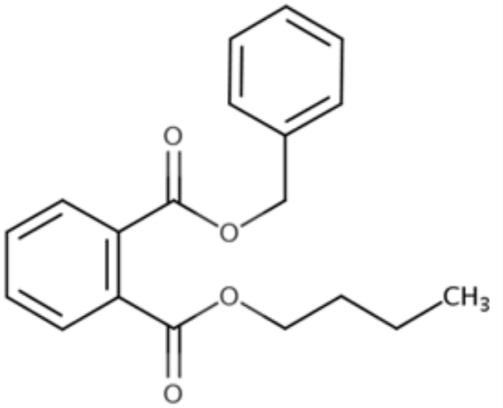
United States
Environmental Protection Agency

July 2025
Office of Chemical Safety and
Pollution Prevention

Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for Butyl benzyl phthalate (BBP) (1,2-Benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester)

Systematic Review Support Document for the Draft Risk Evaluation

CASRN: 85-68-7



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 Butyl benzyl phthalate (BBP) – 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 Butyl benzyl phthalate (BBP) – Systematic Review Protocol*.

Table of Contents

Study Citation:	Ahmad, R., Gautam, A. K., Verma, Y., Sedha, S., Kumar, S. (2014). Effects of in utero di-butyl phthalate and butyl benzyl phthalate exposure on offspring development and male reproduction of rat. Environmental Science and Pollution Research 21(4):3156-3165.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic: Body weight of dams; Clinical signs: Clinical signs of toxicity in dams; Reproductive/Developmental: PND1 (Litter size, sex ratio, and number of live and dead pups), PND 4 (viability index), PND 21 (weaning index). Gross external abnormalities, development landmarks (eye opening, fur formation, pinna detachment, testis descent), AGD; PND 5 and PND 25, pup body weight, PND 75: male offspring organ weights (testes, epididymis, prostate, vas deference, and seminal vesicle, liver, kidney, and adrenal gland), sperm quality parameters (sperm motility, sperm count, testicular spermatid count, daily sperm production, and sperm head shape abnormality), 17β-hydroxy steroidehydrogenase levels in testis, serum testosterone levels.; Mortality: Mortality of dams;
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-F0 - gestation (GD 14- parturition)
Species:	Rat-Albino - [rat]-Female
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	2219796

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Low	Test substance was identified as butyl benzyl phthalate (BBP), purity was not reported. The supplier was reported. Dose levels, route, duration of exposure and frequency were reported. The test species, strain, sex, source of the animals, and age at the start of the experiment were reported. Starting body weights were not reported. Husbandry conditions were not reported. The number of animals treated/group was not clearly disclosed and reported as "a minimum of six rats in each group". Experimental design was adequately reported. Endpoints evaluated are clearly reported and quantitative data are presented. All critical information however the study failed to report important information which impacts the study evaluation.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study states animals were randomly divided into study groups but does not describe the specific procedure used.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints evaluated were either not subjective in nature (e.g., mortality, body weight, organ weights, number of live/dead pups, developmental milestones).
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	Negative control groups included an untreated and a vehicle treated group. A positive control group was included that gave expected results. Husbandry conditions were not reported; therefore, we cannot assess if there may have been differences or conditions that could possibly confound the results. Body weights were decreased, but food and water consumption data were not provided to determine confounding effects. It is unclear if the water provided to the animals was in glass or plastic water bottles. Plastic bottles may leach phthalates into the water, thereby potentially confounding results.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Medium	The study reports that no animals died during treatment. It is unclear exactly how many animals were treated/group (minimum of 6 is reported in methods); this information is not reported in results section either.

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Study Citation:	Ahmad, R., Gautam, A. K., Verma, Y., Sedha, S., Kumar, S. (2014). Effects of in utero di-butyl phthalate and butyl benzyl phthalate exposure on offspring development and male reproduction of rat. Environmental Science and Pollution Research 21(4):3156-3165.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic: Body weight of dams; Clinical signs: Clinical signs of toxicity in dams; Reproductive/Developmental: PND1 (Litter size, sex ratio, and number of live and dead pups), PND 4 (viability index), PND 21 (weaning index). Gross external abnormalities, development landmarks (eye opening, fur formation, pinna detachment, testis descent), AGD; PND 5 and PND 25, pup body weight, PND 75: male offspring organ weights (testes, epididymis, prostate, vas deference, and seminal vesicle, liver, kidney, and adrenal gland), sperm quality parameters (sperm motility, sperm count, testicular spermatid count, daily sperm production, and sperm head shape abnormality), 17β-hydroxy steroidehydrogenase levels in testis, serum testosterone levels.; Mortality: Mortality of dams;
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-F0 - gestation (GD 14- parturition)
Species:	Rat-Albino - [rat]-Female
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	2219796

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	The purity of the test substance is not reported and was not found on the supplier's website (product supplied with a Certificate of Analysis when shipped to customer). Details on preparation and storage of test substance were not provided. It is unclear if test substance was prepared in corn oil daily or one batch was made. Gavage volume was 1 ml/kg based on animal body weight which appropriate (0.1ml/10 g is acceptable).
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure timing, frequency and duration were appropriate for the study's aim; to study effects of test substance during late gestation period on offspring's development and male reproductive system.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Rats were treated orally with 20, 100, and 500 times of reference dose, defined as "an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily oral exposure to the human population, including sensitive subgroups that are likely to be without an appreciable risk of deleterious effects during a lifetime". Outcome assessment methodology was sensitive for the outcomes of interest and were consistently assessed across groups.
	Metric 9:	Results presentation	Low	Statistics was performed comparing the treated groups to untreated control instead the vehicle control group, which would have been more appropriate. It is unclear how many dams were treated/group and how many pups were evaluated/group therefore independent statistics cannot be performed. Also, statistics on offspring were presented as means of individual animals rather than litter means, this has the potential to overestimate the statistical significance of experimental findings.

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Ahmad, R., Verma, Y., Gautam, A., Kumar, S. (2015). Assessment of estrogenic potential of di-n-butyl phthalate and butyl benzyl phthalate in vivo. Toxicology and Industrial Health 31(12):1296-1303.
Health Outcome(s) and Reported Health Effect(s):	Evaluation of estrogenic effects only (uterotrophic assay)
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-3-3-day(s)
Species:	Rat-Not specified-Female
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	1936013

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and some important information were reported. The test material was identified as BBP; the CASRN, and source were reported. Other reported information included details on the test model (species, age, initial body weights, source); animal husbandry (food and water availability, temperature, humidity); exposure details, experimental design, number of animals per group, endpoint evaluation methods, and results for the endpoint of interest. Missing information included the test chemical purity, animal strain, photoperiod, and animals per cage.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The method of animal allocation into study groups was not reported.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not specified; however, the endpoint is a simple measure (uterine and ovary weights).
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	The study included a both a control (not defined, presumed to be untreated) as well as a vehicle (corn oil) control. A positive control, which is required for uterotrophic assays, was also included. All of the controls gave the expected responses. Control animals were maintained in a similar fashion as the treatment groups. However, the study did not provide details on housing or bedding materials, or levels of phytoestrogens in the feed, and did not indicate whether measures were taken to minimize exposure to other plasticizers. These details are important when endocrine disruption is being tested and is specified in OECD 440.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Medium	The study did not report mortality as an endpoint but did specify that there were no abnormal clinical signs. The sample sizes were not provided in the data tables, so it is unknown whether the data were derived from all 6 animals per group. This evaluation considers only estrogenic endpoints and data for this endpoint were reported.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Ahmad, R., Verma, Y., Gautam, A., Kumar, S. (2015). Assessment of estrogenic potential of di-n-butyl phthalate and butyl benzyl phthalate in vivo. Toxicology and Industrial Health 31(12):1296-1303.
Health Outcome(s) and Reported Health Effect(s):	Evaluation of estrogenic effects only (uterotrophic assay)
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-3-3-day(s)
Species:	Rat-Not specified-Female
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	1936013

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	The source of the test material (Allied Chemicals) was reported, but purity was not specified. No certificate of analysis was provided and there is no indication that the performing laboratory independently verified the test material. Limited details of preparation and storage were provided; the stock and working solutions were "prepared in corn oil and stored in brown glass containers at low temperature." Stability and homogeneity were not reported. Animals were treated orally, presumably via gavage, although this was not explicitly stated, and a gavage volume was not reported.
	Metric 7:	Exposure timing, frequency, and duration	Medium	Animals were dosed for 3 days starting on PND20. Completion of dosing by PND21 is preferred (OECD 440), but completion prior to PND25 is acceptable.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Low	No guideline was specified; however, the study was conducted in a manner similar to OECD 440 (with some deviations) using young non-ovariectomized rats (immature method). The rat strain used was not reported and some strains are less responsive to the assay type. It was not specified whether animals were group-housed. The number of animals per group (n=6), was appropriate, but the sample sizes for the outcome of interest were not provided. The study used two dose groups (10 and 100 mg/kg-day) that represented 100 and 1000 times the reference dose (RfD). The study authors justified the dose selection but did not specify whether the highest dose represented the maximum tolerated dose. The methods only included uterine wet weight. OECD 440 specifies that blotted uterine weights should also be measured.
	Metric 9:	Results presentation	Medium	Results for the Uterotrophic assay were reported in figures (bar graphs) showing means ± SE. Statistical significance was shown and determined using Student's t test. The figures did not include sample sizes.

Additional Comments: None

Overall Quality Determination — Low

Study Citation:	Ahmad, R., Verma, Y., Gautam, A., Kumar, S. (2015). Assessment of estrogenic potential of di-n-butyl phthalate and butyl benzyl phthalate in vivo. Toxicology and Industrial Health 31(12):1296-1303.
Health Outcome(s) and Reported Health Effect(s):	Evaluation of estrogenic effects only (uterotrophic assay)
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-3-3-day(s)
Species:	Rat-Not specified-Female
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	1936013

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and some important information were reported. The test material was identified as BBP; the CASRN, and source were reported. Other reported information included details on the test model (species, age, initial body weights, source); animal husbandry (food and water availability, temperature, humidity); exposure details, experimental design, number of animals per group, endpoint evaluation methods, and results for the endpoint of interest. Missing information included the test chemical purity, animal strain, photoperiod, and animals per cage.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The method of animal allocation into study groups was not reported.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not specified; however, the endpoint is a simple measure (uterine and ovary weights).
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	The study included both a control (not defined, presumed to be untreated) as well as a vehicle (corn oil) control. A positive control was also included. All of the controls gave the expected responses. Control animals were maintained in a similar fashion as the treatment groups. However, the study did not provide details on housing or bedding materials, or levels of phytoestrogens in the feed, and did not indicate whether measures were taken to minimize exposure to other plasticizers. These details are important when endocrine disruption potential is being tested.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Low	The study did not report mortality as an endpoint. The sample sizes were not provided in the data tables, so it is unknown whether the data were derived from all 6 animals per group. This evaluation considers only estrogenic endpoints including vaginal opening, estrous cyclicity, and uterine and ovary weights. Results for estrous cyclicity in animals treated with the test material were not reported.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Ahmad, R., Verma, Y., Gautam, A., Kumar, S. (2015). Assessment of estrogenic potential of di-n-butyl phthalate and butyl benzyl phthalate in vivo. Toxicology and Industrial Health 31(12):1296-1303.
Health Outcome(s) and Reported Health Effect(s):	Evaluation of estrogenic effects only (uterotrophic assay)
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-3-3-day(s)
Species:	Rat-Not specified-Female
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	1936013

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	The source of the test material (Allied Chemicals) was reported, but purity was not specified. No certificate of analysis was provided and there is no indication that the performing laboratory independently verified the test material. Limited details of preparation and storage were provided; the stock and working solutions were "prepared in corn oil and stored in brown glass containers at low temperature." Stability and homogeneity were not reported. Animals were treated orally, presumably via gavage, although this was not explicitly stated, and a gavage volume was not reported.
	Metric 7:	Exposure timing, frequency, and duration	Medium	This was a non-guideline female prebuteral assay study. Animals were dosed for 20 days starting on PND21. The selected duration was not justified, but methods were cited to another publication.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	This was a non-guideline 20-day pubertal female assay. The outcome assessment methods were clearly described and were sensitive to the endpoints of interest. The rat strain used was not reported. It was not specified whether animals were group-housed. The number of animals per group (n=6), was appropriate, but the sample sizes for the outcome of interest were not provided. The study used two dose groups; the doses and dose spacing for this experiment were not justified by the study authors and a NOAEL could not be determined.
	Metric 9:	Results presentation	Low	Results were reported for organ weights in a figure (bar graph) showing means ± SE. Statistical significance was shown and determined using Student's t test. The figure did not include sample sizes. Vaginal opening results were qualitatively reported. No results for estrous cyclicity in animals treated with BBP were reported.

