, 2023a) and adapted from (Conley et al., 2021; Gray et al., 2021; Schwartz et al., 2021; Howdeshell et al., 2017). Abbreviations: AR = androgen receptor; INSL3 = insulin-like growth factor 3; MNG = multinucleated gonocytes; PPARα = peroxisome proliferator-activated receptor alpha.

Phthalate syndrome is characterized by both androgen-dependent (*e.g.*, reduced AGD, increased male NR) and -independent effects (*e.g.*, germ cell effects) on the male reproductive system (U.S. EPA, 2023a). The MOA underlying phthalate syndrome has not been fully established; however, key cellular-, organ-, and organism-level effects are generally understood (Figure 3-1). The molecular events preceding cellular changes remain unknown. Although androgen receptor antagonism and peroxisome proliferator-activated receptor alpha activation have been hypothesized to play a role, studies have generally ruled out the involvement of these receptors (Foster, 2005; Foster et al., 2001; Parks et al., 2000).

Exposure to DIBP during the masculinization programming window (*i.e.*, GDs 15.5 to 18.5 for rats; GDs 14 to 16 for mice; gestational weeks 8 to 14 for humans), in which androgen action drives development of the male reproductive system, can lead to antiandrogenic effects on the male reproductive system (MacLeod et al., 2010; Welsh et al., 2008; Carruthers and Foster, 2005). Consistent with the MOA outlined in Figure 3-1, seven studies (5 of rats, 2 of mice) of DIBP have demonstrated that oral exposure to DIBP during the masculinization programming window can reduce mRNA and/or protein expression of insulin-like growth factor 3 (INSL3), as well as genes involved in steroidogenesis in the testes of rats (Gray et al., 2021; Saillenfait et al., 2017; Hannas et al., 2012; Hannas et al., 2011; Borch et al., 2006) and mice (Pan et al., 2017; Wang et al., 2017). Consistently, nine studies (7 of rats, 2 of mice) have also demonstrated that oral exposure to DIBP during the masculinization programming window can reduce testicular testosterone content and/or testosterone production in rats (Gray et al., 2021; Saillenfait et al., 2017; Furr et al., 2014; Hannas et al., 2012; Hannas et al., 2011; Howdeshell et al., 2008; Borch et al., 2006) and mice (Pan et al., 2017; Wang et al., 2017). Oral exposure of rats to DIBP during the masculinization programming window has also been shown to reduce male pup anogenital distance (AGD) in three studies (Saillenfait et al., 2017; Saillenfait et al., 2008; Borch et al., 2006) and cause male pup nipple retention (NR) in one study (Saillenfait et al., 2008), which are two hallmarks of antiandrogenic substances (see Sections 3.1.3.3 and 3.1.3.4 of (U.S. EPA, 2023a) for additional discussion). Additional effects consistent with phthalate syndrome observed in mice and rats following oral exposure to DIBP during the critical window of development include: reproductive tract malformations (*i.e.*, hypospadias, undescended testes, exposed os penis, cleft prepuce) in two studies of rats (Saillenfait et al., 2008; Saillenfait et al., 2006); delayed preputial separation (PPS) in one study of rats (Saillenfait et al., 2008); testicular pathology in two studies of rats (*e.g.*, degeneration of seminiferous tubules, oligospermia, azoospermia, Leydig cell aggregation, Sertoli cell vacuolation, multinucleated gonocytes) (Saillenfait et al., 2008; Borch et al., 2006); and decreased sperm concentration and motility in two studies of mice (Pan et al., 2017; Wang et al., 2017).

Collectively, available studies consistently demonstrate that oral exposure to DIBP during the masculinization programming window in rats and mice can disrupt androgen action, leading to a spectrum of effects on the developing male reproductive system consistent with development of phthalate syndrome. As noted above, this conclusion was supported by the Science Advisory Committee on Chemicals (SACC) (U.S. EPA, 2023b) and readers are directed to EPA's *Draft Proposed Approach for Cumulative Risk Assessment of High-Priority and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act* (U.S. EPA, 2023a) for additional discussion of DIBP's effects on the developing male reproductive system and EPA's MOA analysis.

3.1.2.2 Other Developmental Outcomes

In addition to effects on the developing male reproductive system, other developmental effects (*e.g.*, decreased fetal weight, decreased offspring body weight, resorptions, post-implantation loss, skeletal variations) have been observed in experimental animal models following oral exposure to DIBP.

However, these effects occur at higher doses than those that result in effects on the developing male reproductive system and frequently coincide with maternal toxicity (Table 3-3). Data supporting other developmental effects of DIBP are discussed below.

In a study that adhered to OECD test guideline 414, pregnant Wistar rats (22 to 23 per dose) were administered diets containing 0, 1000, 4000, or 11,000 ppm DIBP (equivalent to 88, 363, or 942 mg/kg-day) from GD 6 through 20 and then sacrificed on GD 20 (BASF, 2007). Maternal and developmental effects were limited to the high-dose group and included a 5 percent decrease in maternal food consumption as well as an 11 percent decrease in maternal bodyweight gain from GD 6 through 20, a 5 percent decrease in fetal body weight, and increased incidences of skeletal variations (*e.g.,* incomplete ossification of sternebra, unilateral ossification of sternebra). No significant increases in malformations were observed. No developmental or maternal toxicity was observed in the low- or mid-dose groups.

In a second study, pregnant SD rats (20 to 22 per dose) were exposed to 0, 250, 500, 750, or 1000 mg/kg-day DIBP from GD 6 through 20 via gavage and then sacrificed on GD 21 (Saillenfait et al., 2006). Maternal effects were limited to a decrease in weight gain on GD 6 through 9 and GD 15 through 18 in dams treated with 500 mg/kg-day DIBP and above; however, dam body weight gain on GD 6 through 21 corrected for gravid uterine weight was unaffected. Developmental toxicity was observed at 500 mg/kg-day and above. Observed developmental effects included: increased resorptions and post-implantation loss per litter and decreased live fetuses per litter at 750 mg/kg-day and above; increased incidence of total number of fetuses and/or litters with external, visceral, and skeletal malformations at 750 mg/kg-day and above; and increased incidence of undescended testes and decreased fetal body weight (both sexes) at 500 mg/kg-day and above.

Howdeshell et al. (2008) reported increased fetal mortality and total resorptions, and decreased numbers of live fetuses in pregnant SD rats gavaged with 900 mg/kg-day DIBP from GDs 8 to GD18 and sacrificed on GD 18. Additionally, Borch et al. (2006) reported reduced fetal body weight on GD 19 in pregnant Wistar rats gavaged with 600 mg/kg-day DIBP on GD 7 through 19. In addition to decreased fetal weight, decreased offspring body weight was observed following gestational exposures. Saillenfait et al. (2008) reported reduced male offspring body weight on PND1, PND21 as well as PNW11 to 12 and PNW16 to 17 following gestational exposure to 500 to 625 mg/kg-day DIBP on GD 12 through 21.

Collectively, available studies provide consistent evidence that gestational exposure to DIBP can result in a spectrum of developmental effects in addition to those of the developing male reproductive system. However, effects on the developing male reproductive system (Section 3.1.2.1) occur at much lower doses than the aforementioned other developmental effects. Therefore, effects on the developing male reproductive system are the most sensitive to DIBP exposure and are consistent with a disruption of androgen action and phthalate syndrome. Furthermore, the lowest LOAELs for effects on the developing male reproductive system range from 125 to 300 mg/kg-day, while the lowest LOAELs for other developmental outcomes range from 500 to 600 mg/kg-day (Table 3-3).

4 DOSE-RESPONSE ASSESSMENT

EPA considered reproductive/developmental toxicity as the sole non-cancer hazard endpoint for dose-response analysis. This hazard endpoint was selected for dose-response analysis because EPA has the highest confidence in this hazard endpoint for estimating risk to human health; effects were consistently observed across species and durations of exposure and occurred in a dose-related manner. Other non-cancer hazard endpoints considered by EPA (*i.e.,* liver and kidney toxicity) were not utilized for dose-response analysis due to limitations and uncertainties that reduce EPA's confidence in using these endpoints for estimating risk to human health. For toxicologically similar phthalates (*i.e.,* DEHP, DBP, BBP, DCHP), which include larger databases of animal toxicology studies including numerous well-conducted subchronic and chronic toxicity studies, effects on the developing male reproductive system consistent with a disruption of androgen action have consistently been identified by EPA as the most sensitive and well-characterized hazard in experimental animal models. This is demonstrated by the fact that the acute/intermediate/chronic PODs selected by EPA for use in risk characterization for DEHP (U.S. EPA, 2025k), DBP (U.S. EPA, 2025i), BBP (U.S. EPA, 2025h), DCHP (U.S. EPA, 2025j) are all based on effects related to phthalate syndrome. According to previous assessments, liver is a target organ following DIBP exposure (U.S. CPSC, 2011; NICNAS, 2008a); however, Health Canada (2015b) concluded that DIBP has low systemic toxicity based on a limited number of repeated oral dose toxicity studies. Additionally, a systematic review by Yost et al. (2019) stated that several studies indicate dose dependent increases in liver weight following intermediate and chronic DIBP exposure in rats and male mice (Wang et al., 2017; Foster et al., 1982; Oishi and Hiraga, 1980; University of Rochester, 1953). However, there are no available data on other hepatic endpoints, such as clinical chemistry (*e.g.*, ALT, ALT, bilirubin) and histology effects, following oral DIBP exposure. The lack of such data reduces EPAs confidence in using effects on the liver as an endpoint from which to derive a POD, because there is uncertainty about adversity without corroborating clinical chemistry or histology (Hall et al., 2012; U.S. EPA, 2002a). Likewise, effects on the kidney following exposure to DIBP were evaluated by a limited number of studies, wherein inconsistencies across species were observed, as summarized in previous assessments and publications (Yost et al., 2019; ECHA, 2017b; NICNAS, 2016; U.S. CPSC, 2011; NICNAS, 2008a). No studies were identified that provided data on hepatic or renal effects following exposure to DIBP were identified through the TSCA systematic review process; therefore, EPA is in agreement with the conclusions of these previous assessments as well as those of the systematic review by Yost et al. (2019) [as described previously in Section 1.2.3].

For the DIBP dose-response assessment, EPA first identified NOAEL and LOAEL values from the 11 developmental toxicity studies considered for dose-response assessment (Table 4-5). Four of the 11 studies provided dose-response information and tested doses below 200 mg/kg-day (*i.e.,* (Gray et al., 2021; Hannas et al., 2011; Howdeshell et al., 2008; Saillenfait et al., 2008)). These four studies were subjected to benchmark dose (BMD) modeling using EPA's BMD Software to attempt to refine the identified NOAEL or LOAEL. The remaining 7 studies of the initial 11 were not subjected to BMD analysis as they either evaluated a single dose level of DIBP (5 studies) or were not very sensitive (*e.g.,* evaluated doses of 250 mg/kg-day or higher). For reduced fetal testicular testosterone in rats, EPA conducted meta-analysis and benchmark dose modeling using the approach previously published by NASEM (2017), which is further described in EPA's *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), Dicyclohexyl Phthalate (DCHP), and Diisononyl Phthalate* (U.S. EPA, 2025g). Fetal testicular testosterone data from three studies was included in EPA's meta-analysis (Gray et al., 2021; Hannas et al., 2011; Howdeshell et al., 2008). Data from all three of the individual studies were also subjected to BMD analysis using EPA's BMD Software, so that results between the two analyses could be compared. In subsequent sections below the extent to which BMD modeling was or was not conducted for each study is discussed further.

Acute, intermediate, and chronic non-cancer NOAEL, LOAEL, and $BMDL_5$ values identified by EPA are discussed further in Section 4.2. As discussed further in Section 4.2, EPA considers effects on the developing male reproductive system consistent with a disruption of androgen action relevant for setting a POD for acute exposure durations. However, because these acute effects are the most sensitive effects following exposure to DIBP, they are also considered protective of intermediate and chronic duration exposures. As described in Appendix C, EPA converted oral PODs derived from animal studies to human equivalent doses (HEDs) using allometric body weight scaling to the three-quarters power (U.S. EPA, 2011c). Species differences in dermal and oral absorption are corrected for as part of the dermal exposure assessment (U.S. EPA, 2025f). In the absence of inhalation studies, EPA performed route-to-route extrapolation to convert oral HEDs to inhalation human equivalent concentrations (HECs) (Appendix C).

4.1 Selection of Studies and Endpoints for Non-cancer Health Effects

EPA considered the suite of oral animal toxicity studies primarily indicating effects on the developing male reproductive system consistent with phthalate syndrome when considering non-cancer PODs for estimating risks for acute, intermediate, and chronic exposure scenarios as described in Section 4.2. EPA considered the following factors during study and endpoint selection for POD determination from relevant non-cancer health effects:

- Exposure duration;
- Dose range;
- Relevance (*e.g.*, considerations of species, whether the study directly assesses the effect, whether the endpoint is the best marker for the toxicological outcome, etc);
- Uncertainties not captured by the overall quality determination;
- Endpoint/POD sensitivity; and
- Total uncertainty factors (UFs). EPA considers the overall uncertainty with a preference for selecting studies that provide lower uncertainty (*e.g.*, lower benchmark MOE) because they provide higher confidence (*e.g.*, use of a NOAEL or $BMDL_5$ vs. a LOAEL with additional UF_L applied).

The following sections provide comparisons of the above attributes for studies and hazard outcomes relevant to each of these exposure durations and details related to the studies considered for each exposure duration scenario.

4.2 Non-cancer Oral Points of Departure for Acute, Intermediate, and Chronic Exposures

4.2.1 Studies Considered for the Non-Cancer POD

EPA considered 11 developmental toxicity studies (10 of rats, 1 of mice) with endpoints relevant to acute, intermediate, and chronic exposure duration (U.S. EPA, 1996, 1991), summarized in Table 4-5. Of the considered studies, all 11 evaluated gestational or perinatal exposures to DIBP. No one or two-generation studies on the effects of DIBP on reproduction have been identified by EPA. Further, of the 11 studies considered, 5 only evaluated one exposure level of DIBP (*i.e.*, did not evaluate dose-response across multiple exposure levels) ranging from 200 to 750 mg/kg-day (Table 4-5) (Saillenfait et al., 2017; Wang et al., 2017; Furr et al., 2014; Hannas et al., 2012; Borch et al., 2006). Of the six remaining studies considered, four tested doses as low as 100 to 125 mg/kg-day (Table 4-5) (Gray et al., 2021;

Hannas et al., 2011; Howdeshell et al., 2008; Saillenfait et al., 2008), however, no studies evaluating effects on the developing male reproductive system consistent with a disruption of androgen action have been conducted with DIBP that have evaluated doses below 100 mg/kg-day. Available studies considered for dose-response are discussed further below.

In support of the draft human health hazard assessment of DIBP that was peer-reviewed by SACC in August 2025, EPA conducted BMD modeling of fetal testicular testosterone data reported in the three most sensitive studies that evaluated doses of DIBP as low as 100 mg/kg-day (Appendix E) (Gray et al., 2021; Hannas et al., 2011; Howdeshell et al., 2008). As described further below, Blessinger et al. (2020) has previously conducted BMD modeling of apical outcomes associated with phthalate syndrome reported by Saillenfait et al. (2008). In response to SACC and public comments, EPA evaluated 7 additional studies for potential BMD modeling. However, EPA determined that these 7 studies were not amenable to BMD modeling: five studies only evaluated one exposure level of DIBP; one study did not report any phthalate syndrome-related effects (BASF, 2007); and one study did not evaluate doses below 250 mg/kg-day DIBP and was not considered sensitive enough to warrant BMD modeling (Saillenfait et al., 2006).

As discussed in Sections 3.1.2.1 and 3.1.2.2, oral exposure to DIBP can cause effects on the developing male reproductive system consistent with a disruption of androgen action and other developmental effects (*i.e.*, decreased fetal weight, resorptions, post-implantation loss, skeletal variations). Effects on the developing male reproductive system are more sensitive than other observed developmental effects. This is demonstrated by the fact that the lowest LOAELs for effects on the developing male reproductive system range from 125 to 300 mg/kg-day, while the lowest LOAELs for other developmental outcomes range from 500 to 600 mg/kg-day (Table 3-3, Table 4-5). Therefore, EPA's dose-response assessment in this section focuses on effects on the developing male reproductive system consistent with a disruption of androgen action.

Although single dose studies evaluating the effects of DIBP on the developing male reproductive system are not available, studies of the toxicologically similar phthalate dibutyl phthalate (DBP) have demonstrated that a single exposure during the critical window of development can disrupt expression of steroidogenic genes and decrease fetal testes testosterone. Therefore, EPA considers effects on the developing male reproductive system consistent with a disruption of androgen action to be relevant for setting a POD for acute, intermediate, and chronic duration exposures (see Appendix B for further discussion). Notably, SACC agreed with EPA's decision to consider effects on the developing male reproductive system consistent with a disruption of androgen action to be relevant for setting a POD for acute durations during the July 2024 peer-review meeting of the DINP human health hazard assessment (U.S. EPA, 2024). Studies considered for dose-response assessment are summarized in Table 4-5.

