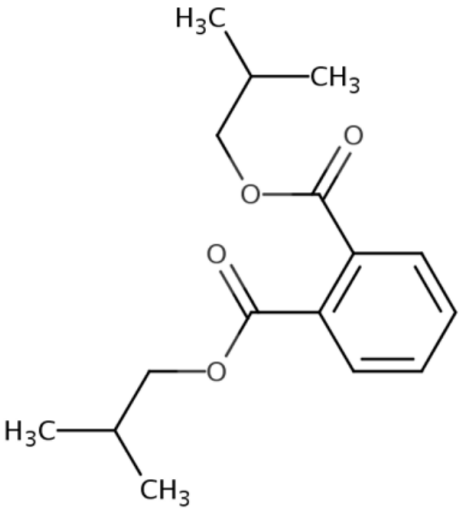
United States
Environmental Protection Agency

July 2025
Office of Chemical Safety and
Pollution Prevention

Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for Di-isobutyl Phthalate (DIBP) (1,2-Benzenedicarboxylic acid, 1,2-bis(2-methylpropyl) ester)

Systematic Review Support Document for the Draft Risk Evaluation

CASRN: 84-69-5



July 2025

This supplemental file contains information regarding the data quality evaluation conducted for references that (1) met PECO screening criteria, (2) were published prior to 2014 which was the preferred literature cutoff date by EPA for data reported in previous assessments, and (3) reported human equivalent dose (HED) derived from points of departure (POD) that contained lowest-observable-effect levels (LOEL) greater than an order of magnitude of the lowest HED lowest-observable-adverse-effect level (LOAEL) identified across existing assessments. For a detailed description on these three criteria, see the *Draft Risk Evaluation for Diisobutyl Phthalate (DIBP) – Systematic Review Protocol*. EPA conducted data quality evaluation based on author-reported descriptions and results; additional analyses (*e.g.*, statistical analyses performed during data integration into the risk evaluation) potentially conducted by EPA are not contained in this supplemental file. For the data quality evaluation, EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as '2021 Draft Systematic Review Protocol'). Any updated steps in the systematic review process since the publication of the 2021 Draft Systematic Review Protocol are described in the *Draft Risk Evaluation for Diisobutyl Phthalate (DIBP) – Systematic Review Protocol*.

Table of Contents

Study Citation:	Gray, L. E., Jr, Lambright, C. S., Conley, J. M., Evans, N., Furr, J. R., Hannas, B. R., Wilson, V. S., Sampson, H., Foster, D., P.M. (2021). Genomic and Hormonal Biomarkers of Phthalate-Induced Male Rat Reproductive Developmental Toxicity Part II: A Targeted RT-qPCR Array Approach That Defines a Unique Adverse Outcome Pathway. Toxicological Sciences 182(2):195-214.
Health Outcome(s) and Reported Health Effect(s):	Fetal testosterone production ex vivo
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD14-GD18)
Species:	Rat-Other (Crl:(CD)SD)-Female
Chemical:	Diisobutyl Phthalate- Parent compound
HERO ID:	9419406; Linked HERO ID(s): 9419406, 12162058

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information is reported. The test chemical was identified by name and CASRN. The source, lot, catalogue number, and purity are provided in a supplemental file by Fur et al. (2014). Other reported information includes test animal details (species, strain, source, age, initial body weights, and parity), animal husbandry details (number per cage, food and water availability, photoperiod, temperature, and humidity), exposure methods, experimental design, endpoint evaluations, and presentation of results.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The authors stated that pregnant dams were randomly assigned to treatment groups on GD14 in a manner that provided each group with similar means and variances in body weight. The method of randomization was not specified.
	Metric 3:	Observational Bias / Blinding Changes	Medium	The paper did not indicate that whether investigators were blinded during outcome assessment. However, the outcome of interest was measured using standard laboratory kits.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Vehicle (laboratory-grade corn oil) and gavage volume were the same in the control and treatment groups. Animals were housed individually. The study did not specify whether measures were taken to reduce the potential for exposure to plasticizers, which could influence study results in a study focused on assessing the potential for endocrine disruption. Municipal drinking water was tested monthly for Pseudomonas and every 4 months for a suite of chemicals including pesticides and heavy metals. However, the materials used to dispense water to animals were not specified and it was not reported whether food was tested for phthalate contamination. Animals were housed in polycarbonate rather than metal cages. The experimental conditions described provided no indication of different practices across treatment groups.
Domain 4: Selective Reporting and Attrition				

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HERO ID:	9419406; Linked HERO ID(s): 9419406, 12162058