Additional Comments: None

Overall Quality Determination — Low

Study Citation:	BIBRA, (1986). Rat liver and lipid effects of representative phthalate esters with EPA acknowlegement letter.
Health Outcome(s) and Reported Health Effect(s):	Testis weight and histology
Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-24-21-day(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	1325511; Linked HERO ID(s): 1325511, 674933, 1325463, 1325547

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	This study is considered Medium for Metric 1. The test substance was identified as along with the source. Purity was not reported. Test animal species, strain, sex, age, initial body weight and source were reported. Husbandry conditions (temperature, humidity, and light cycle) were reported. Animals were individually housed. Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. Food intake and body weights were reported. Endpoint evaluation methods were reported along with quantitative data. All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	Animals were randomly allocated to study groups by use of random number tables. Group weights were checked, and further randomization was made if a significantly unequal distribution was identified.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints evaluated were either not subjective in nature (e.g., body weight, organ weights, clinical chemistry) or consisted of initial histopathology review, and no secondary histopathology review was conducted.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	A negative and positive control group were included, and responses were appropriate. Water was delivered in glass bottles with stainless-steel drinking nozzles eliminating potential confounding from phthalates leaching into water from plastic water bottles. Food and water were analyzed for contamination and authors conclude ”contaminates present in food and water are unlikely to adversely affect the outcome of the study”. There was marked differences in food intake between the groups. Food intake was significantly reduced (>20% difference from control at some points), this could have led to malnourishment in these animals and potentially confounding the results. The data suggest palatability issues with diet since reduction in food intake occurred during the first week.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	All animals were accounted for in results. There is no indication that treated animals were excluded from analysis.

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Study Citation:	BIBRA, (1986). Rat liver and lipid effects of representative phthalate esters with EPA acknowlegement letter.
Health Outcome(s) and Reported Health Effect(s):	Testis weight and histology
Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-24-21-day(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	1325511; Linked HERO ID(s): 1325511, 674933, 1325463, 1325547

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	Purity of test substance was not reported. Diets were analyzed for concentration of test substance (not reported) but were deemed acceptable if concentration was within 5% of target concentration and coefficient of variation between samples was <10%. Preparation of diet with test substance was not fully reported. Stability tests were performed by authors or study sponsor which determined how often diets would be prepared (approximately one week in advance or shorter). Study authors calculated doses based on food intake and body weights.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure timing, frequency and duration were acceptable for the endpoints of interest. Young rats were chosen since they are known to be susceptible to the induction of peroxisomes, which was the primary aim of the study.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	The test animal studied was appropriate and justification for age and strain was provided. The outcome methodology addressed the intended outcomes of interest and assessed consistently across the study groups. Organ weighs and histology (liver, kidney, testis) and serum triglycerides and total cholesterol. The number of animals/group was appropriate (n=5/sex/group).
	Metric 9:	Results presentation	High	Data were reported with means and standard error or incidence of histological findings. Statistical analysis was reported and appropriate. No deaths were reported, all animals were accounted for in the results.

Additional Comments: None

Overall Quality Determination Medium

Study Citation:	BIBRA, (1986). Rat liver and lipid effects of representative phthalate esters with EPA acknowlegement letter.
Health Outcome(s) and Reported Health Effect(s):	Clinical signs of toxicity
Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-24-21-day(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	1325511; Linked HERO ID(s): 1325511, 674933, 1325463, 1325547

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	This study is considered Medium for Metric 1. The test substance was identified as along with the source. Purity was not reported. Test animal species, strain, sex, age, initial body weight and source were reported. Husbandry conditions (temperature, humidity, and light cycle) were reported. Animals were individually housed. Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. Food intake and body weights were reported. Endpoint evaluation methods were reported along with quantitative data. All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	Animals were randomly allocated to study groups by use of random number tables. Group weights were checked, and further randomization was made if a significantly unequal distribution was identified.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported for evaluation of clinical signs.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	A negative and positive control group were included, and responses were appropriate. Water was delivered in glass bottles with stainless-steel drinking nozzles eliminating potential confounding from phthalates leaching into water from plastic water bottles. Food and water were analyzed for contamination and authors conclude "contaminates present in food and water are unlikely to adversely affect the outcome of the study". There was marked differences in food intake between the groups. Food intake was significantly reduced (>20% difference from control), this could have led to malnourishment in these animals and potentially confounding the results.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	All animals were accounted for in results. There is no indication that treated animals were excluded from analysis.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	BIBRA, (1986). Rat liver and lipid effects of representative phthalate esters with EPA acknowlegement letter.
Health Outcome(s) and Reported Health Effect(s):	Clinical signs of toxicity
Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-24-21-day(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	1325511; Linked HERO ID(s): 1325511, 674933, 1325463, 1325547

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	Purity of test substance was not reported. Diets were analyzed for concentration of test substance (not reported) but were deemed acceptable if concentration was within 5% of target concentration. and coefficient of variation between samples was <10%. Preparation of diet with test substance was not fully reported. Stability tests were performed by authors or study sponsor which determined how often diets would be prepared (approximately one week in advance or shorter). Study authors calculated doses based on food intake and body weights.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure timing, frequency and duration were acceptable for the endpoints of interest. Young rats were chosen since they are known to be susceptible to the induction of peroxisomes, which was the primary aim of the study.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	The test animal studied was appropriate and justification for age and strain was provided. The outcome methodology addressed the intended outcomes of interest and assessed consistently across the study groups. The number of animals/group was appropriate (n=5/sex/group).
	Metric 9:	Results presentation	Uninformative	No information was provided on clinical signs.

Additional Comments: None

Overall Quality Determination — Uninformative

Study Citation:	BIBRA, (1986). Rat liver and lipid effects of representative phthalate esters with EPA acknowlegement letter.
Health Outcome(s) and Reported Health Effect(s):	Body weight and food intake
Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-24-21-day(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	1325511; Linked HERO ID(s): 1325511, 674933, 1325463, 1325547

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	This study is considered Medium for Metric 1. The test substance was identified as along with the source. Purity was not reported. Test animal species, strain, sex, age, initial body weight and source were reported. Husbandry conditions (temperature, humidity, and light cycle) were reported. Animals were individually housed. Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. Food intake and body weights were reported. Endpoint evaluation methods were reported along with quantitative data. All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	Animals were randomly allocated to study groups by use of random number tables. Group weights were checked, and further randomization was made if a significantly unequal distribution was identified.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints evaluated were either not subjective in nature (e.g., body weight, organ weights, clinical chemistry) or consisted of initial histopathology review, and no secondary histopathology review was conducted.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Uninformative	A negative and positive control group were included, and responses were appropriate. Water was delivered in glass bottles with stainless-steel drinking nozzles eliminating potential confounding from phthalates leaching into water from plastic water bottles. Food and water were analyzed for contamination and authors conclude "contaminates present in food and water are unlikely to adversely affect the outcome of the study". There was marked differences in food intake between the groups. Food intake was significantly reduced (>20% difference from control at some points), this could have led to malnourishment in these animals and potentially confounding the results. The data suggest palatability issues with diet since reduction in food intake occurred during the first week. Based on the significant decrease in food intake, this would substantially impact body weight outcomes. Therefore, this study was deemed uninformative for body weight outcomes.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	All animals were accounted for in results. There is no indication that treated animals were excluded from analysis.

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Study Citation:	BIBRA, (1986). Rat liver and lipid effects of representative phthalate esters with EPA acknowlegement letter.
Health Outcome(s) and Reported Health Effect(s):	Body weight and food intake
Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-24-21-day(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	1325511; Linked HERO ID(s): 1325511, 674933, 1325463, 1325547

Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Low	Purity of test substance was not reported. Diets were analyzed for concentration of test substance (not reported) but were deemed acceptable if concentration was within 5% of target concentration and coefficient of variation between samples was <10%. Preparation of diet with test substance was not fully reported. Stability tests were performed by authors or study sponsor which determined how often diets would be prepared (approximately one week in advance or shorter). Study authors calculated doses based on food intake and body weights.
	Metric 7: Exposure timing, frequency, and duration	High	The exposure timing, frequency and duration were acceptable for the endpoints of interest. Young rats were chosen since they are known to be susceptible to the induction of peroxisomes, which was the primary aim of the study.
Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	High	The test animal studied was appropriate and justification for age and strain was provided. The outcome methodology addressed the intended outcomes of interest and assessed consistently across the study groups. Organ weighs and histology (liver, kidney, testis) and serum triglycerides and total cholesterol. The number of animals/group was appropriate (n=5/sex/group).
	Metric 9: Results presentation	High	Data were reported with means and standard error. Statistical analysis was reported and appropriate. No deaths were reported, all animals were accounted for in the results.

Additional Comments: None

Overall Quality Determination — Uninformative

Study Citation:	Kwack, S., Kim, K., Kim, H., Lee, B. (2009). Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for risk assessment. Journal of Toxicology and Environmental Health, Part A: Current Issues 72(21-22):1446-1454.
Health Outcome(s) and Reported Health Effect(s):	Mortality
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	697382

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All of the critical information was reported, including test animal species, test substance (name, CAS. No., molecular weight, chemical structure), dose and duration of exposure, route, and results for at least one endpoint. Most of the important information was also reported. The test animal source, strain, age, sex, and starting body weights were reported, along with the general husbandry conditions (temperature, humidity, ventilation, light- dark cycle, diet, water availability), although the number of animals per cage was not reported. The test animal was obtained from a commercial source and were an appropriate animal model for the study. A list of sources for the test substances was provided, although it is unclear which substances came from which sources. The purity/grade were not reported. The frequency of exposure (assumed 1/day, 7 days/week) and number of animals per exposure group (figures show 5-6 animals) were not explicitly described. The assays used to evaluate the outcomes were adequately reported.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The animals were randomly allocated to groups based on their body weight, but the specific methods were not described.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Measures to reduce observational bias were not described, but the potential concern for bias was mitigated because the outcomes was a simple objective measure.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Not enough information was reported to determine confounding. A negative control group was used and similarly gavaged with corn oil alone. A positive control is not required for this type of study. Food consumption was measured and similar across control and treated animals (negative results reported qualitatively). Water intake was not reported. There is no indication that there were differences in husbandry conditions between the control and treatment groups.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Kwack, S., Kim, K., Kim, H., Lee, B. (2009). Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for risk assessment. Journal of Toxicology and Environmental Health, Part A: Current Issues 72(21-22):1446-1454.
Health Outcome(s) and Reported Health Effect(s):	Mortality
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	697382

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition or health outcomes unrelated to exposure. Urinalysis results were not reported quantitatively, although an incomplete qualitative statement was present (some parameters were changed in some groups, but no indication of the direction or magnitude of the changes). The number of animals per group was not defined in the methods, although most tables showed n=6. However, the body weight graph stated that the data represented 5 to 6 animals, and it is not clear why some of the animals were missing or which groups had 5 or 6 animals.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	The test substance was identified definitively (name, CAS No., structure). A list of sources was provided, although it is unclear which substance came from which source. The purity and/or grade of test substance were not reported, and there is no indication that the purity was tested. No information was reported on the preparation or storage of the test substance. The dose was reported, but no mention of analytical verification. The route and method of exposure were reported and appropriate for the test substance, but the test volume was not reported.
	Metric 7:	Exposure timing, frequency, and duration	Low	Details of the exposure administration were incompletely reported. There is no information on the timing of the dosing, and the frequency of dosing is not explicitly stated (assuming 1x/day, 7 days/week). There is not enough information to determine if the exposures were administered consistently between treatment groups.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	Only a single dose was tested, and the concentration selection was not justified. The test animal was obtained from a commercial source and were appropriate for the study. The animal numbers per group were not reported, although most tables suggested that there were 5-6 males in each group. The outcome assessment protocols were reported, although there is not enough information to determine if they were evaluated consistently, such as time of day. The outcome methodology addressed the intended outcome.
	Metric 9:	Results presentation	Medium	Data were presented qualitatively (no animals died), and statistical analysis not required.