Of the 11 developmental toxicity studies considered for dose-response, two studies (BASF, 2007; Saillenfait et al., 2006) were not considered further for dose-response analysis because of limitations and other factors that increase uncertainty. In Saillenfait et al. (2006), rats were exposed to doses of DIBP ranging from 250 to 1000 mg/kg-day on GD 6 through 20 via gavage. Decreased fetal body weight and increased incidence of cryptorchidism were observed at 500 mg/kg-day. Based on these effects, EPA identified a NOAEL of 250 mg/kg-day. Similarly, BASF (2007) conducted a dietary study of pregnant Wistar rats in which animals were exposed to 88 to 942 mg/kg-day of DIBP from GDs 6 through 20. A NOAEL of 363 mg/kg-day was identified based on decreases in fetal body weight, maternal food consumption, and maternal body weight gain at 942 mg/kg-day. However, the doses at which developmental effects were observed in these studies were higher than doses at which more sensitive

effects of androgen insufficiency (*e.g.*, decreased fetal testicular testosterone) were observed in other studies. Neither study was subjected to BMD analysis, as other studies that evaluated lower doses provided more sensitive outcomes for modeling. Therefore, EPA did not select these studies and endpoints because they do not provide the most sensitive robust endpoint for an acute/intermediate/chronic POD.

Seven studies reported across five publications (Saillenfait et al., 2017; Wang et al., 2017; Furr et al., 2014; Hannas et al., 2012; Borch et al., 2006) that exposed pregnant mice or rats to DIBP via gavage have observed effects on the developing male reproductive system. However, experiments in each of these studies only tested one dose level in addition to vehicle controls, and support LOAELs ranging from 200 to 750 mg/kg-day DIBP. These studies do not allow for the identification of a NOAEL, which increases the uncertainty in the data set. These five studies were not amenable to BMD modeling, as each study only evaluated a single dose level. Ultimately, these studies were not further considered because other developmental studies of DIBP are available that test more than one dose level, including doses less than 200 mg/kg-day and support identification of more sensitive NOAELs.

In contrast, three studies of pregnant SD rats provide consistent evidence of dose-related reductions in *ex vivo* fetal testicular testosterone production and support NOAEL and LOAEL values of 100 and 300 mg/kg-day, respectively (Table 4-5) (Gray et al., 2021; Hannas et al., 2011; Howdeshell et al., 2008). Notably, the magnitude of effect on *ex vivo* fetal testicular testosterone production was consistent across tested doses in all three studies when measured on GD18. For example, the response compared to the control ranged from 95 to 110 percent at 100 mg/kg-day and 44 to 66 percent at 300 mg/kg-day. Across the three studies, there is consistent evidence of no effect on *ex vivo* fetal testicular testosterone production in rats dosed with 100 mg/kg-day DIBP.

In 2017, NASEM (2017) assessed experimental animal evidence for effects on fetal testicular testosterone following *in utero* exposure to DIBP using the systematic review methodology developed by the National Toxicology Program's (NTP) Office of Health Assessment and Translation (OHAT). Based on results from two studies of rats (Hannas et al., 2011; Howdeshell et al., 2008), NASEM found high confidence in the body of evidence and a high level of evidence that fetal exposure to DIBP is associated with a reduction in fetal testosterone in rats. NASEM further conducted a meta-regression analysis and benchmark dose (BMD) modeling analysis on decreased fetal testicular testosterone production data from the same two prenatal exposure studies of rats (Hannas et al., 2011; Howdeshell et al., 2008). NASEM found a statistically significant overall effect and linear trends in $\log_{10}$(dose) and dose, with an overall large magnitude of effect (greater than 50 percent) in its meta-analysis for DIBP. BMD analysis determined $BMDL_5$ and $BMDL_{40}$ values of 23 and 225 mg/kg-day, respectively, the 95 percent lower confidence limits of the BMDs associated with a benchmark response (BMR) of 5 and 40 percent (Table 4-1).

Table 4-1. Summary of NASEM (2017) Meta-Analysis and BMD Modeling for Effects of DIBP in Fetal Testosterone [a] [b]

Database Supporting Outcome	Confidence in Evidence	Evidence of Outcome	Heterogeneity in Overall Effect	Model with Lowest AIC	BMD_5 mg/kg-day (95% CI)	BMD_{40} mg/kg-day (95% CI)
2 rat studies	High	High	$I^2 > 60\%$	Linear	27 (23, 34) [c]	270 (225, 340)

[a] R code supporting NASEM's meta-regression and BMD analysis of DIBP is publicly available through GitHub (https://github.com/wachiuphd/NASEM-2017-Endocrine-Low-Dose).
[b] NASEM (2017) calculated BMD40s for this endpoint because "previous studies have shown that reproductive-tract malformations were seen in male rats when fetal testosterone production was reduced by about 40%."
[c] EPA noted an apparent discrepancy in the NASEM (2017) report. In Table 3-26, NASEM (2017) notes that no BMD/BMDL estimates could be generated at the 5% response level for DIBP because "the 5% change was well below the range of the data, but it will be 10 times lower because a linear model was used." However, in Table C6-12 of the NASEM (2017) report, BMD/BMDL estimates at the 5% response level are provided for DIBP for the best-fit linear model. In EPA's replicate analysis, which is provided in EPA's Meta-Analysis and BMD of Fetal Testicular Testosterone for DEHP, DBP, BBP, DIBP, and DCHP (U.S. EPA, 2025g), identical BMD/BMDL estimates for the 5% response level were obtained. Therefore, BMD/BMDL estimates at the 5% response level for DIBP are reported in this table.

Since EPA identified new fetal testicular testosterone data (Gray et al., 2021) for DIBP, an updated meta-analysis was conducted. Using the publicly available R code provided by NASEM (https://github.com/wachiuphd/NASEM-2017-Endocrine-Low-Dose), EPA applied the same meta-analysis and BMD modeling approach used by NASEM, with the exception that the most recent Metafor package available at the time of EPA's updated analysis was used (*i.e.,* EPA used Metafor package Version 4.6.0, whereas NASEM used Version 2.0.0), and an additional BMR of 10 percent was modeled. Appendix D provides justification for the evaluated BMRs of 5, 10, and 40 percent. Fetal rat testosterone data from three studies were included in the analysis (Gray et al., 2021; Hannas et al., 2011; Howdeshell et al., 2008). Overall, the meta-analysis found a statistically significant overall effect and linear trends in $\log_{10}$(dose) and dose, with an overall effect that is large in magnitude (>50% change) (Table 4-2). There was substantial, statistically significant heterogeneity in all cases (I^2>60%). The statistical significance of these effects was robust to leaving out individual studies. The linear-quadratic model provided the best fit (based on lowest AIC) (Table 4-2). BMD estimates from the linear-quadratic model were 270 mg/kg-day [95% confidence interval: 136, 517] for a 40 percent change (BMR = 40%) and 55 mg/kg-day [NA, 266] for a 10 percent change (BMR = 10%), although a $BMDL_{10}$ could not be estimated (Table 4-3). No BMD could be estimated for a 5 percent change (BMR = 5%). Further methodological details and results (*e.g.,* forest plots, figures of BMD model fits) for the updated meta-analysis and BMD modeling of fetal testicular testosterone data are provided in the *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), Dicyclohexyl Phthalate (DCHP), and Diisononyl Phthalate* (U.S. EPA, 2025g).

Table 4-2. Overall Analyses of Rat Studies of DIBP and Fetal Testosterone (Updated Analysis Conducted by EPA)

Analysis	Estimate	Beta	CI, Lower Bound	CI, Upper Bound	P value	Tau	I^2	P value for Heterogeneity	AICs
Primary Analysis									
Overall	intercept	-82.21	-122.85	-41.56	0.000	68.02	96.52	0.000	130.45
Trend in log10(dose)	log10(dose)	-165.55	-205.47	-125.64	0.000	19.89	65.48	0.004	106.31
Linear in dose100	dose100	-18.48	-25.14	-11.81	0.000	60.86	96.92	0.000	120.04
Linear-Quadratic in dose100	dose100	-19.18	-41.21	2.85	0.088	48.79	94.49	0.000	111.51*
Linear-Quadratic in dose100	I(dose100^2)	0.09	-2.70	2.88	0.950	48.79	94.49	0.000	111.51
Sensitivity Analysis									
Overall minus Gray et al. 2021	intercept	-82.31	-135.11	-29.52	0.002	71.76	96.96	0.000	87.28
Overall minus Hannas et al. 2011b	intercept	-69.98	-110.63	-29.34	0.001	55.43	95.94	0.000	83.66
Overall minus Howdeshell et al. 2008	intercept	-94.90	-151.74	-38.06	0.001	78.38	94.86	0.000	88.36

* Indicates model with lowest Akaike information criterion (AIC).
Abbreviations: CI = confidence interval; I^2 = describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error; Tau = estimated standard deviation of the true underlying effect sizes across studies in the random-effects model meta-analysis

Table 4-3. Benchmark Dose Estimates for DIBP and Fetal Testosterone in Rats

Analysis	Benchmark Response (BMR)	Benchmark Dose (BMD)	Confidence Interval, Lower Bound	Confidence Interval, Upper Bound
Linear in dose100	5%	28	20	43
Linear in dose100	10%	57	42	89
Linear in dose100	40%	276	203	432
Linear-Quadratic in dose100*	5%	NA	NA	207
Linear-Quadratic in dose100*	10%	55	NA	266
Linear-Quadratic in dose100*	40%	270	136	517

* Indicates model with lowest Akaike information criterion (AIC).
'NA' indicates a BMD or BMDL estimate could not be derived.

Since no $BMDL_5$ could be derived through the updated meta-analysis and BMD modeling analysis, EPA modeled individual fetal testicular testosterone data from the three studies included in the updated meta-analysis using EPA's BMD Software (BMDS version 3.3.2) (Gray et al., 2021; Hannas et al., 2011; Howdeshell et al., 2008). This analysis included the full suite of standard continuous models (Exponential, Hill, Polynomial, Power, Linear), compared to the meta-analysis that only included the linear and linear-quadratic models. Further methodological details and results from this BMD analysis

are provided in Appendix E. As can be seen from Table_Apx E-1, no models adequately fit the fetal testicular testosterone data from Hannas et al. (2011), and therefore this study is considered to support a NOAEL of 100 mg/kg-day based on a statistically significant 56 percent reduction in fetal testicular testosterone production at the LOAEL of 300 mg/kg-day. In contrast, BMD_5 and $BMDL_5$ values of 63 and 24 mg/kg-day were derived from the fetal testicular testosterone data reported in Gray et al. (2021) based on the best fitting exponential 3 model (constant variance), while BMD_5 and $BMDL_5$ values of 103 and 52 mg/kg-day were derived from the fetal testicular testosterone data reported in Howdeshell et al. (2008) based on the best fitting hill model (constant variance). Both studies by Howdeshell et al. and Gray et al. are high-confidence studies. However, there are several lines of evidence that indicate that the $BMDL_5$ estimate of 24 mg/kg-day is more appropriate for use in human health risk assessment compared to the $BMDL_5$ estimate of 52 mg/kg-day from Howdeshell et al. (2008). First, the $BMDL_5$ of 52 mg/kg-day (BMR of 5%) from Howdeshell et al. (2008) is similar to the derived BMD_{10} of 55 mg/kg-day (BMR of 10%) from the best-fitting linear-quadratic model derived as part of EPA's updated meta-analysis, which includes data from three studies (Table 4-3). Next, although it would be more appropriate to compare the $BMDL_5$ of 52 mg/kg-day from Howdeshell et al. (2008) to a $BMDL_5$ from the meta-analysis, no $BMDL_5$ estimate could be derived from the best-fitting linear-quadratic model as part of the meta-analysis. However, $BMDL_{10}$ and $BMDL_5$ estimates of 42 and 20 mg/kg-day were derived from the linear model as part of EPA's updated meta-analysis (Table 4-3), and both of these BMDL estimates are lower than the $BMDL_5$ estimate of 52 mg/kg-day from Howdeshell et al. (2008). Although, the linear model in EPA's updated meta-analysis did not provide the best-fit (*i.e.*, the linear-quadratic model had a lower AIC), the linear model did adequately fit the data set. Finally, the $BMDL_5$ estimate of 24 mg/kg-day from Gray et al. (2021) is less than the BMD_{10} estimate of 55 mg/kg-day using the linear-quadratic model from EPA's updated meta-analysis, and is similar to the $BMDL_5$ estimate of 20 mg/kg-day from the linear model from EPA's updated meta-analysis. Notably, the meta-analysis is expected to provide more precise BMD estimates compared to the BMD analysis of single studies, as it integrates combined data from three studies. Although there is some uncertainty because derived $BMDL_5$ estimates are below the lowest dose with empirical data (*i.e.*, 100 mg/kg-day), EPA considers this BMD analysis to support a $BMDL_5$ of 24 mg/kg-day based on reduced fetal testicular testosterone in the study by Gray et al. (2021) because data from Gray et al. provides BMD/BMDL estimates that more closely align to BMD/BMDL estimates from EPA's updated meta-analysis of data from three studies.

Lastly, Saillenfait et al. (2008) reported the results of oral exposure to 0, 125, 250, 500, or 625 mg/kg-day y DIBP on GD 12 through 21 on F1 male offspring. Treatment-related effects at 250 mg/kg-day DIBP and above include decreased F1 male AGD on PND 1, increased male nipple retention on PND 12 to 14 and PNW 11 to 12 or PNW 16 to 17, while more severe reproductive tract malformations (*e.g.*, hypospadias, exposed os penis, nonscrotal testes) were observed at 500 mg/kg-day DIBP and above. In the low dose group (125 mg/kg-day), low incidence of testicular pathology was observed in F1 males from PNW 11 to 12, including oligospermia (low sperm) (incidence: 0/24, 1/20, 3/28, 2/22, 1/20), azoospermia (no sperm present) (0/24, 1/20, 3/28, 10/22, 18/20), and tubular degeneration, which showed evidence of increasing severity with dose. However, the study is limited due to a lack of statistical analysis on the testicular pathology data and due to the small sample size (only two F1 males were examined per litter). Although the incidence of testicular pathology at 125 mg/kg-day is low, EPA considers the study to support a LOAEL of 125 mg/kg-day (no NOAEL identified) due to the severity of the observed effects (*i.e.*, reduced and/or absence of sperm in 2/20 adult F1 males). BMD modeling of data from Saillenfait et al. (2008) was previously reported by Blessinger et al. (2020). As can be seen from Table 4-4, the BMD_5 and $BMDL_5$ values for the more sensitive outcomes evaluated by Saillenfait et al. (*i.e.*, combined azoospermia and oligospermia) fall outside of the range of measured tested doses. 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 the derived BMD_5 and $BMDL_5$ values (Table 4-4).

Table 4-4. Summary of Dichotomous BMD Analysis of Data from Saillenfait et al. (2008) by Blessinger et al. (2020)[a]

Endpoint	BMR	BMD (mg/kg-day)	BMDL (mg/kg-day)
Hypospadias	1% extra risk	401	242
Undescended testes	1% extra risk	342	194
Exposed os penis	1% extra risk	361	112
Areola or nipple retention	5% extra risk	317	205
Azoospermia or grade 2-5 oligospermia	5% extra risk	117	60
Tubular degeneration	5% extra risk	480	266
Sloughed cells	5% extra risk	112	67

[a] Adapted from Table 6 in Blessinger et al. (2020). See Blessinger et al. for a description of the BMD modeling approach. BMD modeling outputs from Blessinger et al. are available at: https://doi.org/10.23719/1503702.

4.2.2 POD Selected for Acute, Intermediate, and Chronic Durations

For the draft human health hazard assessment of DIBP that was peer-reviewed by SACC in August 2025, EPA considered several options as described further in Appendix F. For the final human health hazard assessment of DIBP, EPA selected the $BMDL_5$ of 24 mg/kg-day based on reduced fetal testicular testosterone from the study by Gray et al. (2021). Notably, the SACC supported EPA's selection of a $BMDL_5$ of 24 mg/kg-day from Gray et al. (2021) for use as the basis for the POD, given the lack of studies evaluating doses of DIBP less than 100 mg/kg-day (U.S. EPA, 2025o). EPA considered the POD derived from the BMD analysis of data in this study to have the least uncertainty and highest confidence upon examination of the weight of scientific evidence. This POD is more sensitive than the lowest NOAEL of 100 mg/kg-day based on fetal testicular testosterone data from 3 studies (Gray et al., 2021; Hannas et al., 2011; Howdeshell et al., 2008) and LOAEL of 125 mg/kg-day based on increased incidence of testicular pathology (Saillenfait et al., 2008), which are likely under-protective due to the limited number of studies and lack of testing at doses lower than 100 mg/kg-day.