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Medium	Quantitative data for the endpoint of interest were provided. Testicular testosterone production data (see supplemental file) shows data from males from only n=2 litters in the 900 mg/kg-day dose group; however, the fetal data file shows three litters at 900 mg/kg-day. It was not specified why data for the last littler were not reported.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	The test substance source, catalog number, lot number, and purity (>99%) were reported (Furr et al. 2014). The test substance was not analytically verified by the performing laboratory. No details of the preparation or storage of the test solutions were provided. Doses were adjusted daily based on dam body weights. The doses were inconsistently reported. For example, the methods note that there was a 400 mg/kg-day group; however, the data tables (fig. 2a) show a 200 and 500 mg/kg-day group in the initial test, and then 7 doses ranging from 100 to 900 mg/kg-day in Harlan SD rats and 4 doses in Charles River SD rats (fig. 2b), and 400 mg/kg-day was not included. The gavage volume (2.5 mL/kg) was appropriate. Concentrations of the test substance in the dosing solutions were not analytically verified.
	Metric 7:	Exposure timing, frequency, and duration	High	Pregnant dams were dosed daily from GD14-GD18. The authors reported this as a critical period of sexual differentiation. This paper was a continuation of a previous publication (Furr et al. 2014) and maintained the same exposure details.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	No concerns regarding the specificity and validity of the protocols and measures were identified. Testosterone production in an ex vivo assay was measured using a commercial radioimmunoassay kit according to the manufacturer's protocols. Samples were incubated individually for 3 hours. Measurements were collected from 1 testis/male from 3 males/litter from 3-4 litters for most test groups. Based on the raw data files, data for the highest exposure group (900 mg/kg-day) were derived from 3 males/litter for n = 2 litters, which is of some concern, although the sample sizes in the other treatment groups were larger. This laboratory has validated that n=3 litters is a sufficient sample size for this assay (Furr et al. 2014 [2510906]).
	Metric 9:	Results presentation	High	Results for testosterone production are shown in Figure 2. The figure does not specify the sample size and is reported as a % of control so lacks measures of variance. However, raw data are available in the supplemental files. There are no notable concerns about the way the results are analyzed.

Additional Comments: Only fetal testosterone was evaluated for data quality.

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Chemical:	Diisobutyl Phthalate- Parent compound
HERO ID:	9419406; Linked HERO ID(s): 9419406, 12162058

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

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Health Outcome(s) and Reported Health Effect(s):	Fetal testosterone production ex vivo
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD14-GD18)
Species:	Rat-Other (Harlan Sprague Dawley)-Female
Chemical:	Diisobutyl Phthalate- Parent compound
HERO ID:	9419406; Linked HERO ID(s): 9419406, 12162058

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information is reported. The test chemical was identified by name and CASRN. The source, lot, catalogue number, and purity are provided in a supplemental file by Fur et al. (2014). Other reported information includes test animal details (species, strain, source, age, initial body weights, and parity), animal husbandry details (number per cage, food and water availability, photoperiod, temperature, and humidity), exposure methods, experimental design, endpoint evaluations, and presentation of results.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The authors stated that pregnant dams were randomly assigned to treatment groups on GD14 in a manner that provided each group with similar means and variances in body weight. The method of randomization was not specified.
	Metric 3:	Observational Bias / Blinding Changes	Medium	The paper did not indicate that whether investigators were blinded during outcome assessment. However, the outcome of interest was measured using standard laboratory kits.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Vehicle (laboratory-grade corn oil) and gavage volume were the same in the control and treatment groups. Animals were housed individually. The study did not specify whether measures were taken to reduce the potential for exposure to plasticizers, which could influence study results in a study focused on assessing the potential for endocrine disruption. Municipal drinking water was tested monthly for Pseudomonas and every 4 months for a suite of chemicals including pesticides and heavy metals. However, the materials used to dispense water to animals were not specified and it was not reported whether food was tested for phthalate contamination. Animals were housed in polycarbonate rather than metal cages. The experimental conditions described provided no indication of different practices across treatment groups.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Medium	Quantitative data for the endpoint of interest were provided. Testicular testosterone production data (see supplemental file) shows data from males from only n=2 litters in the 900 mg/kg-day dose group; however, the fetal data file shows three litters at 900 mg/kg-day. It was not specified why data for the last littler were not reported.