Additional Comments: None

Overall Quality Determination — Low

Study Citation:	Kwack, S., Kim, K., Kim, H., Lee, B. (2009). Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for risk assessment. Journal of Toxicology and Environmental Health, Part A: Current Issues 72(21-22):1446-1454.
Health Outcome(s) and Reported Health Effect(s):	Body weight, food consumption
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	697382

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All of the critical information was reported, including test animal species, test substance (name, CAS. No., molecular weight, chemical structure), dose and duration of exposure, route, and results for at least one endpoint. Most of the important information was also reported. The test animal source, strain, age, sex, and starting body weights were reported, along with the general husbandry conditions (temperature, humidity, ventilation, light- dark cycle, diet, water availability), although the number of animals per cage was not reported. The test animal was obtained from a commercial source and were an appropriate animal model for the study. A list of sources for the test substances was provided, although it is unclear which substances came from which sources. The purity/grade were not reported. The frequency of exposure (assumed 1/day, 7 days/week) and number of animals per exposure group (figures show 5-6 animals) were not explicitly described. The assays used to evaluate the outcomes were adequately reported.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The animals were randomly allocated to groups based on their body weight, but the specific methods were not described.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Measures to reduce observational bias were not described, but the potential concern for bias was mitigated because the outcomes was a simple objective measure.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Not enough information was reported to determine confounding. A negative control group was used and similarly gavaged with corn oil alone. A positive control is not required for this type of study. Food consumption was measured and similar across control and treated animals (negative results reported qualitatively). Water intake was not reported. There is no indication that there were differences in husbandry conditions between the control and treatment groups.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Low	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition or health outcomes unrelated to exposure. Urinalysis results were not reported quantitatively, although an incomplete qualitative statement was present (some parameters were changed in some groups, but no indication of the direction or magnitude of the changes). The number of animals per group was not defined in the methods, although most tables showed n=6. However, the body weight graph stated that the data represented 5 to 6 animals, and it is not clear why some of the animals were missing or which groups had 5 or 6 animals.

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Study Citation:	Kwack, S., Kim, K., Kim, H., Lee, B. (2009). Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for risk assessment. Journal of Toxicology and Environmental Health, Part A: Current Issues 72(21-22):1446-1454.
Health Outcome(s) and Reported Health Effect(s):	Body weight, food consumption
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	697382

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	The test substance was identified definitively (name, CAS No., structure). A list of sources was provided, although it is unclear which substance came from which source. The purity and/or grade of test substance were not reported, and there is no indication that the purity was tested. No information was reported on the preparation or storage of the test substance. The dose was reported, but no mention of analytical verification. The route and method of exposure were reported and appropriate for the test substance, but the test volume was not reported.
	Metric 7:	Exposure timing, frequency, and duration	Low	Details of the exposure administration were incompletely reported. There is no information on the timing of the dosing, and the frequency of dosing is not explicitly stated (assuming 1x/day, 7 days/week). There is not enough information to determine if the exposures were administered consistently between treatment groups.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	Only a single dose was tested, and the concentration selection was not justified. The test animal was obtained from a commercial source and were appropriate for the study. The animal numbers per group were not reported, although most tables suggested that there were 5-6 males in each group. The outcome assessment protocols were reported, although there is not enough information to determine if they were evaluated consistently. The outcome methodology addressed the intended outcome.
	Metric 9:	Results presentation	Medium	Data were presented graphically with the appropriate statistical analysis, although it was difficult to determine the quantitative results.

Additional Comments: None

Overall Quality Determination — Low

Study Citation:	Kwack, S., Kim, K., Kim, H., Lee, B. (2009). Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for risk assessment. Journal of Toxicology and Environmental Health, Part A: Current Issues 72(21-22):1446-1454.
Health Outcome(s) and Reported Health Effect(s):	Clinical signs, endocrine: Clinical signs, adrenal gland weight; Cancer/Carcinogenesis: Heart weight;
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	697382

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All of the critical information was reported, including test animal species, test substance (name, CAS. No., molecular weight, chemical structure), dose and duration of exposure, route, and results for at least one endpoint. Most of the important information was also reported. The test animal source, strain, age, sex, and starting body weights were reported, along with the general husbandry conditions (temperature, humidity, ventilation, light- dark cycle, diet, water availability), although the number of animals per cage was not reported. The test animal was obtained from a commercial source and were an appropriate animal model for the study. A list of sources for the test substances was provided, although it is unclear which substances came from which sources. The purity/grade were not reported. The frequency of exposure (assumed 1/day, 7 days/week) and number of animals per exposure group (figures show 5-6 animals) were not explicitly described. The assays used to evaluate the outcomes were adequately reported.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The animals were randomly allocated to groups based on their body weight, but the specific methods were not described.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Measures to reduce observational bias were not described, but the potential concern for bias was mitigated because the outcomes were based on use of automated/computer-driven systems, standard laboratory kits, or simple objective measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Not enough information was reported to determine confounding. A negative control group was used and similarly gavaged with corn oil alone. A positive control is not required for this type of study. Food consumption was measured and similar across control and treated animals (negative results reported qualitatively). Water intake was not reported. There is no indication that there were differences in husbandry conditions between the control and treatment groups.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Kwack, S., Kim, K., Kim, H., Lee, B. (2009). Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for risk assessment. Journal of Toxicology and Environmental Health, Part A: Current Issues 72(21-22):1446-1454.
Health Outcome(s) and Reported Health Effect(s):	Clinical signs, endocrine: Clinical signs, adrenal gland weight; Cancer/Carcinogenesis: Heart weight;
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	697382

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition or health outcomes unrelated to exposure. Urinalysis results were not reported quantitatively, although an incomplete qualitative statement was present (some parameters were changed in some groups, but no indication of the direction or magnitude of the changes). The number of animals per group was not defined in the methods, although most tables showed n=6. However, the body weight graph stated that the data represented 5 to 6 animals, and it is not clear why some of the animals were missing or which groups had 5 or 6 animals.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	The test substance was identified definitively (name, CAS No., structure). A list of sources was provided, although it is unclear which substance came from which source. The purity and/or grade of test substance were not reported, and there is no indication that the purity was tested. No information was reported on the preparation or storage of the test substance. The dose was reported, but no mention of analytical verification. The route and method of exposure were reported and appropriate for the test substance, but the test volume was not reported.
	Metric 7:	Exposure timing, frequency, and duration	Low	Details of the exposure administration were incompletely reported. There is no information on the timing of the dosing, and the frequency of dosing is not explicitly stated (assuming 1x/day, 7 days/week). There is not enough information to determine if the exposures were administered consistently between treatment groups.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Low	Only a single dose was tested, and the concentration selection was not justified. The test animal was obtained from a commercial source and were appropriate for the study. The animal numbers per group were not reported, although most tables suggested that there were 5-6 males in each group. The outcome assessment protocols were reported, although there is not enough information to determine if they were evaluated consistently. The outcome methodology only partially addressed the outcome of interests as histopathology and functionality were not evaluated.
	Metric 9:	Results presentation	Medium	Data were presented quantitatively along with the appropriate statistical analysis. Urinalysis data was not reported.

Additional Comments: None

Overall Quality Determination — Low

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Study Citation:	Kwack, S., Kim, K., Kim, H., Lee, B. (2009). Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for risk assessment. Journal of Toxicology and Environmental Health, Part A: Current Issues 72(21-22):1446-1454.
Health Outcome(s) and Reported Health Effect(s):	Clinical signs, endocrine: Clinical signs, adrenal gland weight; Cancer/Carcinogenesis: Heart weight;
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	697382

Domain	Metric	Rating	Comments

Study Citation:	Kwack, S., Kim, K., Kim, H., Lee, B. (2009). Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for risk assessment. Journal of Toxicology and Environmental Health, Part A: Current Issues 72(21-22):1446-1454.
Health Outcome(s) and Reported Health Effect(s):	Testis and epididymis weights, sperm count and motility
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	697382

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All of the critical information was reported, including test animal species, test substance (name, CAS. No., molecular weight, chemical structure), dose and duration of exposure, route, and results for at least one endpoint. Most of the important information was also reported. The test animal source, strain, age, sex, and starting body weights were reported, along with the general husbandry conditions (temperature, humidity, ventilation, light- dark cycle, diet, water availability), although the number of animals per cage was not reported. The test animal was obtained from a commercial source and were an appropriate animal model for the study. A list of sources for the test substances was provided, although it is unclear which substances came from which sources. The purity/grade were not reported. The frequency of exposure (assumed 1/day, 7 days/week) and number of animals per exposure group (figures show 5-6 animals) were not explicitly described. The assays used to evaluate the outcomes were adequately reported.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The animals were randomly allocated to groups based on their body weight, but the specific methods were not described.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Measures to reduce observational bias were not described, but the potential concern for bias was mitigated because the outcomes were based on use of automated/computer-driven systems, standard laboratory kits, or simple objective measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Not enough information was reported to determine confounding. A negative control group was used and similarly gavaged with corn oil alone. A positive control is not required for this type of study. Food consumption was measured and similar across control and treated animals (negative results reported qualitatively). Water intake was not reported. There is no indication that there were differences in husbandry conditions between the control and treatment groups.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Kwack, S., Kim, K., Kim, H., Lee, B. (2009). Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for risk assessment. Journal of Toxicology and Environmental Health, Part A: Current Issues 72(21-22):1446-1454.
Health Outcome(s) and Reported Health Effect(s):	Testis and epididymis weights, sperm count and motility
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	697382

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition or health outcomes unrelated to exposure. Urinalysis results were not reported quantitatively, although an incomplete qualitative statement was present (some parameters were changed in some groups, but no indication of the direction or magnitude of the changes). The number of animals per group was not defined in the methods, although most tables showed n=6. However, the body weight graph stated that the data represented 5 to 6 animals, and it is not clear why some of the animals were missing or which groups had 5 or 6 animals.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	The test substance was identified definitively (name, CAS No., structure). A list of sources was provided, although it is unclear which substance came from which source. The purity and/or grade of test substance were not reported, and there is no indication that the purity was tested. No information was reported on the preparation or storage of the test substance. The dose was reported, but no mention of analytical verification. The route and method of exposure were reported and appropriate for the test substance, but the test volume was not reported.
	Metric 7:	Exposure timing, frequency, and duration	Low	Details of the exposure administration were incompletely reported. There is no information on the timing of the dosing, and the frequency of dosing is not explicitly stated (assuming 1x/day, 7 days/week). There is not enough information to determine if the exposures were administered consistently between treatment groups.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	Only a single dose was tested, and the concentration selection was not justified. The test animal was obtained from a commercial source and were appropriate for the study. The animal numbers per group were not reported, although most tables suggested that there were 5-6 males in each group. The outcome assessment protocols were reported, although there is not enough information to determine if they were evaluated consistently. The outcome methodology addressed the intended outcome.
	Metric 9:	Results presentation	High	Data were presented quantitatively along with the appropriate statistical analysis.

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Lee, B. M., Koo, H. J. (2007). Hershberger assay for antiandrogenic effects of phthalates. Journal of Toxicology and Environmental Health, Part A: Current Issues 70(15-16):1365-1370.
Health Outcome(s) and Reported Health Effect(s):	Kidney weight
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-10-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	673292

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	This study is considered Medium for Metric 1. The test substance was reported along with the source. Purity was reported to be ≥98% for DEHP, DBP and BBP; purity not reported for DINP, or DIDP. Test animals species, strain, sex, age, initial body weight and source were reported. Husbandry conditions (temperature, humidity, and light cycle) were reported. Number of animals housed per cage were not reported. Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. Endpoint evaluation methods were reported along with quantitative data. All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	No information on the methods of allocation of animals into test groups was provided. No other methods to control for modifying factors across groups were noted.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints evaluated were either not subjective in nature (e.g., mortality, body weight, organ weights, serum hormone levels).
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Husbandry conditions were reported and similar between groups. Negative and positive control groups were included and responses were appropriate. Food intake was not reported, however body weight was not different between the groups. Animals were housed in polycarbonate cages. Polycarbonate contains BPA, which have been linking to developmental and reproductive health problems. This could potentially confound results, although if control animals were exposed to the same levels, this may not substantially impact interpretation of results. Similarly, it is unclear if glass or plastic water bottles were used. Again plastic bottles could leach phthalates that could confound results.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	Study reported no animals died and there is no indication of health effects (no clinical signs were seen).
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Lee, B. M., Koo, H. J. (2007). Hershberger assay for antiandrogenic effects of phthalates. Journal of Toxicology and Environmental Health, Part A: Current Issues 70(15-16):1365-1370.
Health Outcome(s) and Reported Health Effect(s):	Kidney weight
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-10-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	673292

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	Purity was reported to be ≥98% for DEHP, DBP and BBP; purity not reported for DINP, or DIDP. Source of test substance was reported. Gavage volume was not reported. Preparation and storage of test substance were not fully reported.
	Metric 7:	Exposure timing, frequency, and duration	High	Exposure duration, timing and frequency was consistent with OECD guidelines 441 for Hershberger Bioassay.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Endpoints evaluated were in agreement with OECD guidelines 441 for Hershberger Bioassay.
	Metric 9:	Results presentation	High	Results were fully reported with means +/- SD. Statistics were appropriate.