Using allometric body weight scaling to the three-quarters power (U.S. EPA, 2011c), EPA extrapolated an HED of 5.7 mg/kg-day from the $BMDL_5$ of 24 mg/kg-day. A total uncertainty factor of 30 was selected for use as the benchmark margin of exposure (based on an interspecies uncertainty factor (UF_A) of 3 and an intraspecies uncertainty factor (UF_H) of 10). Consistent with EPA guidance (2022, 2002b, 1993), EPA reduced the UF_A from a value of 10 to 3 because allometric body weight scaling to the three-quarter power was used to adjust the POD to obtain a HED (Appendix C).

EPA considered reducing the UF_A further to a value of 1 based on apparent differences in toxicodynamics between rats and humans. As discussed in Section 3.1.4 of EPA's *Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act* (U.S. EPA, 2023a), several explant (Lambrot et al., 2009; Hallmark et al., 2007) and xenograft studies (van Den Driesche et al., 2015; Spade et al., 2014; Heger et al., 2012; Mitchell et al., 2012) using human donor fetal testis tissue have been conducted to investigate the antiandrogenicity of mono-2-ethylhexyl phthalate (MEHP; a monoester metabolite of DEHP), DBP, and monobutyl phthalate (MBP; a monoester metabolite of DBP) in a human model. Generally, results from human explant and xenograft studies suggest that human fetal testes are less sensitive than rat testes to the antiandrogenic effects of phthalates, however, effects on Sertoli cells and increased incidence of MNGs have been observed in four human xenograft studies of DBP (van Den Driesche et al., 2015; Spade et al., 2014; Heger et al., 2012; Mitchell et al., 2012). As discussed in EPA's draft approach document (U.S. EPA, 2023a), the available human explant and xenograft studies have limitations and uncertainties, which preclude definitive conclusions related to species differences in sensitivity. For example, key limitations and uncertainties of the human explant and xenograft studies include: small sample size; human testis tissue was collected from donors of variable age and by variable non-standardized methods; and most of the testis tissue was taken from fetuses older than 14 weeks, which is outside of the critical window of development (*i.e.*, gestational weeks 8 to 14 in humans). Therefore, EPA did not reduce the UF_A.

Table 4-5. Dose-Response Analysis of Selected Studies Considered for Acute, Intermediate, and Chronic Exposure Scenarios

Brief Study Description (Reference) (TSCA Study Quality Rating)	Study POD/ Type (mg/kg-day)	Effect	HED (mg/kg)	Uncertainty Factors[a b c]	BMD Analysis Notes
Sprague-Dawley rats; GD 14-18; oral/gavage; 0, 100, 300, 600, 900 (Gray et al., 2021) (High)	$BMDL_5$ = 24	↓ *ex vivo* testicular testosterone production (34%)	5.7	UF_A = 3 UF_H = 10 *Total UF = 30*	- See 6Appendix E for BMD results
Sprague-Dawley rats; GD 8-18; 0, 100, 300, 600, 900 (Howdeshell et al., 2008) (High)	$BMDL_5$ = 52	↓ *ex vivo* testicular testosterone production (40%)	12.3	UF_A = 3 UF_H = 10 *Total UF = 30*	- See 6Appendix E for BMD results
Sprague-Dawley rats; GD 12-21; oral/gavage; 0, 125, 250, 500, 625 (Saillenfait et al., 2008) (High)	LOAEL = 125	Testicular pathology (degeneration of seminiferous tubules and oligo-/azoospermia in epididymis)	29.6	UF_A = 3 UF_H = 10 UF_L = 10 *Total UF = 300*	- BMD modeling reported by (Blessinger et al., 2020) and discussed in Section 4.2.1
	$BMDL_5$ = 60	Testicular pathology (increased incidence of azoospermia or oligospermia)	14.2	UF_A = 3 UF_H = 10 *Total UF = 30*	
Sprague-Dawley rats; GD 14-18; oral/gavage; 0, 100, 300, 600, 900 (Hannas et al., 2011) (High)	NOAEL = 100	↓ *ex vivo* fetal testicular testosterone production (56%); ↓ expression of steroidogenic genes in fetal testes	23.6	UF_A = 3 UF_H = 10 *Total UF = 30*	- BMD modeling attempted - No models adequately fit the data set (6Appendix E)
Sprague-Dawley rats; GD 14-18; oral/gavage; 0, 200 (Block 30) (Furr et al., 2014) (High)	LOAEL = 200	↓ *ex vivo* fetal testicular testosterone production	47.3	UF_A = 3 UF_H = 10 UF_L = 10 *Total UF = 300*	- Study not amendable to BMD modeling (evaluated one dose level)
Sprague-Dawley rats; GD 6-20; oral/gavage; 0, 250, 500, 750, 1000 (Saillenfait et al., 2006) (High)	NOAEL = 250	↓ fetal body weight (both sexes); ↑ incidence of cryptorchidism	59.1	UF_A = 3 UF_H = 10 *Total UF = 30*	- Study not subjected to BMD analysis, as other studies evaluated lower doses and provided more sensitive outcomes for modeling (Section 4.2.1)
Sprague-Dawley rats; GD 13-19; oral/gavage; 0, 250 (Saillenfait et al., 2017) (High)	LOAEL = 250	↓AGD, ↓ testicular testosterone & androstenedione production, altered mRNA expression of steroidogenesis genes in the testes	59.1	UF_A = 3 UF_H = 10 UF_L = 10 *Total UF = 300*	- Study not amendable to BMD modeling (evaluated one dose level)
ICR Mice; GD 0-21; oral/gavage; 0, 450 (Wang et al., 2017) (Medium)	LOAEL = 450	↓ absolute testes weight on PND 21; ↓ serum and testes testosterone; ↓ expression of steroidogenic genes in	59.8	UF_A = 3 UF_H = 10 UF_L = 10	- Study not amendable to BMD modeling (evaluated one dose level)

Brief Study Description (Reference) (TSCA Study Quality Rating)	Study POD/ Type (mg/kg-day)	Effect	HED (mg/kg)	Uncertainty Factors[a b c]	BMD Analysis Notes
		testes; ↓sperm concentration and motility on PND 80		*Total UF = 300*	
Wistar Rat; oral/diet; 0, 88, 363, 942 (BASF, 2007) (High)	NOAEL = 363	↓ maternal food consumption, ↓ maternal body weight gain, ↓ fetal body weight	85.8	UF_A = 3 UF_H = 10 *Total UF = 30*	- Study not subjected to BMD analysis, as other studies provided more sensitive outcomes for modeling (Section 4.2.1)
Sprague-Dawley rats; GD 14-18; oral/gavage; 0, 500 (Block 14) (Furr et al., 2014) (High)	LOAEL = 500	↓ *ex vivo* fetal testicular testosterone production	118	UF_A = 3 UF_H = 10 UF_L = 10 *Total UF = 300*	- Study not amendable to BMD modeling (evaluated one dose level)
Sprague-Dawley rats; GD 14-18; oral/gavage; 0, 500 (Hannas et al., 2012) (High)	LOAEL = 500	↓ *ex vivo* fetal testicular testosterone production	118	UF_A = 3 UF_H = 10 UF_L = 10 *Total UF = 300*	- Study not amendable to BMD modeling (evaluated one dose level)
Wistar Rat; GD 7-19 or 7-20/21; oral/gavage; 0, 600 (Borch et al., 2006) (High)	LOAEL = 600	↓ testes testosterone, ↓ AGD, ↑ testicular histopathology	142	UF_A = 3 UF_H = 10 UF_L = 10 *Total UF = 300*	- Study not amendable to BMD modeling (evaluated one dose level)
Sprague-Dawley rats; GD 14-18; oral/gavage; 0, 750 (Block 2) (Furr et al., 2014) (High)	LOAEL = 750	↓ *ex vivo* fetal testicular testosterone production	177	UF_A = 3 UF_H = 10 UF_L = 10 *Total UF = 300*	- Study not amendable to BMD modeling (evaluated one dose level)

Abbreviations: ↓ = statistically significant decrease; ↑ = statistically significant increase; POD = Point of Departure; HED = Human equivalent Dose; UF = uncertainty factor; NOAEL = No observed adverse effect level; LOAEL = Lowest observed adverse effect level; GD = Gestational Day; PND = Postnatal Day AGD = Anogenital distance; BMD = benchmark dose

[a] EPA used allometric body weight scaling to the three-quarters power to derive the HED. Consistent with EPA Guidance (U.S. EPA, 2011c), the interspecies uncertainty factor (UF_A), was reduced from 10 to 3 to account remaining uncertainty associated with interspecies differences in toxicodynamics.

[b] EPA used a default intraspecies (UF_H) of 10 to account for variation in sensitivity within human populations due to limited information regarding the degree to which human variability may impact the disposition of or response to DIBP.

[c] EPA used a LOAEL-to-NOAEL uncertainty factor (UF_L) of 10 to account for the uncertainty inherent in extrapolating from the LOAEL to the NOAEL.

[d] Two studies with similar designs were included in the meta-analysis by NASEM (2017), each of which exposed Sprague-Dawley rats (≤ 3 dams/dose) to 0, 100, 300, 600, 900 mg/kg-day DIBP during the masculinization programming window during gestational development.

4.3 Weight of Scientific Evidence Conclusion: POD for Acute, Intermediate, and Chronic Durations

EPA considered BMD modeling from the study by Gray et al. to support a $BMDL_5$ of 24 mg/kg-day (Gray et al., 2021). EPA has concluded that the HED of 5.7 mg/kg-day ($BMDL_5$ of 24 mg/kg-day) based on decreased fetal testicular testosterone production from the gestational exposure study of rats by Gray et al. is appropriate for calculation of risk from acute, intermediate, and chronic durations. A total uncertainty factor of 30 was selected for use as the benchmark margin of exposure (based on an interspecies uncertainty factor (UF_A) of 3 and an intraspecies uncertainty factor (UF_H) of 10). Consistent with EPA guidance (2022, 2002b, 1993), EPA reduced the UF_A from a value of 10 to 3 because allometric body weight scaling to the three-quarter power was used to adjust the POD to obtain a HED (Appendix C).

There is a limited database of studies for DIBP that have evaluated outcomes other that developmental toxicity and effects on the developing male reproductive system. For toxicologically similar phthalates (*i.e.*, DEHP, DBP, BBP, DCHP), which include larger databases of animal toxicology studies including numerous well-conducted subchronic and chronic toxicity studies, effects on the developing male reproductive system consistent with a disruption of androgen action have consistently been identified by EPA as the most sensitive and well-characterized hazard in experimental animal models. This is demonstrated by the fact that the acute/intermediate/chronic PODs selected by EPA for use in risk characterization for DEHP (U.S. EPA, 2025k), DBP (U.S. EPA, 2025i), BBP (U.S. EPA, 2025h), DCHP (U.S. EPA, 2025j) are all based on effects related to phthalate syndrome. EPA has robust overall confidence in the selected POD based on the following weight of scientific evidence:

- EPA has previously considered the weight of scientific evidence and concluded that oral exposure to DIBP can induce effects on the developing male reproductive system consistent with a disruption of androgen action (see EPA's *Draft Proposed Approach for Cumulative Risk Assessment of High-Priority and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act* (U.S. EPA, 2023a)). Notably, EPA's conclusion was supported by the SACC (U.S. EPA, 2023b).
- DIBP exposure resulted in treatment-related effects on the developing male reproductive system consistent with a disruption of androgen action during the critical window of development in 13 studies of rats (Section 3.1.2.1). Observed effects included: reduced fetal testicular testosterone content and/or testosterone production; reduced male pup anogenital distance; male pup nipple retention; reproductive tract malformations (*i.e.*, hypospadias, undescended testes, exposed os penis, cleft prepuce); delayed preputial separation; testicular pathology (*e.g.*, degeneration of seminiferous tubules, oligospermia, azoospermia, Leydig cell aggregation, Sertoli cell vacuolation, multinucleated gonocytes); decreased sperm concentration and motility.
- The selected POD is a $BMDL_5$ based on reduced *ex vivo* fetal testicular testosterone production in one gestational exposure studies of rats (Gray et al., 2021).
- Consistently, other regulatory and authoritative bodies have also concluded that DIBP induces effects on the developing male reproductive system consistent with a disruption of androgen action and phthalate syndrome and that these effects are relevant for estimating human risk (ECCC/HC, 2020; ECHA, 2017a, b; U.S. CPSC, 2014; ECHA, 2012a, b; NICNAS, 2008a).
- EPA considers effects on the developing male reproductive system consistent with a disruption of androgen action to be relevant for setting a POD for acute, intermediate, and chronic duration exposures, based on studies of the toxicologically similar phthalate dibutyl phthalate (DBP)

which have demonstrated that a single exposure during the critical window of development in rats can disrupt expression of steroidogenic genes and decrease fetal testes testosterone production.

4.4 Route-to-Route Extrapolation

EPA did not identify any studies conducted via the dermal or inhalation exposure routes that are relevant for determining human health risk. Therefore, EPA is using the oral HED of 5.7 mg/kg-day DIBP to extrapolate risk for the dermal and inhalation routes. When conducting route-to-route extrapolations, the preferred approach is to use validated physiologically-based pharmacokinetic (PBPK) models or chemical-specific pharmacokinetic data to account for potential route-specific differences in toxicokinetics (IGHRC, 2006; U.S. EPA, 1994). For DIBP, no PBPK model is available to support route-to-route extrapolation. Therefore, EPA used a combination of empirical absorption data, and default assumptions regarding potential route-specific differences in metabolism. As discussed further below, the available data accounting for differential absorption across routes (oral, dermal, inhalation) and similarities in metabolism indicate that the hazard derivation from different routes of exposures is reasonably supported.

Dermal Route

EPA has accounted for differences in absorption between the oral and dermal exposures routes. As discussed in Section 2.1, available data indicate 100 percent absorption of DIBP through the gastrointestinal tract following oral exposure, while EPA estimated steady-state dermal flux values for DIBP to estimate dermal exposure (Section 2.3). However, potential route-specific differences in metabolism were not accounted for. Following oral exposure, phthalate diesters (including DIBP) are metabolized to a monoester metabolite (*e.g.,* MIBP) by esterases in the intestines or liver. Further oxidative metabolism or phase two conjugation reactions (*e.g.,* glucuronidation) may also occur in the liver prior to systemic circulation. Esterases are also present in the skin, and therefore metabolism of DIBP to its monoester metabolite MIBP also likely occurs via the dermal route prior to systemic circulation. For example, as discussed in the non-cancer human health hazard assessments of DBP (U.S. EPA, 2025i), DEHP (U.S. EPA, 2025k), and BBP (U.S. EPA, 2025h) dermal absorption studies with metabolically active human or rat skin demonstrate metabolism of DBP, DEHP, and BBP to their respective monoester metabolites MBP, MEHP, and MBzP, as well as other oxidative metabolites. No dermal absorption studies of DIBP with metabolically active skin are available; however, EPA considers it reasonable to assume that DIBP would undergo similar metabolism to MIBP and other oxidative metabolites in the skin before being absorbed and undergoing systemic circulation.

Despite some remaining uncertainty, EPA is confident that its human health risk characterization via the dermal route for DIBP is health protective.

Inhalation Route

For the inhalation route, EPA extrapolated the daily oral HED to an inhalation HEC using a human body weight and breathing rate relevant to a continuous exposure of an individual at rest (see Appendix C for further details). EPA assumes similar absorption for the oral and inhalation routes, and no adjustment was made when extrapolating to the inhalation route. As discussed above, available data indicate 100 percent absorption of DIBP through the gastrointestinal tract following oral exposure (Section 2.1). Although no inhalation toxicokinetic study of DIBP is available, studies of other phthalates (*i.e.*, DEHP, DIDP, and DINP) indicate phthalates are nearly completely absorbed through the respiratory tract, and 100 percent absorption is assumed for DIBP. Similar to the oral route of exposure, metabolism of DIBP

to its monoester metabolite MIBP is expected to occur in the lung, however, the rate of metabolism in the lung may be slower than in the gastrointestinal tract and liver. For example, Ito et al. (2005) reported lipase activity in rat liver and lung homogenate; however, lipase activity was approximately 12.6 times higher in the liver compared to the lung. Similarly, Choi et al. (2012) demonstrate metabolism of DEHP to MEHP in human small intestine, liver, and lung tissue samples, however, the metabolic rate of MEHP formation was highest in the small intestine and liver compared to the lung. Although no studies of DIBP metabolism in the lung are available, EPA considers it reasonable to assume that DIBP is metabolized to MIBP in the lung, due to the presence of lipases. However, when extrapolating the inhalation HEC from the oral HED EPA did not account for differences in rates of metabolism of DIBP (or any other phthalate) between exposure routes.