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HERO ID:	9419406; Linked HERO ID(s): 9419406, 12162058

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	The test substance source, catalog number, lot number, and purity (>99%) were reported (Furr et al. 2014). The test substance was not analytically verified by the performing laboratory. No details of the preparation or storage of the test solutions were provided. Doses were adjusted daily based on dam body weights. The doses were inconsistently reported. For example, the methods note that there was a 400 mg/kg-day group; however, the data tables (fig. 2a) show a 200 and 500 mg/kg-day group in the initial test, and then 7 doses ranging from 100 to 900 mg/kg-day in Harlan SD rats and 4 doses in Charles River SD rats (fig. 2b), and 400 mg/kg-day was not included. The gavage volume (2.5 mL/kg) was appropriate. Concentrations of the test substance in the dosing solutions were not analytically verified.
	Metric 7:	Exposure timing, frequency, and duration	High	Pregnant dams were dosed daily from GD14-GD18. The authors reported this as a critical period of sexual differentiation. This paper was a continuation of a previous publication (Furr et al. 2014) and maintained the same exposure details.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	No concerns regarding the specificity and validity of the protocols and measures were identified. Testosterone production in an ex vivo assay was measured using a commercial radioimmunoassay kit according to the manufacturer's protocols. Samples were incubated individually for 3 hours. Measurements were collected from 1 testis/male from 3 males/litter from 3-4 litters for most test groups. Based on the raw data files, data for the highest exposure group (900 mg/kg-day) were derived from 3 males/litter for n = 2 litters, which is of some concern, although the sample sizes in the other treatment groups were larger. This laboratory has validated that n=3 litters is a sufficient sample size for this assay (Furr et al. 2014 [2510906]).
	Metric 9:	Results presentation	Medium	Results for testosterone production are shown in Figure 2. The figure does not specify the sample size and is reported as a % of control so no measures of variance are included. Raw data for the Harlan SD rats are not included in the supplemental files. There are no notable concerns about the way the results are analyzed and statistical significance is specified.

Additional Comments: None

Overall Quality Determination Medium

Study Citation:	Hannas, B. R., Lambright, C. S., Furr, J., Howdeshell, K. L., Wilson, V. S., Gray, L. E. (2011). Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following in utero exposure to diethylhexyl phthalate, diisobutyl phthalate, diisoheptyl phthalate, and diisononyl phthalate. Toxicological Sciences 123(1):206-216.
Health Outcome(s) and Reported Health Effect(s):	Male Reproductive - testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 14-18)
Species:	Rat-Other (Sprague-Dawley- Harlan)-Female
Chemical:	Diisobutyl Phthalate- Parent compound
HERO ID:	788239

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	Good. Important information is provided for test animals, exposure methods, experimental design, endpoint evaluations, and the presentation of results.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	Adequate. Authors stated that dams were weight ranked and assigned to dose groups to minimize differences in means and variance among treatment groups. It is not clear whether this was done randomly, but this description indicates that normalization procedures were performed to balance important variables across groups.
	Metric 3:	Observational Bias / Blinding Changes	Medium	All outcomes: Adequate. The paper did not indicate that whether investigators were blinded during outcome assessment. However, via personal correspondence, authors indicated that fetal dissections were performed by investigators that were unaware of the treatment group. Potential concern for bias was mitigated because all outcomes reported in this study are relatively objective measurements.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	High	Good. Vehicle (corn oil) and gavage volume were the same in control and treatment groups. The experimental conditions described provided no indication of different practices across treatment groups.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	Good. All endpoints described in methods were reported qualitatively or quantitatively. Methods state that there were n=3 litters per DIBP dose group. All appear to be accounted for in the T production data. The text states that there was no mortality, overt toxicity, or reduced maternal body weight or reduced litter size at any of the tested doses, indicating no attrition for other endpoints.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	Adequate. Source of DIBP was reported (Sigma-Aldrich; purity not reported). There was no indication that authors independently verified the concentration or stability of the test chemical. Dams were dosed daily by oral gavage between 8-10am each day. It is not reported whether doses were adjusted daily based on maternal body weight, but this is inferred based on other publications by this laboratory.

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Health Outcome(s) and Reported Health Effect(s):	Male Reproductive - testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 14-18)
Species:	Rat-Other (Sprague-Dawley- Harlan)-Female
Chemical:	Diisobutyl Phthalate- Parent compound
HERO ID:	788239

Domain	Metric		Rating	Comments
	Metric 7:	Exposure timing, frequency, and duration	High	Testosterone: Good. Pregnant dams were dosed daily with DIBP from GD 14-18, which coincides with the critical window of male sexual differentiation (Dent et al. 2015 [3452649]; Scott et al. 2009 [673313]).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Testosterone: Good. No concerns regarding the specificity and validity of the protocols and measures were identified. Testosterone production in an ex vivo assay was measured using a commercial radioimmunoassay kit according to the manufacturer's protocols. One testis each was dissected from the first 3 male fetuses/litter.The remaining testes were pooled to evaluate expression of insl3, StAR, and Cyp11a. It is not clear whether the individual testes used in the testosterone assay were left or right, so differential/bilateral effects are not evaluated. Sample size is small (n=3 dams/dose group), but was validated by the authors to have sufficient statistical power to evaluate changes in fetal testosterone production, although authors stated that changes less than 20-25% may not be consistently detected (see Furr et al. 2014 [2510906]).
	Metric 9:	Results presentation	High	Testosterone: Good. There are no notable concerns about the way the results are analyzed or presented.