Additional Comments: None

Overall Quality Determination Medium

Study Citation:	Lee, B. M., Koo, H. J. (2007). Hershberger assay for antiandrogenic effects of phthalates. Journal of Toxicology and Environmental Health, Part A: Current Issues 70(15-16):1365-1370.
Health Outcome(s) and Reported Health Effect(s):	Clinical signs
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-10-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	673292

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	This study is considered Medium for Metric 1. The test substance was reported along with the source. Purity was reported to be ≥98% for DEHP, DBP and BBP; purity not reported for DINP, or DIDP. Test animals species, strain, sex, age, initial body weight and source were reported. Husbandry conditions (temperature, humidity, and light cycle) were reported. Number of animals housed per cage were not reported. Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. Endpoint evaluation methods were reported along with quantitative data. All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	No information on the methods of allocation of animals into test groups was provided. No other methods to control for modifying factors across groups were noted.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported to assess clinical signs of toxicity.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Husbandry conditions were reported and similar between groups. Negative and positive control groups were included and responses were appropriate. Food intake was not reported, however body weight was not different between the groups. Animals were housed in polycarbonate cages. Polycarbonate contains BPA, which have been linking to developmental and reproductive health problems. This could potentially confound results, although if control animals were exposed to the same levels, this may not substantially impact interpretation of results. Similarly, it is unclear if glass or plastic water bottles were used. Again plastic bottles could leach phthalates that could confound results.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	Study reported no animals died and there is no indication of health effects (no clinical signs were seen).
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	Purity was reported to be ≥98% for DEHP, DBP and BBP; purity not reported for DINP, or DIDP. Source of test substance was reported. Gavage volume was not reported. Preparation and storage of test substance were not fully reported.

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Study Citation:	Lee, B. M., Koo, H. J. (2007). Hershberger assay for antiandrogenic effects of phthalates. Journal of Toxicology and Environmental Health, Part A: Current Issues 70(15-16):1365-1370.
Health Outcome(s) and Reported Health Effect(s):	Clinical signs
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-10-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	673292

Domain	Metric		Rating	Comments
	Metric 7:	Exposure timing, frequency, and duration	High	Exposure duration, timing and frequency was consistent with OECD guidelines 441 for Hershberger Bioassay.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Endpoints evaluated were in agreement with OECD guidelines 441 for Hershberger Bioassay.
	Metric 9:	Results presentation	Medium	Clinical signs were reported as negative in text.

Additional Comments: None

Overall Quality Determination Medium

Study Citation:	(CIVO),, TNO (1993). Dietary one-generation reproduction study with butyl benzyl phthalate in rats with cover letter dated 040793.
Health Outcome(s) and Reported Health Effect(s):	Clinical signs: General condition and behavior; Nutritional/Metabolic: Body weight, body weight gain, food consumption; Endocrine system: Histopathology and gross necropsy of the pituitary gland; Hepatic/Liver: Liver weight, histopathology, and gross necropsy; Cardiovascular: Gross necropsy on heart; Renal/Kidney: Gross necropsy on kidneys, urinary bladder, uretrer/urethra; Gastrointestinal: Gross necropsy on stomach; Immune/Hematological: Gross necropsy on renal lymph node; Skin/Connective Tissue: Gross necropsy of skin/subcutaneous;
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (2-weeks)-F0- mating (up to 3 week (exact time not reported))-F0 - gestation (3 weeks)-F0- lactation (3 weeks)-F1- premating-F1- mating-F0- premating (10 weeks)-F0- mating (up to 3 week (exact time not reported))-F1- premating-F1- mating
Species:	Rat-Wistar - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	1359183

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical information is reported (rat, butyl benzyl phthalate identified by name and CASRN, test doses of 0.2, 0.4, and 0.8%, daily oral reproductive exposure via diet, and results of all qualitative and quantitative endpoint). All important information is reported directly in the reference (animal source, animal strain, age, sex, starting body weight, animal husbandry conditions, test substance source and purity, experimental design and endpoint evaluation methods).
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	Authors report that the experimental groups were randomized via computer randomization based on mean body weight.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints evaluated were either not subjective in nature or consisted of clinical signs, gross pathology or histology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	An appropriate negative control group was included, and the response was acceptable. A positive control condition was not required in this study type. Control animals were maintained in a similar fashion as the treatment groups. Authors took precautions to avoid exposure to plasticizers (steel cages, food stored in stainless steel cans, glass bottles for water). Contaminant of stock diet and drinking water were determined throughout the study. The bedding was saw dust and wood shavings; study authors do not report if bedding was tested for contaminants. Husbandry conditions were mostly consistent with the exception of fluctuation in humidity that occurred over a four-month period (ranging from 55% to 85%; with a short spell at 95%). Food intake was reported; there was no indication of palatability issues.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	All animals were accounted for in results. Quantitative data for the endpoint of interest were provided. There is no evidence suggesting attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	(CIVO),, TNO (1993). Dietary one-generation reproduction study with butyl benzyl phthalate in rats with cover letter dated 040793.
Health Outcome(s) and Reported Health Effect(s):	Clinical signs: General condition and behavior; Nutritional/Metabolic: Body weight, body weight gain, food consumption; Endocrine system: Histopathology and gross necropsy of the pituitary gland; Hepatic/Liver: Liver weight, histopathology, and gross necropsy; Cardiovascular: Gross necropsy on heart; Renal/Kidney: Gross necropsy on kidneys, urinary bladder, uretrer/urethra; Gastrointestinal: Gross necropsy on stomach; Immune/Hematological: Gross necropsy on renal lymph node; Skin/Connective Tissue: Gross necropsy of skin/subcutaneous;
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (2-weeks)-F0- mating (up to 3 week (exact time not reported))-F0 - gestation (3 weeks)-F0- lactation (3 weeks)-F1- premating-F1- mating-F0- premating (10 weeks)-F0- mating (up to 3 week (exact time not reported))-F1- premating-F1- mating
Species:	Rat-Wistar - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	1359183

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	Chemical administration and characterization are complete. Test substance source and purity are reported, and analytic verification of the test article is provided. There are no concerns about the composition, stability, or purity of the administered chemical, or the specific methods of administration as the authors tested the homogeneity, stability and content of the test article in the vehicle. There are no concerns about the appropriateness of the method of administration (oral-diet). Food intake and body weights were recorded, and author calculated average dose in mg/kg/day.
	Metric 7:	Exposure timing, frequency, and duration	High	Exposure timing, frequency and duration (10 weeks prior to mating for males and 2 weeks prior to mating for females and continuing through gestation and lactation) agrees with OECD 415 guidelines for this study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	The procedures used by the authors in this study were appropriate, sensitive and valid. The species (Wistar rats) was appropriate for the study. The sample size was slightly below OECD 415 guidelines. Guidelines suggest mating enough animals in order "to yield about 20 pregnant females at or near term". In this study, two groups (0.2% and 0.8%) only had 18 pregnant dams. The timing of endpoint assessment was appropriate for a reproductive study. The outcome assessment methodology was appropriate for all endpoints and, given the information reported, it appears the authors applied their outcome assessment methodology consistently across groups. Three dose groups and a control group were included. A NOAEL and LOAEL were obtained. Doses were selected based on previously reported findings.
	Metric 9:	Results presentation	High	Results are fully reported. Means and SD are provided for continuous data and incidence data is provided for categorical data. Both continuous and categorical data is analyzed in a way that is appropriate. The statistical tests utilized were reported and appropriate.

Additional Comments: None

Overall Quality Determination High

Study Citation:	(CIVO),, TNO (1993). Dietary one-generation reproduction study with butyl benzyl phthalate in rats with cover letter dated 040793.
Health Outcome(s) and Reported Health Effect(s):	F0: number of successful copulations, pregnant females, implantation sites, females surviving delivery, females giving birth to live pups, and females giving birth to stillborn pups, and duration of gestation; histopathology of reproductive organs, including the ovaries, uterus (including cervix), vagina, testes, epididymides, seminal vesicles, prostate, and coagulating glands; gross necropsy on preputial/clitoral gland, testes, uterus, coagulating glands, epididymides, ovaries, prostate, seminal vesicles, vaginaIn offspring: litter size, sex, number of male and female pups, number of pups with external abnormalities, body weight of pups
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (2-weeks)-F0- mating (up to 3 week (exact time not reported))-F0 - gestation (3 weeks)-F0- lactation (3 weeks)-F1- premating-F1- mating-F0- premating (10 weeks)-F0- mating (up to 3 week (exact time not reported))-F1- premating-F1- mating
Species:	Rat-Wistar - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	1359183

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical information is reported (rat, butyl benzyl phthalate identified by name and CASRN, test doses of 0.2, 0.4, and 0.8%, daily oral reproductive exposure via diet, and results of all qualitative and quantitative endpoint). All important information is reported directly in the reference (animal source, animal strain, age, sex, starting body weight, animal husbandry conditions, test substance source and purity, experimental design and endpoint evaluation methods).
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	Authors report that the experimental groups were randomized via computer randomization based on mean body weight.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints evaluated were either not subjective in nature or consisted of clinical signs, gross pathology or histology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	An appropriate negative control group was included, and the response was acceptable. A positive control condition was not required in this study type. Control animals were maintained in a similar fashion as the treatment groups. Authors took precautions to avoid exposure to plasticizers (steel cages, food stored in stainless steel cans, glass bottles for water). Contaminant of stock diet and drinking water were determined throughout the study. The bedding was saw dust and wood shavings; study authors do not report if bedding was tested for contaminants. Husbandry conditions were mostly consistent with the exception of fluctuation in humidity that occurred over a four-month period (ranging from 55% to 85%; with a short spell at 95%). Food intake was reported; there was no indication of palatability issues.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	All animals were accounted for in results. Quantitative data for the endpoint of interest were provided. There is no evidence suggesting attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	(CIVO),, TNO (1993). Dietary one-generation reproduction study with butyl benzyl phthalate in rats with cover letter dated 040793.
Health Outcome(s) and Reported Health Effect(s):	F0: number of successful copulations, pregnant females, implantation sites, females surviving delivery, females giving birth to live pups, and females giving birth to stillborn pups, and duration of gestation; histopathology of reproductive organs, including the ovaries, uterus (including cervix), vagina, testes, epididymides, seminal vesicles, prostate, and coagulating glands; gross necropsy on preputial/clitoral gland, testes, uterus, coagulating glands, epididymides, ovaries, prostate, seminal vesicles, vaginaIn offspring: litter size, sex, number of male and female pups, number of pups with external abnormalities, body weight of pups
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (2-weeks)-F0- mating (up to 3 week (exact time not reported))-F0 - gestation (3 weeks)-F0- lactation (3 weeks)-F1- premating-F1- mating-F0- premating (10 weeks)-F0- mating (up to 3 week (exact time not reported))-F1- premating-F1- mating
Species:	Rat-Wistar - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	1359183

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	Chemical administration and characterization are complete. Test substance source and purity are reported, and analytic verification of the test article is provided. There are no concerns about the composition, stability, or purity of the administered chemical, or the specific methods of administration as the authors tested the homogeneity, stability and content of the test article in the vehicle. There are no concerns about the appropriateness of the method of administration (oral-diet). Food intake and body weights were recorded, and author calculated average dose in mg/kg/day.
	Metric 7:	Exposure timing, frequency, and duration	High	Exposure timing, frequency and duration (10 weeks prior to mating for males and 2 weeks prior to mating for females and continuing through gestation and lactation) agrees with OECD 415 guidelines for this study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	The procedures used by the authors in this study were appropriate, sensitive and valid. The species (Wistar rats) was appropriate for the study. The sample size was slightly below OECD 415 guidelines. Guidelines suggest mating enough animals in order "to yield about 20 pregnant females at or near term". In this study, two groups (0.2% and 0.8%) only had 18 pregnant dams. The timing of endpoint assessment was appropriate for a reproductive study. The outcome assessment methodology was appropriate for all endpoints and, given the information reported, it appears the authors applied their outcome assessment methodology consistently across groups. Three dose groups and a control group were included. A NOAEL and LOAEL were obtained. Doses were selected based on previously reported findings.
	Metric 9:	Results presentation	Medium	Results are fully reported. Means and SD are provided for continuous data and incidence data is provided for categorical data. Both continuous and categorical data is analyzed in a way that is appropriate. The statistical tests utilized were reported. The study does not report if litter was used as statistical unit although individual pup data are reported.