Despite some remaining uncertainty, EPA is confident that its human health risk characterization via the inhalation route for DIBP is health protective.

5 CONSIDERATION OF PESS AND AGGEGRATE EXPOSURE

5.1 Hazard Considerations for Aggregate Exposure

For use in the risk evaluation and assessing risks from other exposure routes, EPA conducted route-to-route extrapolation of the toxicity values from the oral studies for use in the dermal and inhalation exposure routes and scenarios. Health outcomes that serve as the basis for acute, intermediate, and chronic hazard values are systemic and assumed to be consistent across routes of exposure. EPA therefore concludes that for consideration of aggregate exposures, it is reasonable to assume that exposures and risks across oral, dermal, and inhalation routes may be additive for the selected PODs in Section 6.

5.2 PESS Based on Greater Susceptibility

In this section, EPA addresses subpopulations likely to be more susceptible to DIBP exposure than other populations. Table 5-1 presents the data sources that were used in the potentially exposed or susceptible subpopulations (PESS) analysis evaluating susceptible subpopulations and identifies whether and how the subpopulation was addressed quantitatively in the risk evaluation of DIBP.

Although ample human epidemiologic data are available on health effects of DIBP (see Section 3.1.1), EPA was unable to identify direct evidence of differences in susceptibility among human populations. Animal studies demonstrating effects on male reproductive development and other developmental outcomes provide direct evidence that gestation is a particularly sensitive lifestage. Evidence from animal studies also suggests that the liver may also be a target organ; however, there is not enough evidence to reliably inform specific health outcomes or to be used in risk quantification. Therefore, EPA is quantifying risks including those for PESS based on reproductive and developmental toxicity in the DIBP risk evaluation.

As summarized in Table 5-1, EPA identified a range of factors that may have the potential to increase biological susceptibility to DIBP, including lifestage, pre-existing diseases, physical activity, nutritional status, stress, and co-exposures to other environmental stressors that contribute to related health outcomes. The effect of these factors on susceptibility to health effects of DIBP is not known; therefore, EPA is uncertain about the directions and magnitude of any possible increased risk from effects associated with DIBP exposure for relevant subpopulations.

For non-cancer endpoints, EPA used a default value of 10 for human variability (UF_H) to account for increased susceptibility when quantifying risks from exposure to DIBP. 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). Although U.S. EPA (2002b) did not discuss all the factors presented in Table 5-1, EPA considers the POD selected for use in characterizing risk from exposure to DIBP to be protective of effects on the developing male reproductive system consistent with phthalate syndrome in humans.

As discussed in U.S. EPA (2023a), exposure to DIBP and other toxicologically similar phthalates (*i.e.*, DEHP, DBP, BBP, DCHP, DINP) that disrupt androgen action during the development of the male reproductive system cause dose additive effects. Cumulative effects from exposure to DIBP and other toxicologically similar phthalates will be evaluated as part of U.S. EPA's cumulative risk assessment of phthalates.

Table 5-1. PESS Evidence Crosswalk for Biological Susceptibility Considerations

Susceptibility Category	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to DIBP		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to DIBP		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Citations	Description of Interaction	Key Citation(s)	
Lifestage	Embryos/ fetuses/infants	Direct quantitative animal evidence for developmental toxicity (*e.g.,* increased skeletal variations, decreased fetal body weight, increased resorptions, and post-implantation loss). There is direct quantitative animal evidence for effects on the developing male reproductive system consistent with a disruption of androgen action.	(U.S. EPA, 2023a) (U.S. EPA, 2023b) (Howdeshell et al., 2008) (Hannas et al., 2011) (Wang et al., 2017) (Saillenfait et al., 2008) (BASF, 2007) (Borch et al., 2006) (Saillenfait et al., 2006)			POD selected for assessing risks from acute, intermediate, and chronic exposures to DIBP is based on developmental toxicity (*i.e.*, reduced fetal testicular testosterone production) and is protective of effects on the fetus and offspring.
	Pregnancy/ lactating status	Rodent dams not particularly susceptible during pregnancy and lactation, except for effects related to reduced maternal weight gain and food consumption evident only at high concentrations.	(Howdeshell et al., 2008) (Saillenfait et al., 2006) (BASF, 2007)			POD selected for assessing risks from acute, intermediate, and chronic exposures to DIBP based on developmental toxicity (*i.e.*, reduced fetal testicular testosterone production) is protective of effects on dams

Susceptibility Category	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to DIBP		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to DIBP		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Citations	Description of Interaction	Key Citation(s)	
	Males of reproductive age	Consistent evidence of effects on endpoints related to male reproductive development in rats and mice, including steroidogenesis in the testes and effects on sperm (*i.e.*, decreased concentration and motility, increased malformation).	(Pan et al., 2017)			POD selected for assessing risks from acute, intermediate, and chronic exposures to DIBP is based on effects on male reproductive development (*i.e.*, reduced fetal testicular testosterone production) is expected to be protective of adult male reproductive effects.
	Children	Reduced rodent offspring body weight gain between PNDs 1 to 21 was observed in three gestational exposure studies.	(Saillenfait et al., 2008) (Wang et al., 2017) (BASF, 2007)			POD selected for assessing risks from acute, intermediate, and chronic exposures to DIBP based on developmental toxicity (*i.e.*, reduced fetal testicular testosterone production) is expected to be protective of effects of offspring bodyweight gain. Use of default 10x UF_H
	Elderly	No direct evidence identified				Use of default 10x UF_H

Susceptibility Category	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to DIBP		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to DIBP		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Citations	Description of Interaction	Key Citation(s)	
Pre-existing disease or disorder	Health outcome/ target organs	No direct evidence identified		Several preexisting conditions may contribute to adverse developmental outcomes (*e.g.*, diabetes, high blood pressure, certain viruses). Individuals with chronic liver disease may be more susceptible to effects on these target organs. Viruses such as viral hepatitis can cause liver damage.	CDC (2023e) CDC (2023g)	Use of default 10x UF_H
	Toxicokinetics	No direct evidence identified		Chronic liver disease is associated with impaired metabolism and clearance (altered expression of phase 1 and phase 2 enzymes, impaired clearance), which may enhance exposure duration and concentration of DIBP.		Use of default 10x UF_H
Lifestyle activities	Smoking	No direct evidence identified		Smoking during pregnancy may increase susceptibility for developmental outcomes (*e.g.*, early delivery and stillbirths).	CDC (2023f)	

Susceptibility Category	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to DIBP		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to DIBP		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Citations	Description of Interaction	Key Citation(s)	
	Alcohol consumption	No direct evidence identified		Alcohol use during pregnancy can cause adverse developmental outcomes (*e.g.*, fetal alcohol spectrum disorders). Heavy alcohol use may affect susceptibility to liver disease.	CDC (2023d) CDC (2023a)	
	Physical activity	No direct evidence identified		Insufficient activity may increase susceptibility to multiple health outcomes. Overly strenuous activity may also increase susceptibility.	CDC (2022)	
Sociodemo-graphic status	Race/ethnicity	No direct evidence identified (*e.g.*, no information on polymorphisms in DIBP metabolic pathways or diseases associated race/ethnicity that would lead to increased susceptibility to effects of DIBP by any individual group).				
	Socioeconomic status	No direct evidence identified		Individuals with lower incomes may have worse health outcomes due to social needs that are not met, environmental concerns, and barriers to health care access.	ODPHP (2023b)	

Susceptibility Category	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to DIBP		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to DIBP		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Citations	Description of Interaction	Key Citation(s)	
	Sex/gender	Male reproductive development is a sex-specific endpoint and consistent evidence indicates it is the most sensitive effect following gestational or early life DIBP exposure.	See discussion in Section 3.1.2.1.			POD selected for assessing risks from acute, intermediate, and chronic exposures to DIBP is based on effects on male reproductive development (*i.e.*, reduced fetal testicular testosterone production)
Nutrition	Diet	No direct evidence identified		Poor diets can lead to chronic illnesses such as heart disease, type 2 diabetes, and obesity, which may contribute to adverse developmental outcomes. Additionally, diet can be a risk factor for fatty liver, which could be a pre-existing condition to enhance susceptibility to DIBP-induced liver toxicity.	CDC (2023e) CDC (2023b)	

Susceptibility Category	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to DIBP		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to DIBP		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Citations	Description of Interaction	Key Citation(s)	
	Malnutrition	No direct evidence identified		Micronutrient malnutrition can lead to multiple conditions that include birth defects, maternal and infant deaths, preterm birth, low birth weight, poor fetal growth, childhood blindness, undeveloped cognitive ability. Thus, malnutrition may increase susceptibility to some developmental outcomes associated with DIBP.	CDC (2021) CDC (2023b)	
Genetics/ epigenetics	Target organs	No direct evidence identified		Polymorphisms in genes may increase susceptibility to liver or developmental toxicity.		Use of default 10x UF_H
	Toxicokinetics	No direct evidence identified		Polymorphisms in genes encoding enzymes (*e.g.*, esterases) involved in metabolism of DIBP may influence metabolism and excretion of DIBP.		Use of default 10x UF_H
Other chemical and nonchemical stressors	Built environment	No direct evidence identified		Poor-quality housing is associated with a variety of negative health outcomes.	ODPHP (2023a)	
	Social environment	No direct evidence identified		Social isolation and other social determinants (*e.g.*, decreased social capital, stress) can lead to negative health outcomes.	CDC (2023c) ODPHP (2023c)	

Susceptibility Category	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to DIBP		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to DIBP		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Citations	Description of Interaction	Key Citation(s)	
	Chemical co-exposures	Studies have demonstrated that co-exposure to DIBP and other toxicologically similar phthalates (*e.g.*, DEHP, DBP, BBP, DCHP, DINP) and other classes of antiandrogenic chemicals (*e.g.*, certain pesticides and pharmaceuticals – discussed more in (U.S. EPA, 2023a)) can induce effects on the developing male reproductive system in a dose-additive manner.	See (U.S. EPA, 2023a) and (U.S. EPA, 2023b)			Co-exposures will be quantitatively addressed as part of the phthalate cumulative risk assessment and are not addressed in the individual DIBP assessment.

6 POINTS OF DEPARTURE USED TO ESTIMATE RISKS FROM DIBP EXPOSURE, AND CONCLUSOINS

After considering hazard identification and evidence integration, dose-response evaluation, and weight of scientific evidence of POD candidates, EPA chose one non-cancer endpoint for use in determining the risk from acute, intermediate, and chronic exposure scenarios (see Table ES-1). The critical effect is disruption to androgen action during the critical window of male reproductive development (*i.e.*, during gestation), leading to a spectrum of effects on the developing male reproductive system consistent with phthalate syndrome. Decreased fetal testicular testosterone was selected as the basis for the POD of 24 mg/kg-day (HED = 5.7 mg/kg-day) for acute, intermediate, and chronic durations. EPA has robust overall confidence in the selected POD for acute, intermediate, and chronic durations. There are no studies conducted via the dermal and inhalation route relevant for extrapolating human health risk. In the absence of inhalation studies, EPA performed route-to-route extrapolation to convert the oral HED to an inhalation human equivalent concentration (HEC) of 30.9 mg/m^3 (2.71 ppm). EPA is also using the oral HED to extrapolate to the dermal route. HECs are based on daily continuous (24-hour) exposure, and HEDs are daily values.

The POD of 24 mg/kg-day (HED = 5.7 mg/kg-day) will be used in the Risk Evaluation for DIBP (U.S. EPA, 2025n) to estimate acute, intermediate, and chronic non-cancer risk. EPA summarizes the cancer hazards of DIBP in a separate technical support document, *Cancer Human Health Hazard Assessment for Di(2-ethylhexyl) Phthalate (DEHP), Dibutyl Phthalate (DBP), Butyl Benzyl Phthalate (BBP), and Dicyclohexyl Phthalate (DCHP)* (U.S. EPA, 2025a).

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APPENDICES

Appendix A Existing Assessments of DIBP

The available existing assessments of DIBP are summarized in Table_Apx A-1, which includes details regarding external peer-review, public consultation, and systematic review protocols that were used.

Table_Apx A-1. Summary of Peer-review, Public Comments, and Systematic Review for Existing Assessments of DIBP

Agency	Assessment(s) (Reference)	External Peer-Review?	Public Consultation?	Systematic Review Protocol Employed?	Remarks
U.S. EPA (Publications by the Center for Public Health and Environmental Assessment [CPHEA] within the Office of Research and Development [ORD])	*Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence* (Radke et al., 2018) *Phthalate exposure and female reproductive and developmental outcomes: A systematic review of the human epidemiological evidence* (Radke et al., 2019b) *Phthalate exposure and metabolic effects: A systematic review of the human epidemiological evidence* (Radke et al., 2019a) *Phthalate exposure and neurodevelopment: A systematic review and meta-analysis of human epidemiological evidence* (Radke et al., 2020a). *Hazards of diisobutyl phthalate (DIBP Exposure): A systematic*	No	No	Yes	- Publications were subjected to peer-review prior to being published in a special issue of the journal *Environment International* - Publications employed a systematic review process that included literature search and screening, study evaluation, data extraction, and evidence synthesis. The full systematic review protocol is available as a supplemental file associated with each publication.

Agency	Assessment(s) (Reference)	External Peer-Review?	Public Consultation?	Systematic Review Protocol Employed?	Remarks
	review of animal toxicology studies (Yost et al., 2019)				
U.S. CPSC	*Toxicity review of diisobutyl phthalate (DiBP, CASRN 84-69-5)* (U.S. CPSC, 2011) *Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives* (U.S. CPSC, 2014)	Yes	Yes	No	- Peer-reviewed by panel of four experts. Peer review report available at: https://www.cpsc.gov/s3fs-public/Peer-Review-Report-Comments.pdf -Public comments available at: https://www.cpsc.gov/chap - No formal systematic review protocol employed. - Details regarding CPSC's strategy for identifying new information and literature are provided on page 12 of (U.S. CPSC, 2014)
NASEM	*Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals (*NASEM, 2017*)*	Yes	No	Yes	- Draft report was reviewed by individuals chosen for their diverse perspectives and technical expertise in accordance with the National Academies peer-review process. See Acknowledgements section of (NASEM, 2017) for more details. - Employed NTP's Office of Heath Assessment and Translation (OHAT) systematic review method
Health Canada	*State of the science report: Phthalate substance grouping: Medium-chain phthalate esters: Chemical Abstracts Service Registry Numbers: 84-61-7; 84-*	Yes	Yes	No (Animal studies)	- Ecological and human health portions of the screening assessment report (ECCC/HC, 2020) were subject to external review and/or consultation. See

Agency	Assessment(s) (Reference)	External Peer-Review?	Public Consultation?	Systematic Review Protocol Employed?	Remarks
	64-0; 84-69-5; 523-31-9; 5334-09-8;16883-83-3; 27215-22-1; 27987-25-3; 68515-40-2; 71888-89-6 (EC/HC, 2015b) *Supporting documentation: Evaluation of epidemiologic studies on phthalate compounds and their metabolites for hormonal effects, growth and development and reproductive parameters* (Health Canada, 2018b) *Supporting documentation: Evaluation of epidemiologic studies on phthalate compounds and their metabolites for effects on behaviour and neurodevelopment, allergies, cardiovascular function, oxidative stress, breast cancer, obesity, and metabolic disorders* (Health Canada, 2018a) *Screening Assessment - Phthalate Substance Grouping* (ECCC/HC, 2020)			Yes (Epidemiologic studies)	page 2 of (ECCC/HC, 2020) for additional details. - State of the science report (EC/HC, 2015a) and draft screening assessment report for the phthalate substance group subjected to 60-day public comment periods. Summaries of received public comments available at: https://www.canada.ca/en/health-canada/services/chemical-substances/substance-groupings-initiative/phthalate.html#a1 - No formal systematic review protocol employed to identify or evaluate experimental animal toxicology studies. - Details regarding Health Canada's strategy for identifying new information and literature are provided in Section 1 of (EC/HC, 2015a) and (ECCC/HC, 2020) - Human epidemiologic studies evaluated using Downs and Black Method (Health Canada, 2018a, b)
NICNAS	*Existing chemical hazard assessment report: Diisobutyl phthalate* (NICNAS, 2008a)	No	Yes	No	- No details regarding peer-review are provided. - No formal systematic review protocol employed.

Agency	Assessment(s) (Reference)	External Peer-Review?	Public Consultation?	Systematic Review Protocol Employed?	Remarks
					- No details regarding how NICNAS identified literature for inclusion in its assessment are provided.
ECHA	*Committee for Risk Assessment (RAC) Opinion on an Annex XV dossier proposing restrictions on four phthalates* (ECHA, 2012b) *Committee for Risk Assessment (RAC) Committee for Socio-economic Analysis (SEAC): Background document to the Opinion on the Annex XV dossier proposing restrictions on four phthalates* (ECHA, 2012a) *Opinion on an Annex XV dossier proposing restrictions on four phthalates (DEHP, BBP, DBP, DIBP)* (ECHA, 2017b) *Annex to the Background document to the Opinion on the Annex XV dossier proposing restrictions on four phthalates (DEHP, BBP, DBP, DIBP)* (ECHA, 2017a)	Yes	Yes	No	- Peer-reviewed by ECHA's Committee for Risk Assessment (RAC) - Subject to public consultation - No formal systematic review protocol employed.