Additional Comments: Testosterone: High confidence. This study was well-designed to evaluate effects on fetal testicular testosterone. The sample size was small, but was validated by authors to have sufficient statistical power for this analysis. Evidence was presented clearly and transparently. Results are supplemented by gene expression data.

Overall Quality Determination — High

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental: Developmental -litter size; fetal mortality; Nutritional/Metabolic: Maternal body weight and body weight gain; Clinical signs: Overt toxicity (results reported for DINP and DIBP only);
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 14-18)
Species:	Rat-Other (Sprague-Dawley- Harlan)-Female
Chemical:	Diisobutyl Phthalate- Parent compound
HERO ID:	788239

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	Good. Important information is provided for test animals, exposure methods, experimental design, endpoint evaluations, and the presentation of results.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	Adequate. Authors stated that dams were weight ranked and assigned to dose groups to minimize differences in means and variance among treatment groups. It is not clear whether this was done randomly, but this description indicates that normalization procedures were performed to balance important variables across groups.
	Metric 3:	Observational Bias / Blinding Changes	Medium	All outcomes: Adequate. The paper did not indicate that whether investigators were blinded during outcome assessment. However, via personal correspondence, authors indicated that fetal dissections were performed by investigators that were unaware of the treatment group. Potential concern for bias was mitigated because all outcomes reported in this study are relatively objective measurements.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	High	Good. Vehicle (corn oil) and gavage volume were the same in control and treatment groups. The experimental conditions described provided no indication of different practices across treatment groups.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	Good. All endpoints described in methods were reported qualitatively or quantitatively. Methods state that there were n=3 litters per DIBP dose group. All appear to be accounted for in the T production data. The text states that there was no mortality, overt toxicity, or reduced maternal body weight or reduced litter size at any of the tested doses, indicating no attrition for other endpoints.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	Adequate. Source of DIBP was reported (Sigma-Aldrich; purity not reported). There was no indication that authors independently verified the concentration or stability of the test chemical. Dams were dosed daily by oral gavage between 8-10am each day. It is not reported whether doses were adjusted daily based on maternal body weight, but this is inferred based on other publications by this laboratory.

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental: Developmental -litter size; fetal mortality; Nutritional/Metabolic: Maternal body weight and body weight gain; Clinical signs: Overt toxicity (results reported for DINP and DIBP only);
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Domain	Metric		Rating	Comments
	Metric 7:	Exposure timing, frequency, and duration	Medium	Maternal body weight gain and fetal survival: Adequate. Exposure from GD 14-18 occurs at the end of the critical window of organogenesis and does not include pre-mating or early gestational stages, so may be less sensitive for evaluating maternal effects and effects on fetal survival and growth.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Low	Fetal survival: Deficient. No details are provided on how litter size was calculated and whether it includes both live and dead fetuses. There are also concerns for the sample size; in another publication by this group (Furr et al. 2014 [2510906]), the authors state that n=3 does not have enough statistical power to detect anything other than large changes in fetal survival.; Maternal body weight gain: Deficient. Authors do not correct for gravid uterine weight or report fetal body weights, so maternal toxicity cannot be distinguished from fetal effects. There are also concerns for the sample size; in another publication by this group (Furr et al. 2014 [2510906]), authors state that this sample size (n=3 dams/dose group) is not adequate to consistently detect anything other than rather large alterations of maternal weight gain.
	Metric 9:	Results presentation	Medium	Maternal body weight gain and fetal survival: Adequate. Only qualitative results are reported. No effects were observed, so this is not expected to have a significant impact on the interpretation of results.

Additional Comments: Fetal survival: Low confidence. Experimental details were lacking on this evaluation, and no quantitative data were reported. Sensitivity concerns were raised over the small sample size (which authors stated was inadequate for evaluating anything but rather large changes in fetal survival) and the short exposure window in late gestation (which may be insensitive for detecting effects on survival).; Maternal body weight gain: Low confidence. Body weight was not corrected for gravid uterine weight and fetal body weights were not reported, so maternal effects cannot be distinguished from fetal effects. Sensitivity concerns were raised over the small sample size (which authors stated was inadequate for evaluating anything but rather large changes in maternal body weight) and the short exposure window in late gestation (which may be insensitive for detecting effects on maternal body weight).

Overall Quality Determination — Low