Additional Comments: None

Overall Quality Determination — High

Study Citation:	Aso, S., Ehara, H., Miyata, K., Hosyuyama, S., Shiraishi, K., Umano, T., Minobe, Y. (2005). A two-generation reproductive toxicity study of butyl benzyl phthalate in rats. Journal of Toxicological Sciences 30(Special Issue):S39-S58.
Health Outcome(s) and Reported Health Effect(s):	Mating index, fertility index, gestation index and length, number of implantations, number of pups, hormones, sperm index, sex ratios, reproductive development, body and organ weights, and gross necropsy of the offspring
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (10 weeks)-F0- mating (0-14 days)-F0 - gestation (21-22 days)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1 - gestation (21-22 days)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (10 weeks)-F0- mating (0-14 days)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1- post-natal (3 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	674931

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All of the critical information was reported, including test animal species, test substance, doses and duration of exposure, route, and results for at least one endpoint. Most of the important information was also reported. The test animal source, strain, age at the start of dosing, and sex were provided, although the starting body weights were not reported. Husbandry conditions including temperature, humidity, air ventilation, light/dark cycle, and feed and water availability were reported. The number of animals per cage was somewhat described, but it is not clear if the descriptions apply to each portion of the 2-generation study. The test substance source, purity, and method of administration was also provided. The experimental design was sufficiently detailed, including the frequency of exposure, number of animals per group, and animal ages at each exposure time, although the specific days of exposure are not described. The assays used to measure the intended outcomes were adequately described.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	Animals were allocated to treatment groups using body weight-stratified randomization. F1 parent animals were selected from the F0 litters, with one or two males and females selected at random from each liter.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Measures to reduce observational bias were not described, but the potential concern for bias was mitigated because the outcomes were simple objective measures (e.g., body or organ weight), based on the use of standard laboratory kits, or screening-level evaluations of histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	High	There is no information to suggesting that confounders were present. A negative control group was included and appropriate for the study. Food intake was reported qualitatively, and no significant differences in body weights were observed. Husbandry and treatment conditions were adequate and similar between groups. The F1 generation control animals had a relatively low fertility index (assumed to bed the number of pregnancies following mating, although no explanation is provided) although this wasn't an endpoint that was observed in treated animals.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Aso, S., Ehara, H., Miyata, K., Hosyuyama, S., Shiraishi, K., Umano, T., Minobe, Y. (2005). A two-generation reproductive toxicity study of butyl benzyl phthalate in rats. Journal of Toxicological Sciences 30(Special Issue):S39-S58.
Health Outcome(s) and Reported Health Effect(s):	Mating index, fertility index, gestation index and length, number of implantations, number of pups, hormones, sperm index, sex ratios, reproductive development, body and organ weights, and gross necropsy of the offspring
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (10 weeks)-F0- mating (0-14 days)-F0 - gestation (21-22 days)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1 - gestation (21-22 days)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (10 weeks)-F0- mating (0-14 days)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1- post-natal (3 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	674931

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Medium	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition or health outcomes unrelated to exposure. Most groups had 24 animals/sex, although the groups ranged from 20-24 without explanation. The body weight graphs do not include the number of animals included (assuming all). Some outcomes were only reported for certain groups (control and high exposure group).
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	The test substance identity, source, purity, and lot number were reported. The stability of the preparation was confirmed by analyses (not specified) prior to the beginning and at the end of the study (specific timing not reported). The test substance was dissolved in olive oil, although preparation schedule and storage conditions were not described. Animals received 5ml/kg doses, and different injection syringes were used for the various ages/sizes. Doses were reported in mg/kg, although it is not clear if the doses were adjusted based on body weight changes. The exposure route and method were appropriate for the test substance.
	Metric 7:	Exposure timing, frequency, and duration	Medium	This is a 2-generation reproductive study, and the exposure timing, frequency, and duration are appropriate for the design. F0 animals were exposed daily for 10 weeks prior to mating and throughout mating. Females continued to be exposed throughout gestation and lactation, and F1 offspring began dosing at weaning. Not enough information was provided to determine if the exposures were administered consistently across groups/generations.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	The number and spacing of exposure groups was justified using a range-finding study (data not evaluated). The test animals were either purchased from a commercial source or bred as part of the two-generation study. The sample size is appropriate and match what is outlined in OECD 416. There are no concerns with the sensitivity, specificity, or validity of the protocols used to assess the reproductive and developmental outcomes. The study follows OECD Guidelines 416 for a 2-generation reproductive study and adds additional assessments above the recommendations.
	Metric 9:	Results presentation	High	All of the detailed reproductive and developmental outcomes are presented with the appropriate statistical analyses as needed.

Additional Comments: None

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Study Citation:	Aso, S., Ehara, H., Miyata, K., Hosyuyama, S., Shiraishi, K., Umano, T., Minobe, Y. (2005). A two-generation reproductive toxicity study of butyl benzyl phthalate in rats. Journal of Toxicological Sciences 30(Special Issue):S39-S58.
Health Outcome(s) and Reported Health Effect(s):	Mating index, fertility index, gestation index and length, number of implantations, number of pups, hormones, sperm index, sex ratios, reproductive development, body and organ weights, and gross necropsy of the offspring
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (10 weeks)-F0- mating (0-14 days)-F0 - gestation (21-22 days)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1 - gestation (21-22 days)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (10 weeks)-F0- mating (0-14 days)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1- post-natal (3 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	674931

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

Study Citation:	Aso, S., Ehara, H., Miyata, K., Hosyuyama, S., Shiraishi, K., Umano, T., Minobe, Y. (2005). A two-generation reproductive toxicity study of butyl benzyl phthalate in rats. Journal of Toxicological Sciences 30(Special Issue):S39-S58.
Health Outcome(s) and Reported Health Effect(s):	Body weight, food consumption
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (10 weeks)-F0- mating (0-14 days)-F0 - gestation (21-22 days)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1 - gestation (21-22 days)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (10 weeks)-F0- mating (0-14 days)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1- post-natal (3 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	674931

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All of the critical information was reported, including test animal species, test substance, doses and duration of exposure, route, and results for at least one endpoint. Most of the important information was also reported. The test animal source, strain, age at the start of dosing, and sex were provided, although the starting body weights were not reported. Husbandry conditions including temperature, humidity, air ventilation, light/dark cycle, and feed and water availability were reported. The number of animals per cage was somewhat described, but it is not clear if the descriptions apply to each portion of the 2-generation study. The test substance source, purity, and method of administration was also provided. The experimental design was sufficiently detailed, including the frequency of exposure, number of animals per group, and animal ages at each exposure time, although the specific days of exposure are not described. The assays used to measure the intended outcomes were adequately described.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	Animals were allocated to treatment groups using body weight-stratified randomization. F1 parent animals were selected from the F0 litters, with one or two males and females selected at random from each liter.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Measures to reduce observational bias were not described, but the potential concern for bias was mitigated because the outcomes were simple objective measures (body weight, food consumption).
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	High	There is no information to suggesting that confounders were present. A negative control group was included and appropriate for the study. Food intake was reported qualitatively, and no significant differences in body weights were observed. Husbandry and treatment conditions were adequate and similar between groups.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Medium	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition or health outcomes unrelated to exposure. Most groups had 24 animals/sex, although the groups ranged from 20-24 without explanation. The body weight graphs do not include the number of animals included (assuming all). Some outcomes were only reported for certain groups (control and high exposure group).

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Health Outcome(s) and Reported Health Effect(s):	Body weight, food consumption
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (10 weeks)-F0- mating (0-14 days)-F0 - gestation (21-22 days)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1 - gestation (21-22 days)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (10 weeks)-F0- mating (0-14 days)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1- post-natal (3 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	674931

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	The test substance identity, source, purity, and lot number were reported. The stability of the preparation was confirmed by analyses (not specified) prior to the beginning and at the end of the study (specific timing not reported). The test substance was dissolved in olive oil, although preparation schedule and storage conditions were not described. Animals received 5ml/kg doses, and different injection syringes were used for the various ages/sizes. Doses were reported in mg/kg, although it is not clear if the doses were adjusted based on body weight changes. The exposure route and method were appropriate for the test substance.
	Metric 7:	Exposure timing, frequency, and duration	Medium	This is a 2-generation reproductive study, and the exposure timing, frequency, and duration are appropriate for the design. F0 animals were exposed daily for 10 weeks prior to mating and throughout mating. Females continued to be exposed throughout gestation and lactation, and F1 offspring began dosing at weaning. Not enough information was provided to determine if the exposures were administered consistently across groups/generations.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	The number and spacing of exposure groups was justified using a range-finding study (data not evaluated). The test animals were either purchased from a commercial source or bred as part of the two-generation study. The sample size is appropriate and match what is outlined in OECD 416. There are no concerns with the sensitivity, specificity, or validity of the protocols used to assess body weight changes or food consumption.
	Metric 9:	Results presentation	Medium	Some of the body weight data are presented in graphical form, although statistical comparisons are not provided. Some of the body weight data and the information on food consumption were only presented qualitatively in the text.

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Aso, S., Ehara, H., Miyata, K., Hosyuyama, S., Shiraishi, K., Umano, T., Minobe, Y. (2005). A two-generation reproductive toxicity study of butyl benzyl phthalate in rats. Journal of Toxicological Sciences 30(Special Issue):S39-S58.
Health Outcome(s) and Reported Health Effect(s):	Thyroid: Thyroid weight and histopathology; Hepatic/Liver: Liver weight and histopathology; Renal/Kidney: Kidney weight and histopathology; Neurological/Behavioral: Brain weight and histopathology; Clinical signs, gross necropsy, endocrine organs: Clinical signs, gross necropsy, adrenal weight and histopathology, pituitary weight and histopathology; Immune/Hematological: Spleen weight and histopathology;
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (10 weeks)-F0- mating (0-14 days)-F0 - gestation (21-22 days)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1 - gestation (21-22 days)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (10 weeks)-F0- mating (0-14 days)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1- post-natal (3 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	674931

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All of the critical information was reported, including test animal species, test substance, doses and duration of exposure, route, and results for at least one endpoint. Most of the important information was also reported. The test animal source, strain, age at the start of dosing, and sex were provided, although the starting body weights were not reported. Husbandry conditions including temperature, humidity, air ventilation, light/dark cycle, and feed and water availability were reported. The number of animals per cage was somewhat described, but it is not clear if the descriptions apply to each portion of the 2-generation study. The test substance source, purity, and method of administration was also provided. The experimental design was sufficiently detailed, including the frequency of exposure, number of animals per group, and animal ages at each exposure time, although the specific days of exposure are not described. The assays used to measure the intended outcomes were adequately described.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	Animals were allocated to treatment groups using body weight-stratified randomization. F1 parent animals were selected from the F0 litters, with one or two males and females selected at random from each liter.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Measures to reduce observational bias were not described, but the potential concern for bias was mitigated because the outcomes were simple objective measures (e.g., body or organ weight), based on the use of standard laboratory kits, or screening-level evaluations of histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	High	There is no information to suggesting that confounders were present. A negative control group was included and appropriate for the study. Food intake was reported qualitatively, and no significant differences in body weights were observed. Husbandry and treatment conditions were adequate and similar between groups.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Medium	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition or health outcomes unrelated to exposure. Most groups had 24 animals/sex, although the groups ranged from 20-24 without explanation. The body weight graphs do not include the number of animals included (assuming all). Some outcomes were only reported for certain groups (control and high exposure group).

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Health Outcome(s) and Reported Health Effect(s):	Thyroid: Thyroid weight and histopathology; Hepatic/Liver: Liver weight and histopathology; Renal/Kidney: Kidney weight and histopathology; Neurological/Behavioral: Brain weight and histopathology; Clinical signs, gross necropsy, endocrine organs: Clinical signs, gross necropsy, adrenal weight and histopathology, pituitary weight and histopathology; Immune/Hematological: Spleen weight and histopathology;
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (10 weeks)-F0- mating (0-14 days)-F0 - gestation (21-22 days)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1 - gestation (21-22 days)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (10 weeks)-F0- mating (0-14 days)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1- post-natal (3 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	674931

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	The test substance identity, source, purity, and lot number were reported. The stability of the preparation was confirmed by analyses (not specified) prior to the beginning and at the end of the study (specific timing not reported). The test substance was dissolved in olive oil, although preparation schedule and storage conditions were not described. Animals received 5ml/kg doses, and different injection syringes were used for the various ages/sizes. Doses were reported in mg/kg, although it is not clear if the doses were adjusted based on body weight changes. The exposure route and method were appropriate for the test substance.
	Metric 7:	Exposure timing, frequency, and duration	Medium	This is a 2-generation reproductive study, and the exposure timing, frequency, and duration are appropriate for the design. F0 animals were exposed daily for 10 weeks prior to mating and throughout mating. Females continued to be exposed throughout gestation and lactation, and F1 offspring began dosing at weaning. Not enough information was provided to determine if the exposures were administered consistently across groups/generations.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	The number and spacing of exposure groups was justified using a range-finding study (data not evaluated). The test animals were either purchased from a commercial source or bred as part of the two-generation study. The sample size is appropriate and match what is outlined in OECD 416. There are minor concerns regarding the sensitivity of the assessments for clinical signs and organ weights. These measurements are outlined in OECD 416, but they are not sensitive in determining potential neurological or organ effects other than the reproductive organs (no assessment of function). However, additional assessments of clinical signs or organ-specific toxicity are not required for this type of study.
	Metric 9:	Results presentation	Medium	Clinical signs and gross necropsy results were presented qualitatively in the text. Statistical analysis is not required. Organ weights were reported quantitatively with the appropriate statistical analysis for the F0 and F1 generations. Organ histopathology was not reported for organs other than the reproductive organs. This may be because no other histopathological findings were observed, but this is not specified.