Appendix B Fetal Testicular Testosterone as an Acute Effect

No studies of experimental animal models are available that investigate the antiandrogenic effects of DIBP following single dose, acute exposures. However, there are studies of its isomer, dibutyl phthalate (DBP) available that indicate a single acute exposure during the critical window of development (*i.e.*, GD 15.5 to GD 18.5 in rats) can reduce fetal testicular testosterone production and disrupt testicular steroidogenic gene expression. Two studies were identified that demonstrate single doses of 500 mg/kg DBP can reduce fetal testicular testosterone and steroidogenic gene expression. Johnson et al. (2012; 2011) gavaged pregnant SD rats with a single dose of 500 mg/kg DBP on GD 19 and observed reductions in steroidogenic gene expression in the fetal testes three (*Cyp17a1*) to six (*Cyp11a1, StAR*) hours post-exposure, while fetal testicular testosterone was reduced starting 18 hours post-exposure. Similarly, Thompson et al. (2005) reported a 50 percent reduction in fetal testicular testosterone 1-hour after pregnant SD rats were gavaged with a single dose of 500 mg/kg DBP on GD 19, while changes in steroidogenic gene expression occurred 3 (*StAR*) to 6 (*Cyp11a1, Cyp17a1, Scarb1*) hours post-exposure, and protein levels of these genes were reduced 6 to 12 hours post-exposure. Additionally, studies by Carruthers et al. (2005) further demonstrate that exposure to as few as two oral doses of 500 mg/kg DBP on successive days between GDs 15 to 20 can reduce male pup AGD, cause permanent nipple retention, and increase the frequency of reproductive tract malformations and testicular pathology in adult rats that received two doses of DBP during the critical window.

Studies of DBP provide evidence to support use of effects on fetal testosterone and the developing male reproductive system consistent with phthalate syndrome as an acute effect. However, the database is limited to just a few DBP studies that test relatively high (500 mg/kg) single doses of DBP. Although there are no single exposure studies of DIBP that evaluate antiandrogenic effects on the developing male reproductive system, there are three studies that have evaluated effects on fetal testicular testosterone production and steroidogenic gene expression following daily gavage doses of 100 to 900 mg/kg-day DIBP from GDs 14 to 18 (5 total doses) (Gray et al., 2021; Furr et al., 2014; Hannas et al., 2012; Hannas et al., 2011), all of which consistently report antiandrogenic effects at 300 mg/kg-day DIBP.

Appendix C Calculating Daily Oral Human Equivalent Doses and Human Equivalent Concentrations

For DIBP, all data considered for PODs are obtained from oral animal toxicity studies in rats or mice. Because toxicity values for DIBP are from oral animal studies, EPA must use an extrapolation method to estimate HEDs. The preferred method would be to use chemical-specific information for such an extrapolation. However, no PBPK models or chemical-specific information was identified for DIBP to support a quantitative extrapolation. In the absence of such data, EPA relied on the guidance from U.S. EPA (2011c), which recommends scaling allometrically across species using the three-quarter power of body weight ($BW^{3/4}$) for oral data. Allometric scaling accounts for differences in physiological and biochemical processes, mostly related to kinetics.

For application of allometric scaling in risk evaluations, EPA uses dosimetric adjustment factors (DAFs), which can be calculated using Equation_Apx C-1.

Equation_Apx C-1. Dosimetric Adjustment Factor

$$DAF = \left(\frac{BW_A}{BW_H}\right)^{1/4}$$

Where:

DAF	=	Dosimetric adjustment factor (unitless)
BW_A	=	Body weight of species used in toxicity study (kg)
BW_H	=	Body weight of adult human (kg)

U.S. EPA (2011c), presents DAFs for extrapolation to humans from several species. However, because those DAFs used a human body weight of 70 kg, EPA has updated the DAFs using a human body weight of 80 kg for the DIBP risk evaluation (U.S. EPA, 2011a). EPA used the body weights of 0.025 and 0.25 kg for mice and rats, respectively, as presented in U.S. EPA (2011c). The resulting DAFs for mice and rats are 0.133 and 0.236, respectively.

Use of allometric scaling for oral animal toxicity data to account for differences among species allows EPA to decrease the default intraspecies UF (UF_A) used to set the benchmark MOE; the default value of 10 can be decreased to 3, which accounts for any toxicodynamic differences that are not covered by use of $BW^{3/4}$. Using the appropriate DAF from Equation_Apx C-1, EPA adjusts the POD to obtain the HED using Equation_Apx C-2:

Equation_Apx C-2. Daily Oral Human Equivalent Dose

$$HED_{Daily} = POD_{Daily} \times DAF$$

Where:

HED_{Daily}	=	Human equivalent dose assuming daily doses (mg/kg-day)
POD_{Daily}	=	Oral POD assuming daily doses (mg/kg-day)
DAF	=	Dosimetric adjustment factor (unitless)

For this risk evaluation, EPA assumes similar absorption for the oral and inhalation routes, and no adjustment was made when extrapolating to the inhalation route. For the inhalation route, EPA

extrapolated the daily oral HEDs to inhalation HECs using a human body weight and breathing rate relevant to a continuous exposure of an individual at rest, as follows:

Equation_Apx C-3. Extrapolating from Oral HED to Inhalation HEC

$$HEC_{Daily,continuous} = HED_{Daily} \times \left(\frac{BW_H}{IR_R * ED_C}\right)$$

Where:

$HEC_{Daily,continuous}$	=	Inhalation HEC based on continuous daily exposure (mg/m^3)
HED_{Daily}	=	Oral HED based on daily exposure (mg/kg-day)
BW_H	=	Body weight of adult humans (kg) = 80
IR_R	=	Inhalation rate for an individual at rest (m^3/hr) = 0.6125
ED_C	=	Exposure duration for a continuous exposure (hr/day) = 24

Based on information from U.S. EPA (2011a), EPA assumes an at rest breathing rate of 0.6125 m^3/hr. Adjustments for different breathing rates required for individual exposure scenarios are made in the exposure calculations, as needed.

It is often necessary to convert between ppm and mg/m^3 due to variation in concentration reporting in studies and the default units for different OPPT models. Therefore, EPA presents all PODs in equivalents of both units to avoid confusion and errors. Equation_Apx C-4 presents the conversion of the HEC from mg/m^3 to ppm.

Equation_Apx C-4. Converting Units for HECs (mg/m3 to ppm)

$$X\ ppm = Y\ \frac{mg}{m^3} \times \frac{24.45}{MW}$$

Where:

24.45	=	Molar volume of a gas at standard temperature and pressure (L/mol), default
MW	=	Molecular weight of the chemical (MW of DIBP = 278.35 g/mol)

C.1 DIBP Non-cancer HED and HEC Calculations for Acute, Intermediate, and Chronic Duration Exposures

The acute, intermediate, and chronic duration non-cancer POD is based on a $BMDL_5$ of 24 mg/kg-day and the critical effect is decreased fetal testicular testosterone. The POD was derived from one gestational exposure studies of rats (Gray et al., 2021). This non-cancer POD is considered protective of effects observed following acute, intermediate, and chronic duration exposures to DIBP. EPA used Equation_Apx C-1 to determine a DAF specific to rats (0.236), which was in turn used in the following calculation of the daily HED using Equation_Apx C-2:

$$5.66\ \frac{mg}{kg-day} = 24\ \frac{mg}{kg-day} \times 0.236$$

EPA then calculated the continuous HEC for an individual at rest using Equation_Apx C-3:

$$30.9\ \frac{mg}{m^3} = 5.66\ \frac{mg}{kg-day} \times \left(\frac{80\ kg}{0.6125\ \frac{m^3}{hr} * 24\ hr}\right)$$

Equation_Apx C-4 was used to convert the HEC from mg/m^3 to ppm:

$$2.71\ ppm = 30.9\ \frac{mg}{m^3} \times \frac{24.45}{278.35\ \text{g/mol}}$$

Appendix D Considerations for Benchmark Response (BMR) Selection for Reduced Fetal Testicular Testosterone

D.1 Purpose

EPA has conducted an updated meta-analysis and benchmark dose modeling (BMD) analysis of decreased fetal rat testicular testosterone (U.S. EPA, 2025g). During the July 2024 Science Advisory Committee on Chemicals (SACC) peer-review meeting of the risk evaluation of diisodecyl phthalate (DIDP) and human health hazard assessments for diisononyl phthalate (DINP), the SACC recommended that EPA should clearly state its rational for selection of benchmark response (BMR) levels evaluated for decreases in fetal testicular testosterone relevant to the single chemical assessments (U.S. EPA, 2024). This appendix describes EPA's rationale for evaluating BMRs of 5, 10, and 40 percent for decreases in fetal testicular testosterone. (Note: EPA will assess the relevant BMR for deriving relative potency factors to be used in the cumulative risk assessment separately from this analysis.)

D.2 Methods

As described in EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012), "Selecting a BMR(s) involves making judgments about the statistical and biological characteristics of the dataset and about the applications for which the resulting BMDs/BMDLs will be used." For the updated meta-analysis and BMD modeling analysis of fetal rat testicular testosterone, EPA evaluated BMR values of 5, 10, and 40 percent based on both statistical and biological considerations (U.S. EPA, 2025g).

In 2017, NASEM (2017) modeled BMRs of 5 and 40 percent for decreases in fetal testicular testosterone. NASEM did not provide explicit justification for selection of a BMR of 5 percent. However, justification for the BMR of 5 can be found elsewhere. As discussed in EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012), a BMR of 5 percent is supported in most developmental and reproductive studies. Comparative analyses of a large database of developmental toxicity studies demonstrated that developmental NOAELs are approximately equal to the $BMDL_5$ (Allen et al., 1994a, b; Faustman et al., 1994).

EPA also evaluated a BMR of 10 percent as part of the updated BMD analysis. BMD modeling of fetal testosterone conducted by NASEM (2017) indicated that BMD_5 estimates are below the lowest dose with empirical testosterone data for several of the phthalates (*e.g.*, DIBP). As discussed in EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012) "For some datasets the observations may correspond to response levels far in excess of a selected BMR and extrapolation sufficiently below the observable range may be too uncertain to reliably estimate BMDs/BMDLs for the selected BMR." Therefore, EPA modeled a BMR of 10 percent because datasets for some of the phthalates may not include sufficiently low doses to support modeling of a 5 percent response level.

NASEM (2017) also modeled a BMR of 40 percent using the following justification: "previous studies have shown that reproductive-tract malformations were seen in male rats when fetal testosterone production was reduced by about 40% *(*Gray et al., 2016*;* Howdeshell et al., 2015*)*."

Further description of methods and results for the updated meta-analysis and BMD modeling analysis that evaluated BMRs of 5, 10, and 40 percent for decreased fetal testicular testosterone are provided in EPA's *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)* (U.S. EPA, 2025g).

D.3 Results

BMD estimates, as well as 95 percent upper and lower confidence limits, for decreased fetal testicular testosterone for the evaluated BMRs of 5, 10, and 40 percent are shown in Table_Apx D-1. BMD_5 estimates ranged from 8.4 to 74 mg/kg-day for DEHP, DBP, DCHP, and DINP; however, a BMD_5 estimate could not be derived for BBP or DIBP. Similarly, BMD_{10} estimates ranged from 17 to 152 for DEHP, DBP, DCHP, DIBP and DINP; however, a BMD_{10} estimate could not be derived for BBP. BMD_{40} estimates were derived for all phthalates (*i.e.*, DEHP, DBP, DCHP, DIBP, BBP, DINP) and ranged from 90 to 699 mg/kg-day.

In the mode of action (MOA) for phthalate syndrome, which is described elsewhere (U.S. EPA, 2023a) and in Section 3.1.2 of this document, decreased fetal testicular testosterone is an early, upstream event in the MOA that precedes downstream apical outcomes such as male nipple retention, decrease anogenital distance, and reproductive tract malformations. Decreased fetal testicular testosterone should occur at lower or equal doses than downstream apical outcomes associated with a disruption of androgen action. Because the lower 95 percent confidence limit on the BMD, or BMDL, is used for deriving a point of departure (POD), EPA compared BMDL estimates at the 5, 10, and 40 percent response levels for each phthalate (DEHP, DBP, DCHP, DIBP, BBP, DINP) to the lowest identified apical outcomes associated with phthalate syndrome to determine which response level is protective of downstream apical outcomes.

Table_Apx D-1 provides a comparison of BMD and BMDL estimates for decreased fetal testicular testosterone at BMRs of 5, 10, and 40 percent, the lowest LOAEL(s) for apical outcomes associated with phthalate syndrome, and the POD selected for each phthalate for use in risk characterization. As can be seen from Table_Apx D-1, $BMDL_{40}$ values for DEHP, DBP, DIBP, BBP, DCHP, and DINP are all well above the PODs selected for use in risk characterization for each phthalate by 3X (for BBP) to 25.4X (for DEHP). Further, $BMDL_{40}$ values for DEHP, DBP, DIBP, BBP, and DCHP, but not DINP, are above the lowest LOAELs identified for apical outcomes on the developing male reproductive system. These results clearly demonstrate that a BMR of 40 percent is not appropriate for use in human health risk assessment.

As can be seen from Table_Apx D-1, $BMDL_{10}$ values for DBP ($BMDL_{10}$, POD, LOAEL = 20, 9, 30 mg/kg-day, respectively) and DCHP ($BMDL_{10}$, POD, LOAEL = 12, 10, 20 mg/kg-day, respectively) are slightly higher than the PODs selected for use in risk characterization and slightly less than the lowest LOAELs identified based on apical outcomes associated with the developing male reproductive system. This indicates that a BMR of 10% may be protective of apical outcomes evaluated in available studies for both DBP and DCHP. $BMDL_{10}$ values could not be derived for DIBP or BBP (Table_Apx D-1). Therefore, no comparisons to the POD or lowest LOAEL for apical outcomes could be made for either of these phthalates at the 10 percent response level.

For DEHP, the $BMDL_{10}$ is greater than the POD selected for use in risk characterization by 5X ($BMDL_{10}$ and POD = 24 and 4.8 mg/kg-day, respectively) and is greater than the lowest LOAEL identified for apical outcomes on the developing male reproductive system by 2.4X ($BMDL_{10}$ and LOAEL = 24 and 10 mg/kg-day, respectively). This indicates that a BMR of 10 percent for decreased fetal testicular testosterone is not health protective for DEHP. For DEHP, the $BMDL_5$ (11 mg/kg-day) is similar to the selected POD (NOAEL of 4.8 mg/kg-day) and the lowest LOAEL identified for apical outcomes on the developing male reproductive system (10 mg/kg-day).

D.4 Weight of Scientific Evidence Conclusion

As discussed elsewhere (U.S. EPA, 2023a), DEHP, DBP, BBP, DIBP, DCHP, and DINP are toxicologically similar and induce effects on the developing male reproductive system consistent with a disruption of androgen action. Because these phthalates are toxicologically similar, it is more appropriate to select a single BMR for decreased fetal testicular testosterone to provide a consistent basis for dose response analysis and for deriving PODs relevant to the single chemical assessments. EPA has reached the conclusion that a BMR of 5 percent is the most appropriate and health protective response level for evaluating decreased fetal testicular testosterone when sufficient dose-response data are available to support modeling of fetal testicular testosterone in the low-end range of the dose-response curve. This conclusion is supported by the following weight of scientific evidence considerations.