Additional Comments: None

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Study Citation:	Aso, S., Ehara, H., Miyata, K., Hosyuyama, S., Shiraishi, K., Umano, T., Minobe, Y. (2005). A two-generation reproductive toxicity study of butyl benzyl phthalate in rats. Journal of Toxicological Sciences 30(Special Issue):S39-S58.
Health Outcome(s) and Reported Health Effect(s):	Thyroid: Thyroid weight and histopathology; Hepatic/Liver: Liver weight and histopathology; Renal/Kidney: Kidney weight and histopathology; Neurological/Behavioral: Brain weight and histopathology; Clinical signs, gross necropsy, endocrine organs: Clinical signs, gross necropsy, adrenal weight and histopathology, pituitary weight and histopathology; Immune/Hematological: Spleen weight and histopathology;
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (10 weeks)-F0- mating (0-14 days)-F0 - gestation (21-22 days)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1 - gestation (21-22 days)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (10 weeks)-F0- mating (0-14 days)-F1- premating (10 weeks)-F1- mating (0-14 days)-F1- post-natal (3 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	674931

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

Study Citation:	Furr, J. R., Lambright, C. S., Wilson, V. S., Foster, P. M., Gray, L. E., Jr (2014). A short-term in vivo screen using fetal testosterone production, a key event in the phthalate adverse outcome pathway, to predict disruption of sexual differentiation. Toxicological Sciences 140(2):403-424.
Health Outcome(s) and Reported Health Effect(s):	Male Reproductive - testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (GD14- GD18)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	2510906; Linked HERO ID(s): 2510906, 3045543

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. Pregnant rats were randomly assigned to treatment groups on GD 14 in a manner that provided each group with similar means and variances in body weight. The method for randomization is not detailed, 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 (laboratory grade corn oil) and gavage volume were the same in control and treatment groups. Additionally, water was tested monthly for Pseudomonas and every four months for a suite of chemicals, including pesticides and heavy metals. 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	Adequate. All endpoints described in methods were reported qualitatively or quantitatively. Data are complete for all endpoints (generally 3-4 dams per group) except for T production data in Block 2 and 36, which is only shown for 2 animals. The authors do not provide an explanation.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	Adequate. The authors tested several ”blocks” of animals, and the source, purity, and lot # was reported for each block. Chemicals were supplied by Aldrich and RTI were >98% pure in all cases, although it is not clear that the authors independently verified the chemical purity or stability. Dams were weighed and dosed daily with test chemical in laboratory grade corn oil.

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Study Citation:	Furr, J. R., Lambright, C. S., Wilson, V. S., Foster, P. M., Gray, L. E., Jr (2014). A short-term in vivo screen using fetal testosterone production, a key event in the phthalate adverse outcome pathway, to predict disruption of sexual differentiation. Toxicological Sciences 140(2):403-424.
Health Outcome(s) and Reported Health Effect(s):	Male Reproductive - testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (GD14- GD18)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	2510906; Linked HERO ID(s): 2510906, 3045543

Domain		Metric	Rating	Comments
	Metric 7:	Exposure timing, frequency, and duration	High	Testosterone: Good. Pregnant dams were dosed daily with test substance 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 3 male fetuses/litter; it is not clear whether the individual testes 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.
	Metric 9:	Results presentation	High	All outcomes: 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.

Overall Quality Determination High

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:	Butyl benzyl 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	High	Quantitative data for the endpoint of interest were provided and all of the litters were accounted for. There is no evidence suggesting attrition or selective reporting.

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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:	Butyl benzyl phthalate- Parent compound
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, catalogue number, lot number, and purity (>99%) was reported (Furr et al. 2014). The test substance was not analytically verified by the performing laboratory. No details of preparation or storage of the test solutions were provided. The doses were clearly reported and were adjusted daily based on dam body weights. The gavage volume (2.5 mL/kg) was appropriate. Concentrations of the test substance in the dosing solutions was 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	High	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.
	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.

Overall Quality Determination — High

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 (Harlan Sprague Dawley)-Female
Chemical:	Butyl benzyl 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	High	Quantitative data for the endpoint of interest were provided and all of the litters were accounted for. There is no evidence suggesting attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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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 (Harlan Sprague Dawley)-Female
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	9419406; Linked HERO ID(s): 9419406, 12162058

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	The test substance source, catalogue number, lot number, and purity (>99%) was reported (Furr et al. 2014). The test substance was not analytically verified by the performing laboratory. No details of preparation or storage of the test solutions were provided. The doses were clearly reported and were adjusted daily based on dam body weights. The gavage volume (2.5 mL/kg) was appropriate. Concentrations of the test substance in the dosing solutions was 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	High	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.
	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 it lacks measures of variance. Raw data for Harlan SD rats were not included in the supplemental files. There are no notable concerns about the way the results are analyzed.

Additional Comments: None

Overall Quality Determination — High

Study Citation:	Howdeshell, K. L., Wilson, V. S., Furr, J., Lambright, C. R., Rider, C. V., Blystone, C. R., Hotchkiss, A. K., Gray, L. E., Jr (2008). A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicological Sciences 105(1):153-165.
Health Outcome(s) and Reported Health Effect(s):	Male reproductive - testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 8-18)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675206

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	Good. All critical and most important information was reported. Reported information included information on the test substance (name, source, purity), the test model (species, strain, sex, and source, animal husbandry details (animals per cage, photoperiod, temperature, food and water availability), exposure methods, experimental design, endpoint evaluations, and presentation of results.Missing information included the test animal age, initial body weights, parity, and humidity.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	Adequate. Authors stated pregnant dams were assigned to treatment groups on GD 8 in a manner that provided similar mean body weight per treatment group prior to dosing. 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 (laboratory-grade corn oil) and gavage volume were the same in 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. 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 was 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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Study Citation:	Howdeshell, K. L., Wilson, V. S., Furr, J., Lambright, C. R., Rider, C. V., Blystone, C. R., Hotchkiss, A. K., Gray, L. E., Jr (2008). A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicological Sciences 105(1):153-165.
Health Outcome(s) and Reported Health Effect(s):	Male reproductive - testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 8-18)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675206

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Medium	Adequate. All endpoints described in methods were reported qualitatively or quantitatively. All dams/litters are accounted for in the maternal weight gain, litter size, resorptions, and fetal mortality data (Table 2). A small number of dams died or were removed from the study due to dosing errors, as described in the text. The number of fetuses and litters used to determine testicular testosterone production (Table 6) was reported. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	Adequate. Source of chemical was reported (Sigma-Aldrich, who reported a purity of 99%). There was no indication that the authors independently verified the concentration or stability of the test chemical. The vehicle (laboratory grade corn oil) was also purchased from Sigma-Aldrich. Rat dams were weighed daily during the dosing period to administer the dose per kg body weight.
	Metric 7:	Exposure timing, frequency, and duration	High	All outcomes: Good. Pregnant dams were dosed daily with DIBP from GD 8-18. This exposure covers the period of post-implantation embryonic development, including the critical windows of organogenesis and male sexual differentiation.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	Adequate. There are no concerns regarding the specificity and validity of the protocol for measuring testosterone production. Testosterone production in an ex vivo assay was measured using a commercial radioimmunoassay kit according to the manufacturer's protocols. A shorter testes incubation period (2h) was used for BBP, as compared to the 3 hours used for other phthalates tested in the same study. The authors noted that this resulted in lower total levels of testosterone production. Reasoning for the shorter duration was not provided. The methods stated that both testes were dissected and incubated individually. Results were reported from the following sample sizes per dose (fetuses, litters): 0 (27, 9), 100 (12, 4), 300 (15, 5), 600 (6, 2), and 900 (4, 2) mg/kg-day. The litter sample size is particularly small in the 600 and 900 mg/kg-day group (n=2 litters), which is of some concern. This was due to deaths or dosing errors in the remaining two dams. 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	All outcomes: Good. There are no notable concerns about the way the results are analyzed or presented.
Additional Comments:	None			

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Study Citation:	Howdeshell, K. L., Wilson, V. S., Furr, J., Lambright, C. R., Rider, C. V., Blystone, C. R., Hotchkiss, A. K., Gray, L. E., Jr (2008). A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicological Sciences 105(1):153-165.
Health Outcome(s) and Reported Health Effect(s):	Male reproductive - testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 8-18)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675206

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

Study Citation:	Nagao, T., Ohta, R., Marumo, H., Shindo, T., Yoshimura, S., Ono, H. (2000). Effect of butyl benzyl phthalate in Sprague-Dawley rats after gavage administration: A two-generation reproductive study. Reproductive Toxicology 14(6):513-532.
Health Outcome(s) and Reported Health Effect(s):	F0 and F1: Female: estrous cycle, serum levels of prolactin, LH, FSH, TSH, T3, T4 and estradiol; ovary and uterus weight, histology on ovaries, uterus, mammary gland, and vaginaF0 and F1 Male: testes, serum levels of testosterone, LH, FSH, TSH, T3, and T4epididymides, ventral prostate, and serial vesicle weight; histology on testes, epidiymides, prostate, and seminal vesicle with coagulating gland; percentage of motile sperm, progressive motile sperm, and sperm counts.Mating index, fertility index, gestation length, delivery index, Implantation sites, live and dead pups, pup weight, sex ratio, viability, external and internal abnormalities in pups, anogenital distance, developmental milestones, day of vaginal opening, and preputial separation, performance in behavioral and functional test (open-field, water multiple T-maze, and spontaneous motor activity)
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (2 weeks)-F0- mating (2 weeks)-F0 - gestation (3 weeks)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)-F1 - gestation (3 weeks)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (12 weeks)-F0- mating (2 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675335

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	Test substance was identified s butyl benzyl phthalate (BBP), CAS # 85-68-7 (98.0% pure). The supplier was reported. Dose levels were reported (0, 20, 100 or 500 mg/kg/day), route and duration were reported. The test species, strain, sex, source of the animals, age at the start of the experiment, and starting body weight were reported. Husbandry condition (temperature, humidity, light cycle, water and food availability) were reported. Animals were housed individually except during mating, or when delivering or nursing. Experimental design was adequately reported. Endpoints evaluated are clearly reported and quantitative data are presented. All critical information and important information is provided.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	The study does not report how animals were allocated into test groups. No other methods to control for modifying factors across groups were noted.
	Metric 3:	Observational Bias / Blinding Changes	Low	Blinding or other measures to reduce observational bias were not reported. F1 pups underwent a series of evaluations for developmental neural reflexes (righting response, cliff-drop aversion response, negative geotaxis) and behavior and functional tests (open-field activity, water multiple T-maze test, and spontaneous motor activity test). These tests are subjective in nature and animals should have been evaluated blindly. Other endpoints evaluated were not subjective in nature.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study does not report if plastic or glass water bottles were used or the type of container the diluted test substance was stored in. Plastic bottles may leach phthalates into the water or test substance, thereby potentially confounding results. Body weight and food intake were reported. An appropriate negative control group was included. There is no indication of infection or other health issues occurred in the population.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Nagao, T., Ohta, R., Marumo, H., Shindo, T., Yoshimura, S., Ono, H. (2000). Effect of butyl benzyl phthalate in Sprague-Dawley rats after gavage administration: A two-generation reproductive study. Reproductive Toxicology 14(6):513-532.
Health Outcome(s) and Reported Health Effect(s):	F0 and F1: Female: estrous cycle, serum levels of prolactin, LH, FSH, TSH, T3, T4 and estradiol; ovary and uterus weight, histology on ovaries, uterus, mammary gland, and vaginaF0 and F1 Male: testes, serum levels of testosterone, LH, FSH, TSH, T3, and T4epididymides, ventral prostate, and serial vesicle weight; histology on testes, epidiymides, prostate, and seminal vesicle with coagulating gland; percentage of motile sperm, progressive motile sperm, and sperm counts.Mating index, fertility index, gestation length, delivery index, Implantation sites, live and dead pups, pup weight, sex ratio, viability, external and internal abnormalities in pups, anogenital distance, developmental milestones, day of vaginal opening, and preputial separation, performance in behavioral and functional test (open-field, water multiple T-maze, and spontaneous motor activity)
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (2 weeks)-F0- mating (2 weeks)-F0 - gestation (3 weeks)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)-F1 - gestation (3 weeks)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (12 weeks)-F0- mating (2 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675335

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	High	All animals were accounted for, study reports no animals died during treatment. The number of animals examined were reported in result tables.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	The study reports "The stability of BBP was confirmed by analyses prior to the beginning and the end of the study. Formulations were stable for up to 11 days in a cold room in the dark." The study does not provide any details as to how often the test substance was prepared or any storage conditions. Given the study is reporting that the test substance was stable for only 11 days, and no information is provided on preparation and storage, we cannot be certain the animals were given the reported dosage. Gavage volume was not reported.
	Metric 7:	Exposure timing, frequency, and duration	Low	According to OCED guideline 416, P0 generation should be 5-9 weeks old at the start of dosing. Males were 6 weeks and dosed for 12 weeks prior to mating (this allowed on complete spermatogenic cycle to occur). Females were 13 weeks-old when dosing began. Although older than recommended by OECD guidelines, they were dosed for two for two estrous cycles before mating. The frequency and duration were appropriate.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	The number of exposure groups were appropriate and based on preliminary findings. A NOAEL and LOAEL were obtained for reproductive parameters. The number of animals (25/group) was appropriate for this study type. The endpoints evaluated were sensitive to outcome of interest. Outcomes were assessed consistently across study groups.
	Metric 9:	Results presentation	Medium	Most data are fully reported with mean and SD, however some is reported only in text. A significant increase in F1 female spontaneous motor activity occurred at 500 mg/kg/day, however these data are not shown. Negative data are at times reported as such in the text. Given the extensive amount of data collected and limited space for publishing, the study did show all essential data for determining NOAEL and LOAEL. It is not expected that missing data will have a notable impact on the interpretation of the results.