- For DEHP, the $BMDL_{10}$ estimate is greater than the POD selected for use in risk characterization by 5X and is greater than the lowest LOAEL identified for apical outcomes on the developing male reproductive system by 2.4X. This indicates that a BMR of 10 percent is not protective for DEHP.
- The $BMDL_5$ estimate for DEHP is similar to the selected POD and lowest LOAEL for apical outcomes on the developing male reproductive system.
- $BMDL_{10}$ estimates for DBP ($BMDL_{10}$, POD, LOAEL = 20, 9, 30 mg/kg-day, respectively) and DCHP ($BMDL_{10}$, POD, LOAEL = 12, 10, 20 mg/kg-day, respectively) are slightly higher than the PODs selected for use in risk characterization and slightly less than the lowest LOAELs identified based on apical outcomes associated with the developing male reproductive system. This indicates that a BMR of 10 percent may be protective of apical outcomes evaluated in available studies for both DBP and DCHP. However, this may be a reflection of the larger database of studies and wider range of endpoints evaluated for DEHP, compared to DBP and DCHP.
- NASEM (2017) modeled a BMR of 40 percent using the following justification: "previous studies have shown that reproductive-tract malformations were seen in male rats when fetal testosterone production was reduced by about 40% *(*Gray et al., 2016*;* Howdeshell et al., 2015*)*." However, publications supporting a 40 percent response level are relatively narrow in scope and assessed the link between reduced fetal testicular testosterone in SD rats on GD 18 and later life reproductive tract malformations in F1 males. More specifically, Howdeshell et al. (2015) found reproductive tract malformations in 17 to 100 percent of F1 males when fetal testosterone on GD 18 was reduced by approximately 25 to 72 percent, while Gray et al. (2016) found dose-related reproductive alterations in F1 males treated with dipentyl phthalate (a phthalate not currently being evaluated under TSCA) when fetal testosterone was reduced by about 45 percent on GD 18. Although NASEM modeled a BMR of 40 percent based on biological considerations, there is no scientific consensus on the biologically significant response level and no other authoritative or regulatory agencies have endorsed the 40 percent response level as biologically significant for reductions in fetal testosterone.
- $BMDL_{40}$ values for DEHP, DBP, DIBP, BBP, DCHP, and DINP are above the PODs selected for use in risk characterization for each phthalate by 3X to 25.4X (Table_Apx D-1). $BMDL_{40}$ values for DEHP, DBP, DIBP, BBP, and DCHP, but not DINP, are above the lowest LOAELs identified for apical outcomes on the developing male reproductive system. These results clearly demonstrate that a BMR of 40 percent is not health protective.

Table_Apx D-1. Comparison of BMD/BMDL Values Across BMRs of 5%, 10%, and 40% with PODs and LOAELs for Apical Outcomes for DEHP, DBP, DIBP, BBP, DCHP, and DINP

Phthalate	POD (mg/kg-day) Selected for use in Risk Characterization (Effect)	Lowest LOAEL(s) (mg/kg-day) for Apical Effects on the Male Reproductive System	BMD_5 Estimate [a] (mg/kg-day) [95% CI]	BMD_{10} Estimate [a] (mg/kg-day) [95% CI]	BMD_{40} Estimate [a] (mg/kg-day) [95% CI]	Reference For Further Details on the Selected POD and Lowest Identified LOAEL,
DEHP	NOAEL = 4.8 (↑ male RTM in F1 and F2 males)	10 to 15 (NR, ↓ AGD, RTMs)	17 [11, 31]	35 [24, 63]	178 [122, 284]	(U.S. EPA, 2025k)
DBP	$BMDL_5$ = 9 (↓ fetal testicular testosterone)	30 (↑ Testicular Pathology)	14 [9, 27]	29 [20, 54]	149 [101, 247]	(U.S. EPA, 2025i)
DIBP	$BMDL_5$ = 24 (↓ fetal testicular testosterone)	125 (↑ Testicular Pathology)	–[b]	55 [NA, 266][b]	279 [136, 517]	(U.S. EPA, 2025l)
BBP	NOAEL = 50 (phthalate syndrome-related effects)	100 (↓ AGD)	–[b]	–[b]	284 [150, 481]	(U.S. EPA, 2025h)
DCHP	NOAEL = 10 (phthalate syndrome-related effects)	20 (↑ Testicular Pathology)	8.4 [6.0, 14]	17 [12, 29]	90 [63, 151]	(U.S. EPA, 2025j)
DINP	$BMDL_5$ = 49 (↓ fetal testicular testosterone)	600 (↓ sperm motility)	74 [47, 158]	152 [97, 278]	699 [539, 858]	(U.S. EPA, 2025m)

Abbreviations: AGD = anogenital distance; BMD = benchmark dose; BMDL = lower 95% confidence limit on BMD; CI = 95% confidence interval; LOAEL = lowest observable-adverse-effect level; NOAEL = no observable-adverse-effect level; POD = point of departure; RTM = reproductive tract malformations

[a] The linear-quadratic model provided the best fit (based on lowest AIC) for DEHP, DBP, DIBP, BBP, DCHP, and DINP.

[b] BMD and/or BMDL estimate could not be derived.

Appendix E BENCHMARK DOSE MODELING OF FETAL TESTICULAR TESTOSTERONE DATA FROM GRAY ET AL. (2021), HOWDESHELL ET AL. (2008), HANNAS ET AL. (2011)

EPA conducted benchmark dose (BMD) modeling of *ex vivo* fetal testicular testosterone data from three gestational exposure studies of DIBP (Gray et al., 2021; Hannas et al., 2011; Howdeshell et al., 2008).

The BMD modeling for continuous data was conducted with the EPA's BMD software (BMDS 3.3.2). All standard BMDS 3.3.2 continuous models that use maximum likelihood (MLE) optimization and profile likelihood-based confidence intervals were used in this analysis. Standard forms of these models (defined below) were run so that auto-generated model selection recommendations accurately reflect current EPA model selection procedures EPA's benchmark Dose Technical Guidance (U.S. EPA, 2012). BMDS 3.3.2 models that use Bayesian fitting procedures and Bayesian model averaging were not applied in this work.

Standard BMDS 3.3.2 Models Applied to Continuous Endpoints:

- Exponential 3-restricted (exp3-r)
- Exponential 5-restricted (exp5-r)
- Hill-restricted (hil-r)
- Polynomial Degree 3-restricted (ply3-r
- Polynomial Degree 2-restricted (ply2-r)
- Power-restricted (pow-r)
- Linear-unrestricted (lin-ur)

EPA evaluated benchmark response (BMR) levels of 1 control standard deviation (1 SD) and 5, 10, and 40% relative deviation. BMRs of 5, 10, and 40% relative deviation were included for consistency with EPA's meta-analysis and benchmark dose analysis of fetal testicular testosterone (Appendix D). A BMR of 1 SD was included per EPA's Benchmark Dose Technical Guidance (U.S. EPA, 2012), which recommends that the BMD corresponding to one control SD always be presented for reporting purposes. However, as described in Appendix D, EPA considers a BMR of 5 percent to be the most appropriate and health protective response level for evaluating decreased fetal testicular testosterone for POD determination. Model fit was judged consistent with EPA's Benchmark Dose Technical Guidance (U.S. EPA, 2012). An adequate fit was judged based on the $\chi 2$ goodness-of-fit p-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was constant. If a constant variance model was deemed appropriate based on the statistical test provided in BMDS (*i.e.*, Test 2; p-value > 0.05 [note: this is a change from previous versions of BMDS, which required variance p-value > 0.10 for adequate fit]), the final BMD results were estimated from a constant variance model. If the test for homogeneity of variance was rejected (*i.e.*, p-value < 0.05), the model was run again while modeling the variance as a power function of the mean to account for this nonconstant variance. If this nonconstant variance model did not adequately fit the data (*i.e.*, Test 3; p-value < 0.05), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL was selected if the BMDLs estimated from different adequately fitting models varied >3-fold; otherwise, the BMDL from the model with the lowest AIC was selected.

If no model adequately fit the data set using the approach described above, EPA removed the highest dose group and modeled the data again using the approach described above.

Table_Apx E-1 summarizes BMD modeling results for reduced *ex vivo* fetal testicular testosterone data, while more detailed BMD model results are provided in Appendices E.1 through E.3.

Table_Apx E-1. Summary of BMD Model Results for Decreased *Ex Vivo* Fetal Testicular Testosterone

Data set	BMR	Best-Fit Model (Variance)	BMD (mg/kg-day)	BMDL (mg/kg-day)	Notes	Appendix Containing Results
(Gray et al., 2021)	5%	Exponential 3 (Constant)	63	24		E.1
(Howdeshell et al., 2008)	5%	Hill (Constant)	103	52		E.2
(Hannas et al., 2011)	5%	–	–	–	No models adequately fit the data set	E.3

E.1 BMD Model Results (Gray et al. 2021)

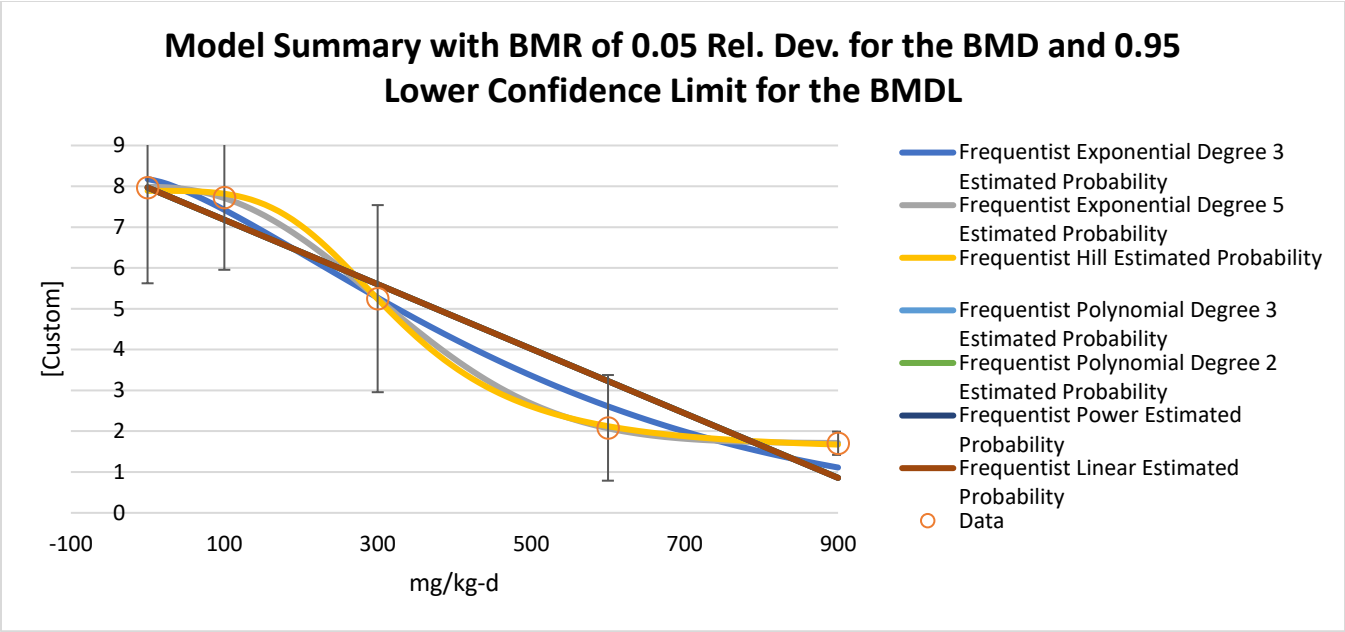
Table_Apx E-2. *Ex Vivo* Fetal Rat Testicular Testosterone Data (Gray et al. 2021)

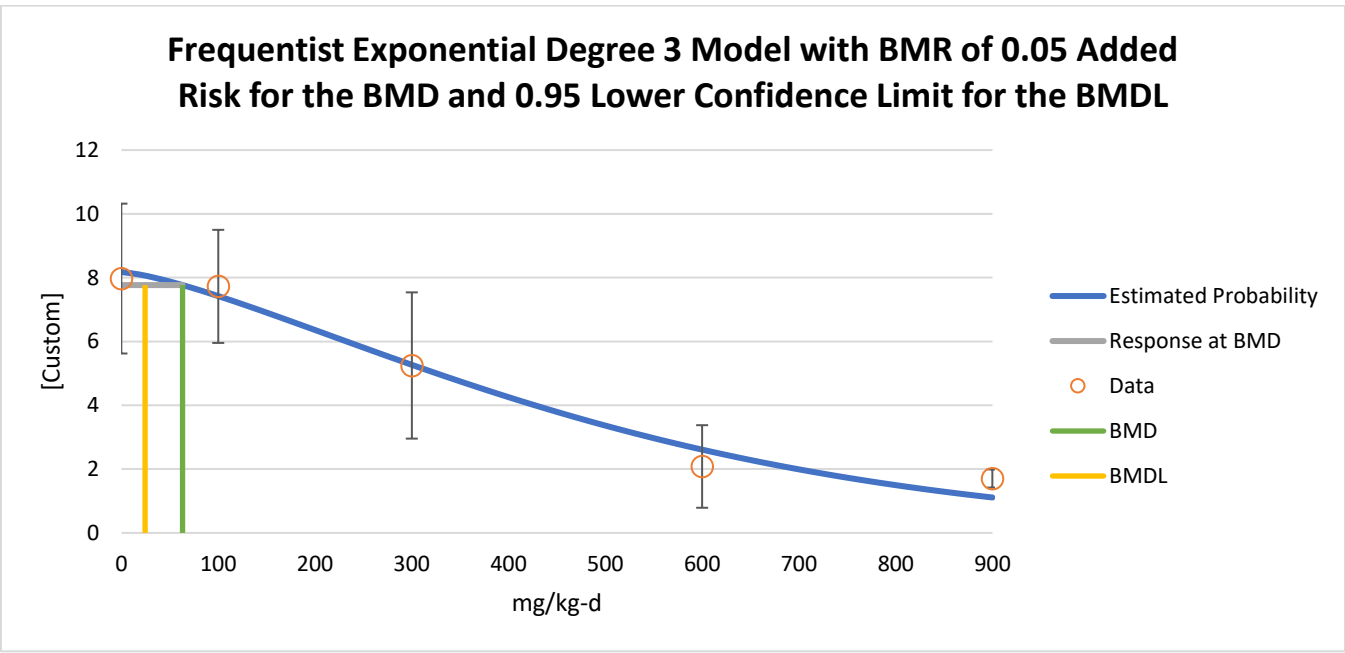
Dose (mg/kg-day)	N (# of litters)	Mean	Standard Deviation	Notes
0	3	7.972888889	1.465303963	Data for Block 67 rats reported in Supplementary Data file associated with (Gray et al., 2021)
100	3	7.727111111	1.105751094	
300	3	5.247777778	1.429576563	
600	2	2.082416667	0.659141371	
900	2	1.705333333	0.145192592	

Table_Apx E-3. BMD Model Results *Ex Vivo* Fetal Testicular Testosterone (Gray et al. 2021)

Models[a]	Restriction[b]	Variance	BMR = 5%		BMR = 10%		BMR = 40%		BMR = 1 SD		P Value	AIC	BMDS Model Fit	BMDS Notes
			BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL				
Exponential 3	**Restricted**	**Constant**	**63.12026**	**24.43019**	**106.4244**	**50.18702**	**334.6495**	**242.737**	**124.0844**	**57.8285**	**0.4081261**	**44.84273867**	**Viable - Recommended**	**Lowest AIC BMDL 3x lower than lowest non-zero dose**
Exponential 5	Restricted	Constant	117.9931	36.28242	161.5201	69.23603	329.678	257.1545	173.525	79.69645	0.9645746	45.05235319	Viable - Alternate	BMD/BMDL ratio > 3
Hill	Restricted	Constant	159.6043	38.88005	195.2869	72.20498	326.5199	255.0622	205.6406	83.34761	0.8074988	45.10974788	Viable - Alternate	BMD/BMDL ratio > 3
Polynomial Degree 3	Restricted	Constant	50.44101	43.48323	100.882	86.96657	403.528	347.8659	143.1312	102.5143	0.1694486	46.08266114	Viable - Alternate	
Polynomial Degree 2	Restricted	Constant	50.4376	43.48294	100.8752	86.96588	403.5008	347.8635	143.1079	102.5161	0.1694491	46.08265471	Viable - Alternate	
Power	Restricted	Constant	50.42151	43.48131	100.843	86.96262	403.3721	347.8505	143.04	102.5174	0.1694501	46.08264079	Viable - Alternate	
Linear	Unrestricted	Constant	50.42151	43.48125	100.843	86.96262	403.3721	347.8505	143.04	102.5173	0.1694501	46.08264079	Viable - Alternate	

AIC = Akaike information criterion; BMD = benchmark dose; BMDL =benchmark dose lower limit; NA = Not Applicable.
[a] Selected Model (bolded and shaded gray).
[b] Restrictions defined in the BMDS 3.3 User Guide.


Model Summary with BMR of 0.05 Rel. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
[Custom]
mg/kg-d
Frequentist Exponential Degree 3 Estimated Probability
Frequentist Exponential Degree 5 Estimated Probability
Frequentist Hill Estimated Probability
Frequentist Polynomial Degree 3 Estimated Probability
Frequentist Polynomial Degree 2 Estimated Probability
Frequentist Power Estimated Probability
Frequentist Linear Estimated Probability
Data


Frequentist Exponential Degree 3 Model with BMR of 0.05 Added Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
[Custom]
mg/kg-d
Estimated Probability
Response at BMD
Data
BMD
BMDL

User Input

Info	
Model	frequentist Exponential degree 3
Model Restriction	Restricted
Dataset Name	Gray et al. (2021) - DIBP Testosterone
User notes	[Add user notes here]
Dose-Response Mode	M[dose] = a * exp(±1 * (b * dose)^d)
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	mg/kg-d
Independent Variable	[Custom]
Total # of Observation	5
Adverse Direction	Automatic

Model Results

Benchmark Dose	
BMD	63.12026381
BMDL	24.43018547
BMDU	136.7436224
AIC	44.84273867
Test 4 P-value	0.40812612
D.O.F.	2

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	8.176712147	0.50528127	7.186379	9.167045
b	0.00183526	2.35E-04	0.001375	0.002296
d	1.377943821	3.25E-01	0.741889	2.013999
log-alpha	-0.003820249	1.44E-01	-0.28666	0.279017

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	3	8.17671215	7.972889	7.972889	0.998092	1.4653	1.4653	-0.353707
100	3	7.42306676	7.727111	7.727111	0.998092	1.1058	1.10575	0.5276271
300	3	5.26924478	5.247778	5.247778	0.998092	1.4296	1.42958	-0.037253
600	2	2.60984715	2.082417	2.082417	0.998092	0.6591	0.65914	-0.747325
900	2	1.11027298	1.705333	1.705333	0.998092	0.1452	0.14519	0.8431514

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-17.5251903	6	47.05038
A2	-13.06218817	10	46.12438
A3	-17.5251903	6	47.05038
fitted	-18.42136934	4	44.84274
R	-31.49407383	2	66.98815

* Includes additive constant of -11.9462. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	36.86377131	8	<0.0001
2	8.926004259	4	0.062976
3	8.926004259	4	0.062976
4	1.792358067	2	0.408126

E.2 BMD Model Results (Howdeshell et al. 2008)

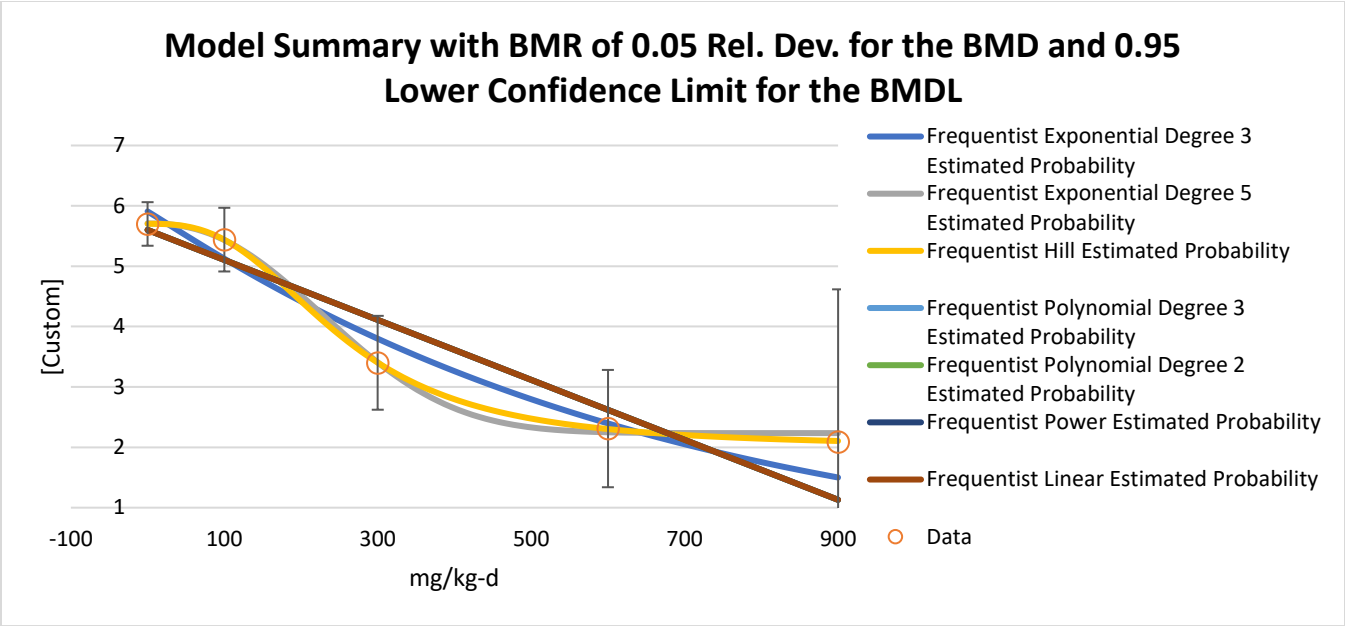
Table_Apx E-4. *Ex Vivo* Fetal Rat Testicular Testosterone Data (Howdeshell et al. 2008)

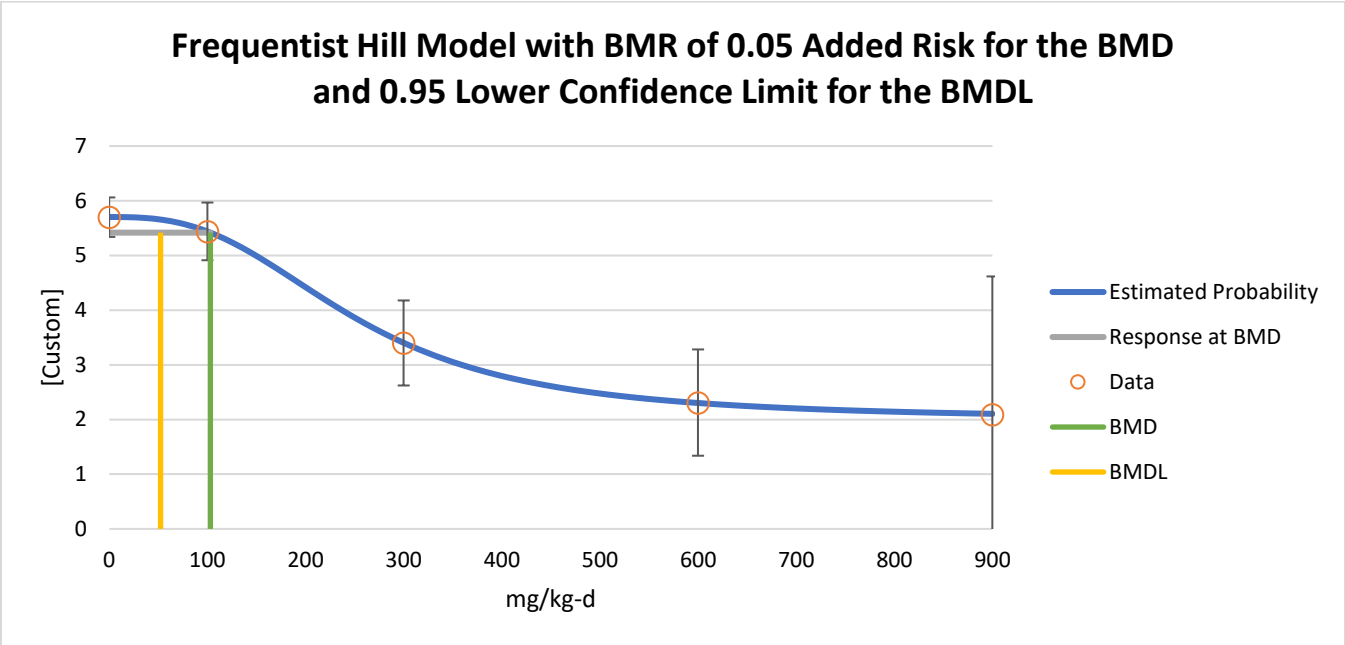
Dose (mg/kg-day)	N (# of litters)	Mean	Standard Deviation	Notes
0	5	5.7	0.290688837	Data from Table 6 in (Howdeshell et al., 2008)
100	8	5.44	0.537401154	
300	5	3.4	0.626099034	
600	5	2.31	0.782623792	
900	2	2.09	1.286934342	

Table_Apx E-5. BMD Model Results *Ex Vivo* Fetal Testicular Testosterone (Howdeshell et al. 2008)

Models[a]	Restriction[b]	Variance	BMR = 5%		BMR = 10%		BMR = 40%		BMR = 1 SD		P Value	AIC	BMDS Model Fit	BMDS Notes
			BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL				
Exponential 3	Restricted	Constant	37.18733	28.33677	74.74254	58.22005	345.5016	282.4184	82.49155	57.22709	0.0322184	57.43690601	Questionable	Goodness of fit p-value < 0.1 BMDL 3x lower than lowest non-zero dose Modeled control response std. dev. >|1.5| actual response std. dev.
Exponential 5	Restricted	Constant	101.588	45.31085	139.2085	77.87386	298.0878	246.6513	139.0035	75.64862	0.6618655	52.75773749	Viable - Alternate	Modeled control response std. dev. >|1.5| actual response std. dev.
Hill	**Restricted**	**Constant**	**102.9819**	**52.24216**	**136.2697**	**82.27878**	**297.6961**	**236.3744**	**135.9319**	**80.08333**	**0.9596039**	**52.56903757**	**Viable - Recommended**	**Lowest AIC** **Modeled control response std. dev. >|1.5| actual response std. dev.**
Polynomial Degree 3	Restricted	Constant	56.3685	49.44861	112.737	98.89673	450.9479	395.5888	149.7341	115.3485	0.0035229	62.15461672	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Polynomial Degree 2	Restricted	Constant	56.36571	49.44887	112.7314	98.89766	450.9255	395.5908	149.7243	115.3486	0.0035229	62.15461883	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Power	Restricted	Constant	56.37483	49.44799	112.7497	98.89597	450.9986	395.5839	149.7562	115.3481	0.0035229	62.15461483	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Linear	Unrestricted	Constant	56.37483	49.448	112.7497	98.89599	450.9986	395.584	149.7562	115.3481	0.0035229	62.15461483	Questionable	Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL =benchmark dose lower limit; NA = Not Applicable.
[a] Selected Model (bolded and shaded gray).
[b] Restrictions defined in the BMDS 3.3 User Guide.


Model Summary with BMR of 0.05 Rel. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
[Custom]
mg/kg-d
7
6
5
4
3
2
1
-100
100
300
500
700
900
Frequentist Exponential Degree 3 Estimated Probability
Frequentist Exponential Degree 5 Estimated Probability
Frequentist Hill Estimated Probability
Frequentist Polynomial Degree 3 Estimated Probability
Frequentist Polynomial Degree 2 Estimated Probability
Frequentist Power Estimated Probability
Frequentist Linear Estimated Probability
Data


Frequentist Hill Model with BMR of 0.05 Added Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
[Custom]
mg/kg-d
7
6
5
4
3
2
1
0
0
100
200
300
400
500
600
700
800
900
Estimated Probability
Response at BMD
Data
BMD
BMDL

User Input

Info	
Model	frequentist Hill
Model Restriction	Restricted
Dataset Name	Howdeshell (2008) - DIBP Testosterone
User notes	[Add user notes here]
Dose-Response Mode	M[dose] = g + v*dose^n/(k^n + dose^n)
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	mg/kg-d
Independent Variable	[Custom]
Total # of Observation	5
Adverse Direction	Automatic

Model Results

Benchmark Dose	
BMD	102.981862
BMDL	52.24216337
BMDU	185.1065152
AIC	52.56903757
Test 4 P-value	0.959603873
D.O.F.	1

Model Parameters				
# of Parameters	5			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	5.702356605	0.24846946	5.215365	6.189348
v	-3.700369546	0.54289795	-4.76443	-2.63631
k	251.0918424	37.2929652	177.999	324.1847
n	2.786041669	1.15019349	0.531704	5.04038
alpha	0.321384979	2.92E-02	0.264127	0.378643

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	5	5.7023566	5.7	5.7	0.566908	0.2907	0.29069	-0.009295
100	8	5.43804842	5.44	5.44	0.566908	0.5374	0.5374	0.0097369
300	5	3.40266882	3.4	3.4	0.566908	0.6261	0.6261	-0.010527
600	5	2.30223684	2.31	2.31	0.566908	0.7826	0.78262	0.0306204
900	2	2.10465068	2.09	2.09	0.566908	1.2869	1.28693	-0.036548

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-21.28323604	6	54.56647
A2	-18.36479748	10	56.72959
A3	-21.28323604	6	54.56647
fitted	-21.28451878	5	52.56904
R	-46.73498878	2	97.46998

* Includes additive constant of -22.97346. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	56.74038261	8	<0.0001
2	5.83687712	4	0.211666
3	5.83687712	4	0.211666
4	0.002565492	1	0.959604

E.3 BMD Model Results (Hannas et al. 2011)

Table_Apx E-6. *Ex Vivo* Fetal Rat Testicular Testosterone Data (Hannas et al. 2011)

Dose (mg/kg-day)	N (# of litters)	Mean	Standard Deviation	Notes
0	3	5.19	1.195115057	Data from Table 1 in (Hannas et al., 2011)
100	3	5.7	0.294448637	
300	3	2.27	1.420281662	
600	3	1.05	0.692820323	
900	3	0.65	0.173205081	

Table_Apx E-7. BMD Model Results *Ex Vivo* Fetal Testicular Testosterone (All Dose Groups) (Hannas et al. 2011)

Models[a]	Restriction[b]	Variance	BMR = 5%		BMR = 10%		BMR = 40%		BMR = 1 SD		P Value	AIC	BMDS Model Fit	BMDS Notes
			BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL				
Exponential 3	Restricted	Constant	53.19681	17.80873	86.18426	36.58139	248.2968	173.5584	121.3679	58.47676	0.0435151	47.56574178	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1 BMDL 3x lower than lowest non-zero dose
Exponential 5	Restricted	Constant	253.0245	60.82534	263.8179	89.98152	289.7556	204.3087	269.3968	109.1352	0.2886587	44.42231369	Questionable	Constant variance test failed (Test 2 p-value < 0.05) BMD/BMDL ratio > 3
Hill	Restricted	Constant	168.4655	62.74761	190.5248	161.2484	259.3454	187.7035	202.9592	104.7965	0.2934707	44.40007786	Questionable	Constant variance test failed (Test 2 p-value < 0.05)
Polynomial Degree 3	Restricted	Constant	44.5932	38.08458	89.1864	76.16924	356.7457	304.6767	191.342	137.0539	0.0060429	51.72768824	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1
Polynomial Degree 2	Restricted	Constant	44.61656	38.08266	89.23315	76.16526	356.9326	304.661	191.5359	137.0482	0.0060428	51.72769929	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1
Power	Restricted	Constant	44.60136	38.08385	89.20272	76.1677	356.8109	304.6708	191.4181	137.0529	0.0060429	51.72768347	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1
Linear	Unrestricted	Constant	44.60135	38.08385	89.20271	76.16769	356.8109	304.6725	191.4181	137.0514	0.0060429	51.72768347	Questionable	Constant variance test failed (Test 2 p-value < 0.05) Goodness of fit p-value < 0.1
Exponential 3	Restricted	Non-Constant	27.99886	15.98305	53.77395	32.81671	224.9883	159.1025	150.5282	68.44409	0.1963944	44.46367306	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) BMD 3x lower than lowest non-zero dose BMDL 3x lower than lowest non-zero dose
Exponential 5	Restricted	Non-Constant	54.67479	14.05239	87.27415	28.92156	246.6568	142.7024	167.4876	74.84092	0.1504498	45.2760973	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) BMD/BMDL ratio > 3 BMDL 3x lower than lowest non-zero dose
Hill	Restricted	Non-Constant	89.27453	18.68063	119.5257	35.15881	243.712	156.1378	171.9022	88.60382	0.2773613	44.38838686	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) BMD/BMDL ratio > 3