Additional Comments: None

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Study Citation:	Nagao, T., Ohta, R., Marumo, H., Shindo, T., Yoshimura, S., Ono, H. (2000). Effect of butyl benzyl phthalate in Sprague-Dawley rats after gavage administration: A two-generation reproductive study. Reproductive Toxicology 14(6):513-532.
Health Outcome(s) and Reported Health Effect(s):	F0 and F1: Female: estrous cycle, serum levels of prolactin, LH, FSH, TSH, T3, T4 and estradiol; ovary and uterus weight, histology on ovaries, uterus, mammary gland, and vaginaF0 and F1 Male: testes, serum levels of testosterone, LH, FSH, TSH, T3, and T4epididymides, ventral prostate, and serial vesicle weight; histology on testes, epidiymides, prostate, and seminal vesicle with coagulating gland; percentage of motile sperm, progressive motile sperm, and sperm counts.Mating index, fertility index, gestation length, delivery index, Implantation sites, live and dead pups, pup weight, sex ratio, viability, external and internal abnormalities in pups, anogenital distance, developmental milestones, day of vaginal opening, and preputial separation, performance in behavioral and functional test (open-field, water multiple T-maze, and spontaneous motor activity)
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (2 weeks)-F0- mating (2 weeks)-F0 - gestation (3 weeks)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)-F1 - gestation (3 weeks)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (12 weeks)-F0- mating (2 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675335

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

Study Citation:	Nagao, T., Ohta, R., Marumo, H., Shindo, T., Yoshimura, S., Ono, H. (2000). Effect of butyl benzyl phthalate in Sprague-Dawley rats after gavage administration: A two-generation reproductive study. Reproductive Toxicology 14(6):513-532.
Health Outcome(s) and Reported Health Effect(s):	Neurological/Behavioral: Brain weight; Cardiovascular: Heart weight; Lung/Respiratory: Lung weight; Immune/Hematological: Spleen and thymus weight;
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (2 weeks)-F0- mating (2 weeks)-F0 - gestation (3 weeks)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)-F1 - gestation (3 weeks)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (12 weeks)-F0- mating (2 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675335

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	Test substance was identified s butyl benzyl phthalate (BBP), CAS # 85-68-7 (98.0% pure). The supplier was reported. Dose levels were reported (0, 20, 100 or 500 mg/kg/day), route and duration were reported. The test species, strain, sex, source of the animals, age at the start of the experiment, and starting body weight were reported. Husbandry condition (temperature, humidity, light cycle, water and food availability) were reported. Animals were housed individually except during mating, or when delivering or nursing. Experimental design was adequately reported. Endpoints evaluated are clearly reported and quantitative data are presented. All critical information and important information is provided.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	The study does not report how animals were allocated into test groups. No other methods to control for modifying factors across groups were noted.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported., however data were not subjective in nature (organ weight).
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study does not report if plastic or glass water bottles were used or the type of container the diluted test substance was stored in. Plastic bottles may leach phthalates into the water or test substance, thereby potentially confounding results. Body weight and food intake were reported. An appropriate negative control group was included. There is no indication of infection or other health issues occurred in the population.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	All animals were accounted for, study reports no animals died during treatment. The number of animals examined were reported in result tables.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Nagao, T., Ohta, R., Marumo, H., Shindo, T., Yoshimura, S., Ono, H. (2000). Effect of butyl benzyl phthalate in Sprague-Dawley rats after gavage administration: A two-generation reproductive study. Reproductive Toxicology 14(6):513-532.
Health Outcome(s) and Reported Health Effect(s):	Neurological/Behavioral: Brain weight; Cardiovascular: Heart weight; Lung/Respiratory: Lung weight; Immune/Hematological: Spleen and thymus weight;
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (2 weeks)-F0- mating (2 weeks)-F0 - gestation (3 weeks)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)-F1 - gestation (3 weeks)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (12 weeks)-F0- mating (2 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675335

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	The study reports "The stability of BBP was confirmed by analyses prior to the beginning and the end of the study. Formulations were stable for up to 11 days in a cold room in the dark." The study does not provide any details as to how often the test substance was prepared or any storage conditions. Given the study is reporting that the test substance was stable for only 11 days, and no information is provided on preparation and storage, we cannot be certain the animals were given the reported dosage. Gavage volume was not reported.
	Metric 7:	Exposure timing, frequency, and duration	Low	According to OCED guideline 416, P0 generation should be 5-9 weeks old at the start of dosing. Males were 6 weeks and dosed for 12 weeks prior to mating (this allowed on complete spermatogenic cycle to occur). Females were 13 weeks-old when dosing began. Although older than recommended by OECD guidelines, they were dosed for two for two estrous cycles before mating. The frequency and duration were appropriate.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	The number of exposure groups were appropriate and based on preliminary findings. A NOAEL and LOAEL were obtained for reproductive parameters. The number of animals (25/group) was appropriate for this study type. Only organ weights were measured (presented as absolute and relative), histological evaluation was not performed.
	Metric 9:	Results presentation	High	Organ weights are fully reported as absolute and relative with mean and SD. Statistical analysis was appropriate.

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Nagao, T., Ohta, R., Marumo, H., Shindo, T., Yoshimura, S., Ono, H. (2000). Effect of butyl benzyl phthalate in Sprague-Dawley rats after gavage administration: A two-generation reproductive study. Reproductive Toxicology 14(6):513-532.
Health Outcome(s) and Reported Health Effect(s):	Renal/Kidney: Kidney weight and histology; Hepatic/Liver: Liver weight and histology; Mortality: Mortality;
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (2 weeks)-F0- mating (2 weeks)-F0 - gestation (3 weeks)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)-F1 - gestation (3 weeks)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (12 weeks)-F0- mating (2 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675335

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	Test substance was identified s butyl benzyl phthalate (BBP), CAS # 85-68-7 (98.0% pure). The supplier was reported. Dose levels were reported (0, 20, 100 or 500 mg/kg/day), route and duration were reported. The test species, strain, sex, source of the animals, age at the start of the experiment, and starting body weight were reported. Husbandry condition (temperature, humidity, light cycle, water and food availability) were reported. Animals were housed individually except during mating, or when delivering or nursing. Experimental design was adequately reported. Endpoints evaluated are clearly reported and quantitative data are presented. All critical information and important information is provided.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	The study does not report how animals were allocated into test groups. No other methods to control for modifying factors across groups were noted.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints evaluated were either not subjective in nature (e.g., mortality, organ weights) or consisted of initial histopathology review, and no secondary histopathology review was conducted.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study does not report if plastic or glass water bottles were used or the type of container the diluted test substance was stored in. Plastic bottles may leach phthalates into the water or test substance, thereby potentially confounding results. Body weight and food intake were reported. An appropriate negative control group was included. There is no indication of infection or other health issues occurred in the population.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	All animals were accounted for, study reports no animals died during treatment. The number of animals examined were reported in result tables.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Nagao, T., Ohta, R., Marumo, H., Shindo, T., Yoshimura, S., Ono, H. (2000). Effect of butyl benzyl phthalate in Sprague-Dawley rats after gavage administration: A two-generation reproductive study. Reproductive Toxicology 14(6):513-532.
Health Outcome(s) and Reported Health Effect(s):	Renal/Kidney: Kidney weight and histology; Hepatic/Liver: Liver weight and histology; Mortality: Mortality;
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (2 weeks)-F0- mating (2 weeks)-F0 - gestation (3 weeks)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)-F1 - gestation (3 weeks)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (12 weeks)-F0- mating (2 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675335

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	The study reports "The stability of BBP was confirmed by analyses prior to the beginning and the end of the study. Formulations were stable for up to 11 days in a cold room in the dark." The study does not provide any details as to how often the test substance was prepared or any storage conditions. Given the study is reporting that the test substance was stable for only 11 days, and no information is provided on preparation and storage, we cannot be certain the animals were given the reported dosage. Gavage volume was not reported.
	Metric 7:	Exposure timing, frequency, and duration	Low	According to OCED guideline 416, P0 generation should be 5-9 weeks old at the start of dosing. Males were 6 weeks and dosed for 12 weeks prior to mating (this allowed on complete spermatogenic cycle to occur). Females were 13 weeks-old when dosing began. Although older than recommended by OECD guidelines, they were dosed for two for two estrous cycles before mating. The frequency and duration were appropriate.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	The number of exposure groups were appropriate and based on preliminary findings. A NOAEL and LOAEL were obtained for reproductive parameters. The number of animals (25/group) was appropriate for this study type. The endpoints evaluated were sensitive to outcome of interest (organ weight and histology or mortality). Outcomes were assessed consistently across study groups.
	Metric 9:	Results presentation	Medium	Data are fully reported. Organ weights are presented as absolute and relative. Histological findings are reported with incidence and mortality was reported.

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Nagao, T., Ohta, R., Marumo, H., Shindo, T., Yoshimura, S., Ono, H. (2000). Effect of butyl benzyl phthalate in Sprague-Dawley rats after gavage administration: A two-generation reproductive study. Reproductive Toxicology 14(6):513-532.
Health Outcome(s) and Reported Health Effect(s):	Adrenal gland, thyroid gland, and pituitary gland weight; and thyroid, parathyroid and adrenal gland histology
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (2 weeks)-F0- mating (2 weeks)-F0 - gestation (3 weeks)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)-F1 - gestation (3 weeks)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (12 weeks)-F0- mating (2 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675335

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	Test substance was identified s butyl benzyl phthalate (BBP), CAS # 85-68-7 (98.0% pure). The supplier was reported. Dose levels were reported (0, 20, 100 or 500 mg/kg/day), route and duration were reported. The test species, strain, sex, source of the animals, age at the start of the experiment, and starting body weight were reported. Husbandry condition (temperature, humidity, light cycle, water and food availability) were reported. Animals were housed individually except during mating, or when delivering or nursing. Experimental design was adequately reported. Endpoints evaluated are clearly reported and quantitative data are presented. All critical information and important information is provided.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	The study does not report how animals were allocated into test groups. No other methods to control for modifying factors across groups were noted.
	Metric 3:	Observational Bias / Blinding Changes	Medium	This study is considered Medium for Metric 2.2. Blinding or other measures to reduce observational bias were not reported; however, the endpoints evaluated were either not subjective in nature (e.g., mortality, body weight, food intake, organ weights) or consisted of initial histopathology review, and no secondary histopathology review was conducted. Clinical signs of toxicity were also evaluated.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study does not report if plastic or glass water bottles were used or the type of container the diluted test substance was stored in. Plastic bottles may leach phthalates into the water or test substance, thereby potentially confounding results. Body weight and food intake were reported. An appropriate negative control group was included. There is no indication of infection or other health issues occurred in the population.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	All animals were accounted for, study reports no animals died during treatment. The number of animals examined were reported in result tables.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Nagao, T., Ohta, R., Marumo, H., Shindo, T., Yoshimura, S., Ono, H. (2000). Effect of butyl benzyl phthalate in Sprague-Dawley rats after gavage administration: A two-generation reproductive study. Reproductive Toxicology 14(6):513-532.
Health Outcome(s) and Reported Health Effect(s):	Adrenal gland, thyroid gland, and pituitary gland weight; and thyroid, parathyroid and adrenal gland histology
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-2-F0- premating (2 weeks)-F0- mating (2 weeks)-F0 - gestation (3 weeks)-F0- lactation (3 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)-F1 - gestation (3 weeks)-F1- lactation (3 weeks)-F1- post-natal (3 weeks)-F0- premating (12 weeks)-F0- mating (2 weeks)-F1- premating (10 weeks)-F1- mating (2 weeks)
Species:	Rat-Crj: CD(SD) - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675335

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	The study reports "The stability of BBP was confirmed by analyses prior to the beginning and the end of the study. Formulations were stable for up to 11 days in a cold room in the dark." The study does not provide any details as to how often the test substance was prepared or any storage conditions. Given the study is reporting that the test substance was stable for only 11 days, and no information is provided on preparation and storage, we cannot be certain the animals were given the reported dosage. Gavage volume was not reported.
	Metric 7:	Exposure timing, frequency, and duration	Low	According to OCED guideline 416, P0 generation should be 5-9 weeks old at the start of dosing. Males were 6 weeks and dosed for 12 weeks prior to mating (this allowed on complete spermatogenic cycle to occur). Females were 13 weeks-old when dosing began. Although older than recommended by OECD guidelines, they were dosed for two for two estrous cycles before mating. The frequency and duration were appropriate.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	The number of exposure groups were appropriate and based on preliminary findings. A NOAEL and LOAEL were obtained for reproductive parameters. The number of animals (25/group) was appropriate for this study type. The endpoints evaluated were sensitive to outcome of interest (body weight, food intake, clinical signs, organ weight and histology). Outcomes were assessed consistently across study groups.
	Metric 9:	Results presentation	Medium	Terminal body weights were reported with SD. Male body weights are shown throughout the study, but not with SDs. Clinical signs that were positive were presented with incidence data; no other information on clinical signs was reported. Organ weights were reported with SD. Histological observations were presented as negative in text.