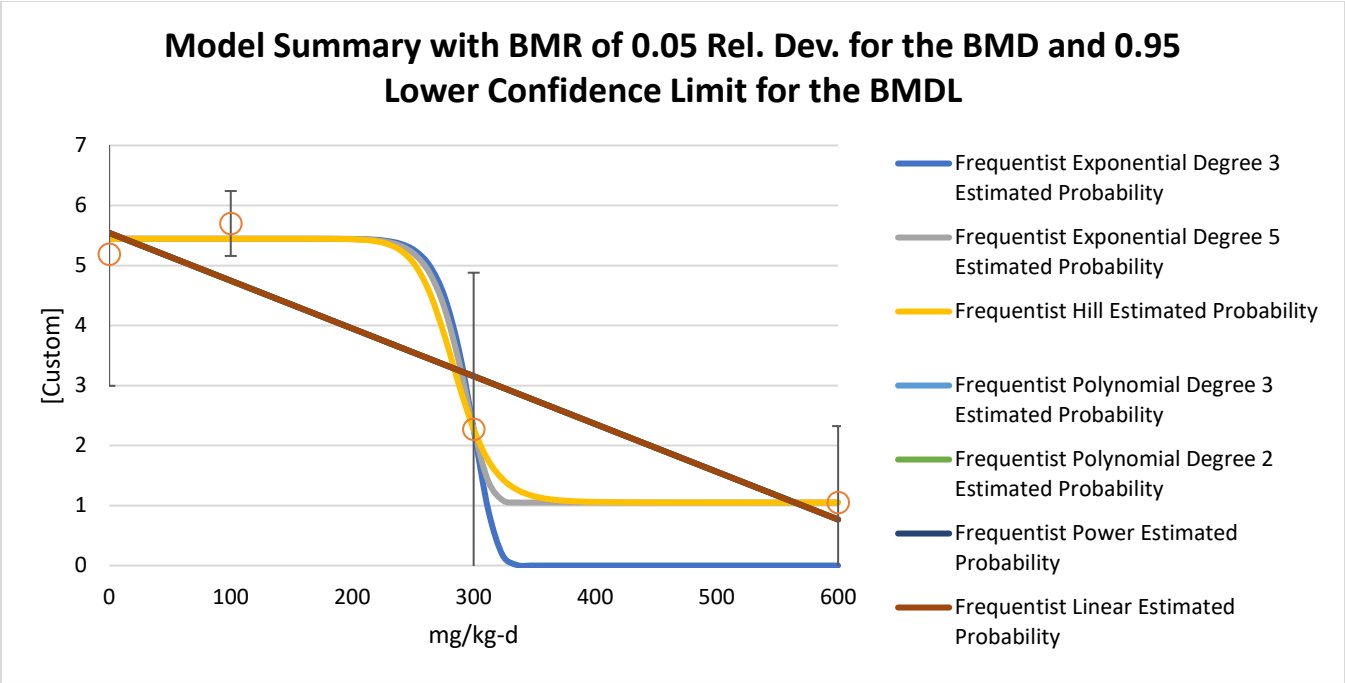
Models[a]	Restriction[b]	Variance	BMR = 5%		BMR = 10%		BMR = 40%		BMR = 1 SD		P Value	AIC	BMDS Model Fit	BMDS Notes
			BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL				
														BMDL 3x lower than lowest non-zero dose
Polynomial Degree 3	Restricted	Non-Constant	52.39019	47.32479	104.7804	94.65019	419.1216	378.5982	500.2151	240.1444	0.0315801	48.04250119	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Polynomial Degree 2	Restricted	Non-Constant	52.38006	47.32657	104.7601	94.65252	419.0404	378.615	499.0547	240.1565	0.0315806	48.04246336	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Power	Restricted	Non-Constant	51.70133	47.10326	103.4027	94.20652	413.6106	376.8261	434.4408	236.6546	0.0300659	48.15086454	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.
Linear	Unrestricted	Non-Constant	52.37973	47.32659	104.7594	94.65314	419.0377	378.6051	499.0851	240.1585	0.0315806	48.04246244	Questionable	Non-constant variance test failed (Test 3 p-value < 0.05) Goodness of fit p-value < 0.1 Modeled control response std. dev. >|1.5| actual response std. dev.

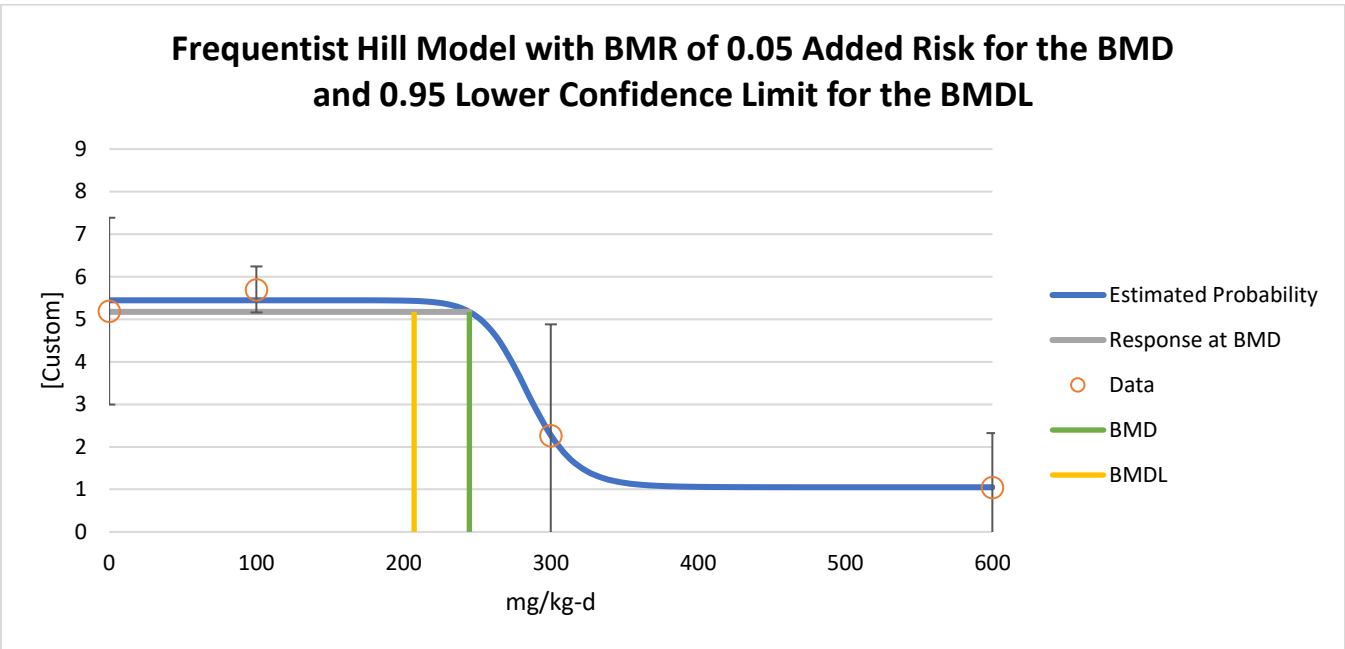
AIC = Akaike information criterion; BMD = benchmark dose; BMDL =benchmark dose lower limit; NA = Not Applicable.
[a] Selected Model (bolded and shaded gray).
[b] Restrictions defined in the BMDS 3.3 User Guide.

Table_Apx E-8. BMD Model Results *Ex Vivo* Fetal Testicular Testosterone (Highest Dose Group Removed) (Hannas et al. 2011)

Models[a]	Restriction[b]	Variance	BMR = 5%		BMR = 10%		BMR = 40%		BMR = 1 SD		P Value	AIC	BMDS Model Fit	BMDS Notes
			BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL				
Exponential 3	Restricted	Constant	256.2599	17.37356	266.7157	35.68542	291.1642	166.2802	276.4071	63.30013	0.0329607	41.77330522	Questionable	Goodness of fit p-value < 0.1 BMD/BMDL ratio > 3 BMDL 3x lower than lowest non-zero dose
Exponential 5	Restricted	Constant	252.0464	55.61988	262.9164	83.58491	289.2605	194.5526	270.1764	108.3206	NA	39.79519328	Questionable	BMD/BMDL ratio > 3 d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Hill	Restricted	Constant	244.6114	207.076	255.1814	217.9335	284.1949	174.1718	262.508	107.2089	0.450376	37.79519327	Viable	Lowest AIC EPA Notes: Poor visual fit. No model selected for this data set.
Polynomial Degree 3	Restricted	Constant	34.81702	28.89754	69.63404	57.79509	278.5362	231.18	134.3093	92.80279	0.0401532	41.65559526	Questionable	Goodness of fit p-value < 0.1 BMDL 3x lower than lowest non-zero dose
Polynomial Degree 2	Restricted	Constant	34.81929	28.89742	69.63859	57.79485	278.5543	231.1794	134.3216	92.80369	0.0401532	41.65559589	Questionable	Goodness of fit p-value < 0.1 BMDL 3x lower than lowest non-zero dose
Power	Restricted	Constant	34.81603	28.89757	69.63207	57.79515	278.5283	231.1806	134.3029	92.80444	0.0401532	41.65559519	Questionable	Goodness of fit p-value < 0.1 BMDL 3x lower than lowest non-zero dose
Linear	Unrestricted	Constant	34.81604	28.89758	69.63208	57.79515	278.5283	231.1806	134.3029	92.80386	0.0401532	41.65559519	Questionable	Goodness of fit p-value < 0.1 BMDL 3x lower than lowest non-zero dose

AIC = Akaike information criterion; BMD = benchmark dose; BMDL =benchmark dose lower limit; NA = Not Applicable.
[a] Selected Model (bolded and shaded gray).
[b] Restrictions defined in the BMDS 3.3 User Guide.


Model Summary with BMR of 0.05 Rel. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
[Custom]
mg/kg-d
0
1
2
3
4
5
6
7
0
100
200
300
400
500
600
Frequentist Exponential Degree 3 Estimated Probability
Frequentist Exponential Degree 5 Estimated Probability
Frequentist Hill Estimated Probability
Frequentist Polynomial Degree 3 Estimated Probability
Frequentist Polynomial Degree 2 Estimated Probability
Frequentist Power Estimated Probability
Frequentist Linear Estimated Probability


Frequentist Hill Model with BMR of 0.05 Added Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
[Custom]
mg/kg-d
0
1
2
3
4
5
6
7
8
9
0
100
200
300
400
500
600
Estimated Probability
Response at BMD
Data
BMD
BMDL

User Input

Info	
Model	frequentist Hill
Model Restriction	Restricted
Dataset Name	as (2011) - DIBP Testosterone (high dose removed)
User notes	[Add user notes here]
Dose-Response Mode	M[dose] = g + v*dose^n/(k^n + dose^n)
Variance Model	Var[i] = alpha

Model Options	
BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Constant

Model Data	
Dependent Variable	mg/kg-d
Independent Variable	[Custom]
Total # of Observation	4
Adverse Direction	Automatic

Model Results

Benchmark Dose	
BMD	244.6114226
BMDL	207.075989
BMDU	256.7691509
AIC	37.79519327
Test 4 P-value	0.450375979
D.O.F.	1

Model Parameters				
# of Parameters	5			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	5.445000004	0.34186044	4.774966	6.115034
v	-4.395006471	0.59212145	-5.55554	-3.23447
k	284.475258	10.8295577	263.2497	305.7008
n	Bounded	NA	NA	NA
alpha	0.701212507	0.20072773	0.307793	1.094632

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	3	5.445	5.19	5.19	0.837384	1.1951	1.19512	-0.527444
100	3	5.44499997	5.7	5.7	0.837384	0.2944	0.29445	0.5274436
300	3	2.27000003	2.27	2.27	0.837384	1.4203	1.42028	-6.12E-08
600	3	1.04999997	1.05	1.05	0.837384	0.6928	0.69282	5.239E-08

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-14.6127439	5	39.22549
A2	-11.4128589	8	38.82572
A3	-14.6127439	5	39.22549
fitted	-14.89759663	4	37.79519
R	-26.01000707	2	56.02001

* Includes additive constant of -11.02726. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	29.19429634	6	<0.0001
2	6.399769998	3	0.0937
3	6.399769998	3	0.0937
4	0.569705469	1	0.450376

Appendix F Options Considered by EPA for Deriving the Acute, Intermediate, and Chronic Non-Cancer POD

In order to derive a non-cancer POD for DIBP, EPA considered three options in the *Draft Non-Cancer Human Health Hazard Assessment for DIBP* and peer reviewed by the SACC in August 2025, including:

- Option 1. NOAEL/LOAEL approach to identify the highest NOAEL below the lowest LOAEL.
- Option 2. Application of a data-derived adjustment factor based on differences in relative potency to reduced fetal testicular testosterone.
- Option 3. BMD modeling of fetal testicular testosterone.

The strengths and limitations of each of the approaches considered by EPA in the *Draft Non-Cancer Human Health Hazard Assessment for DIBP* to derive a non-cancer POD for DIBP are discussed further below. As described above in Section 4.2.2, EPA selected the $BMDL_5$ of 24 mg/kg-day for the risk evaluation of DIBP (Option 3).

F.1 Option 1. NOAEL/LOAEL Approach

Overall, EPA considers Saillenfait et al. (2008) to support a LOAEL of 125 mg/kg-day based on low incidence of testicular histopathological findings. Three additional studies of fetal testicular testosterone all support a NOAEL of 100 mg/kg-day (Gray et al., 2021; Hannas et al., 2011; Howdeshell et al., 2008). In each of these three studies, pregnant SD rats were gavaged with the same DIBP doses (0, 100, 300, 600, 900 mg/kg-day) on GDs 14-18 (Gray et al., 2021; Hannas et al., 2011) or GDs 8-18 (Howdeshell et al., 2008). For each of the three studies, *ex vivo* fetal testicular testosterone production was then measured on GD 18, approximately 2 hours after the final dose of DIBP was administered. No statistically significant changes in *ex vivo* fetal testicular testosterone production were observed in any of these studies at 100 mg/kg-day when measured on GD18; however, at the 300 mg/kg-day DIBP dose, the response compared to the control ranged from 44 to 66 percent, supporting a NOAEL of 100 mg/kg-day in these studies (Gray et al., 2021; Hannas et al., 2011; Howdeshell et al., 2008). Therefore, EPA considers these 4 studies to support a NOAEL for fetal testicular testosterone of 100 mg/kg-day and a LOAEL for testicular histopathology of 125 mg/kg-day.

However, there are several lines of evidence that suggest a NOAEL of 100 mg/kg-day may be under-protective, including:

- The database of studies for DIBP is limited to 11 gestational or perinatal oral exposures studies, 5 of which tested a single high dose level of 200 to 750 mg/kg-day, while no studies have evaluated doses below 100 mg/kg-day.
- BMD modeling of testicular pathology data from Saillenfait et al. (2008) supports $BMDL_5$ values of 56 to 60 mg/kg-day based on incidence of sloughed cells or combined azoospermia/oligospermia (Table 4-4).
- EPA's updated meta-analysis and BMD modeling analysis of fetal testicular testosterone supported a BMD_{10} of 55 mg/kg-day. No $BMDL_5$ could be derived from the best-fitting linear quadratic model as part of the updated analysis (Table 4-3).

F.2 Option 2. Application of a Data-Derived Adjustment Factor

EPA also considered differences in relative potency between toxicologically similar phthalates to derive a data-derived adjustment factor. As discussed in EPA's *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)* (U.S. EPA, 2025r), EPA has derived a relative potency factor (RPF) of 0.53 for DIBP, based on its relative potency compared to the index chemical, dibutyl phthalate (DBP), at reducing fetal testicular testosterone. The POD for the index chemical, DBP, is a $BMDL_5$ of 9 mg/kg-day derived from EPA's updated meta-analysis and BMD modeling analysis of fetal testicular testosterone (U.S. EPA, 2025i, r). The POD of 9 mg/kg-day for the index chemical (DBP) is approximately 11.1 times lower than the NOAEL of 100 mg/kg-day identified for DIBP identified above in Appendix F.1. In contrast, the RPF of 0.53 indicates that the POD for DIBP should be approximately twice that of DBP, since DIBP is approximately half as potent as DBP at reducing fetal testicular testosterone. Therefore, EPA considered adjusting the DIBP NOAEL of 100 by a factor of 5.89 (*i.e.,* (DIBP NOAEL ÷ DBP $BMDL_5$) * RPF_{DIBP}), which would result in an adjusted NOAEL of 17 mg/kg-day.

Notably, ECHA (2017a, b) employed a similar relative potency adjustment for DIBP.

F.3 Option 3. BMD Analysis of Individual Fetal Testicular Testosterone Studies

Because no $BMDL_5$ could be derived via the updated meta-analysis and BMD analysis of fetal testicular testosterone data, EPA modeled individual *ex vivo* fetal testicular testosterone production data sets using EPA's BMD Software (Gray et al., 2021; Hannas et al., 2011; Howdeshell et al., 2008). No models adequately fit the Hannas et al. (2011) data set (Table_Apx E-1). In contrast, BMD_5 and $BMDL_5$ values of 63 and 24 mg/kg-day were derived from the Gray et al. (2021) data set based on the best fitting exponential 3 model, while BMD_5 and $BMDL_5$ values of 103 and 52 mg/kg-day were derived from the Howdeshell et al. (2008) data set based on the best fitting Hill model (Table_Apx E-1).The $BMDL_5$ of 52 mg/kg-day from Howdeshell et al. (2008) is similar to the derived BMD_{10} of 55 mg/kg-day from EPA's updated meta-analysis (Table 4-3) suggesting the $BMDL_5$ of 52 mg/kg-day is not appropriate for use in human health risk characterization. Additionally, although the linear model in EPA's updated meta-analysis did not provide the best-fit (*i.e.,* the linear-quadratic model had a lower AIC), the linear model did appear to adequately fit the data set and supports BMD_5 and $BMDL_5$ values of 28 and 20 mg/kg-day (Table 4-3). The $BMDL_5$ of 24 mg/kg-day from Gray et al. (2021) is similar to the $BMDL_5$ of 20 mg/kg-day derived using the linear model in the updated meta-analysis. Although there is some uncertainty because derived $BMDL_5$ estimates are below the lowest dose with empirical data (*i.e.,* 100 mg/kg-day), EPA considers this BMD analysis to support a $BMDL_5$ of 24 mg/kg-day based on reduced fetal testicular testosterone in the study by Gray et al. (2021).