Additional Comments: None

Overall Quality Determination Medium

Study Citation:	Tyl, R. W., Myers, C. B., Marr, M. C., Fail, P. A., Seely, J. C., Brine, D. R., Barter, R. A., Butala, J. H. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reproductive Toxicology 18(2):241-264.
Health Outcome(s) and Reported Health Effect(s):	Parental: Estrous cyclicity and normality, necropsy with attention to the reproductive system, reproductive organ weights, ovarian primordial follicle counts (high dose F0 and F1 females), sperm parameters, histopathology of ovaries, vagina, uterus, testis, epididymis, seminal vesicles, prostate, reproductive outcomes (mating, fertility, gestational, pregnancy indices, precoital intervals). Developmental F1 and F2 offspring: Live and dead pups, pup weight, AGD, sex, stillbirth, liver birth, and survival indices, necropsy with focus on the reproductive system, retained nipples (males), acquisition of puberty, reproductive organ weights, and weights of brain, spleen, thymus in weanlings (PND 21)
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (10-weeks)-F0- mating-F0 - gestation-F0- lactation-F1- premating (10-weeks)-F1- mating-F1 - gestation-F1- lactation-F0- premating (10-weeks)-F0- mating-F1- premating (10-weeks)-F1- mating-F1- post-natal (necropsy at the end of female gestation period)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675462

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test material was commercial BBP (CASRN 85-68-7), purity 98.5%, sourced from Solutia. The test species, strain (CD(SD) rats) and source were reported. The animal age, parity, and initial body weights of F0 animals were not specified. Animal husbandry conditions were not reported, although it was specified that all facets were in compliance with OPPTS Heath Effects Test Guidelines, OPPTS 870.3800, and adhered to GLP standards as well as the NRC Guide for the Care and Use of Laboratory Animals. Animals were exposed via the diet. Doses were primarily reported as ppm in the diet, although approximate doses in mg/kg-day were provided. The number of animals per group at each stage, and endpoint evaluation methods were clearly described, and qualitative and/or quantitative results were reported for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	The method of allocation of F0 animals into study groups was not specified. F1 litters were randomly culled to 5 pups/sex on PND4, and 3/sex/litter F1 pups were randomly selected for necropsy. F1 males at females were randomly selected to produce the F2 generation. The method of how the random selection was performed was not specified. The study did not indicate whether F0 animals were normalized for body weight.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, none of the endpoints required blinding because they were either non-subjective nature or were initial histopathology examinations.
Domain 3: Confounding / Variable Control				

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Study Citation:	Tyl, R. W., Myers, C. B., Marr, M. C., Fail, P. A., Seely, J. C., Brine, D. R., Barter, R. A., Butala, J. H. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reproductive Toxicology 18(2):241-264.
Health Outcome(s) and Reported Health Effect(s):	Parental: Estrous cyclicity and normality, necropsy with attention to the reproductive system, reproductive organ weights, ovarian primordial follicle counts (high dose F0 and F1 females), sperm parameters, histopathology of ovaries, vagina, uterus, testis, epididymis, seminal vesicles, prostate, reproductive outcomes (mating, fertility, gestational, pregnancy indices, precoital intervals). Developmental F1 and F2 offspring: Live and dead pups, pup weight, AGD, sex, stillbirth, liver birth, and survival indices, necropsy with focus on the reproductive system, retained nipples (males), acquisition of puberty, reproductive organ weights, and weights of brain, spleen, thymus in weanlings (PND 21)
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (10-weeks)-F0- mating-F0 - gestation-F0- lactation-F1- premating (10-weeks)-F1- mating-F1 - gestation-F1- lactation-F0- premating (10-weeks)-F0- mating-F1- premating (10-weeks)-F1- mating-F1- post-natal (necropsy at the end of female gestation period)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675462

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative concurrent control group prepared in the same manner as the test diets but without adding BBP. The negative control responses were appropriate. The study did not provide quantitative food consumption and body weight data for the F0 generation, only qualitative statements were made. In the F1 generation, there were significant reductions in animal body weights, and feed consumption in F1 males was also significantly reduced at the high dose. The study's authors did not indicate there was an issue with palatability. Water intake and animal husbandry conditions were not reported. The study mentioned that food consumption of dams during the last week of lactation might be confounded by the pups self-feeding. It is unclear whether all groups were impacted. The study authors reported that reduced body weights may have "resulted in or confounded the observed delay in acquisition of vaginal patency and preputial separation, " and that the "delays in the acquisition of puberty in F1 males and females may be due to effects on steroidogenesis (especially for the males), confounded by systemic toxicity in both sexes at 11,250 ppm."
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Medium	The number of deaths was low, and the animals reportedly had no clinical signs of toxicity. There is no evidence of attrition based on the data provided. At a minimum, qualitative statements were made for all outcomes and there was no evidence of selective reporting. Two figures did not specify the sample sizes used to generate the data (Fig. 2 and 3). Space was likely an issue in this peer-reviewed publication, but all of the data were not provided as supplementary files.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Tyl, R. W., Myers, C. B., Marr, M. C., Fail, P. A., Seely, J. C., Brine, D. R., Barter, R. A., Butala, J. H. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reproductive Toxicology 18(2):241-264.
Health Outcome(s) and Reported Health Effect(s):	Parental: Estrous cyclicity and normality, necropsy with attention to the reproductive system, reproductive organ weights, ovarian primordial follicle counts (high dose F0 and F1 females), sperm parameters, histopathology of ovaries, vagina, uterus, testis, epididymis, seminal vesicles, prostate, reproductive outcomes (mating, fertility, gestational, pregnancy indices, precoital intervals). Developmental F1 and F2 offspring: Live and dead pups, pup weight, AGD, sex, stillbirth, liver birth, and survival indices, necropsy with focus on the reproductive system, retained nipples (males), acquisition of puberty, reproductive organ weights, and weights of brain, spleen, thymus in weanlings (PND 21)
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (10-weeks)-F0- mating-F0 - gestation-F0- lactation-F1- premating (10-weeks)-F1- mating-F1 - gestation-F1- lactation-F0- premating (10-weeks)-F0- mating-F1- premating (10-weeks)-F1- mating-F1- post-natal (necropsy at the end of female gestation period)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675462

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	The chemical source (Solutia) and purity (98.5%) were reported. The test article was not independently verified by the performing laboratory and cannot be identified on the source website. The study reported target doses in ppm (750, 3,750, and 11,250 ppm); the study authors justified the selected doses. Details of the diet preparation (including frequency) were provided, and stability testing was performed to verify the dosage concentrations (using GC FID). The measured values were not reported, but the desired feed concentrations were met throughout the study (and were within 90-110% of target). The authors indicated that the diet was mixed homogeneously. The authors did not report actual ingested doses or time-weighted average taking into account body weights and food intake which would likely differ between sexes and across generations. The study reported approximate equivalent doses of 50, 250, and 750 mg/kg-day for the 750, 3,750, and 11,250 ppm groups, respectively, but also noted that the ranges in these groups were 40-50, 180-760, and 590-2330 mg/kg-day. The study authors indicated that the top dose was selected as the "positive control" based on data from a previous study. The body weight and food intake data for F0 animals were not provided precluding the ability to determine actual doses. For F1 animals, these data (showing means ± of both sexes combined) are available as figures and the information could be extracted. However, the study authors did note that pups self-feeding during the last week of lactation likely confounded the food consumption measurements for lactating dams. The dietary route of exposure was appropriate and justified by the study authors. Overall, there is substantial ambiguity regarding the actual doses, and information to determine the exact dosing was only provided for the F1 generation.
	Metric 7:	Exposure timing, frequency, and duration	High	Details of exposure administration were reported, and the exposure timing, frequency, and duration were in compliance with U.S. EPA OPPTS 870.3800.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	The study methodology, including outcome measures followed the U.S. EPA OPPTS 870.3800 guideline. Although several methods were provided in the study text, there were some limitations on details, but the authors indicate that all facets were in compliance with the guideline. There were additional assessments performed by this study that were not required by the guideline. The number of exposure groups and spacing were justified by the authors and were appropriate. Outcome assessments were consistent across groups and sampling was adequate. The test species and strain (CD (SD) rats) were appropriate and susceptible based on a previously published study.

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Study Citation:	Tyl, R. W., Myers, C. B., Marr, M. C., Fail, P. A., Seely, J. C., Brine, D. R., Barter, R. A., Butala, J. H. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reproductive Toxicology 18(2):241-264.
Health Outcome(s) and Reported Health Effect(s):	Parental: Estrous cyclicity and normality, necropsy with attention to the reproductive system, reproductive organ weights, ovarian primordial follicle counts (high dose F0 and F1 females), sperm parameters, histopathology of ovaries, vagina, uterus, testis, epididymis, seminal vesicles, prostate, reproductive outcomes (mating, fertility, gestational, pregnancy indices, precoital intervals). Developmental F1 and F2 offspring: Live and dead pups, pup weight, AGD, sex, stillbirth, liver birth, and survival indices, necropsy with focus on the reproductive system, retained nipples (males), acquisition of puberty, reproductive organ weights, and weights of brain, spleen, thymus in weanlings (PND 21)
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (10-weeks)-F0- mating-F0 - gestation-F0- lactation-F1- premating (10-weeks)-F1- mating-F1 - gestation-F1- lactation-F0- premating (10-weeks)-F0- mating-F1- premating (10-weeks)-F1- mating-F1- post-natal (necropsy at the end of female gestation period)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675462

Domain	Metric		Rating	Comments
	Metric 9:	Results presentation	High	Reproductive outcomes for both F0, F1 and F2 animals were quantitatively reported and presented as means ± SEM. The data was clearly presented by dose group, and the results were discussed in detail. A detailed description of statistical methods was included and the methods were appropriate for the datasets. The litter was used as the experimental unit when appropriate.

Additional Comments: None

Overall Quality Determination Medium

Study Citation:	Tyl, R. W., Myers, C. B., Marr, M. C., Fail, P. A., Seely, J. C., Brine, D. R., Barter, R. A., Butala, J. H. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reproductive Toxicology 18(2):241-264.
Health Outcome(s) and Reported Health Effect(s):	Food consumption and body weights
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (10-weeks)-F0- mating-F0 - gestation-F0- lactation-F1- premating (10-weeks)-F1- mating-F1 - gestation-F1- lactation-F0- premating (10-weeks)-F0- mating-F1- premating (10-weeks)-F1- mating-F1- post-natal (necropsy at the end of female gestation period)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675462

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test material was commercial BBP (CASRN 85-68-7), purity 98.5%, sourced from Solutia. The test species, strain (CD(SD) rats) and source were reported. The animal age, parity, and initial body weights of F0 animals were not specified. Animal husbandry conditions were not reported, although it was specified that all facets were in compliance with OPPTS Heath Effects Test Guidelines, OPPTS 870.3800, and adhered to GLP standards as well as the NRC Guide for the Care and Use of Laboratory Animals. Animals were exposed via the diet. Doses were primarily reported as ppm in the diet, although approximate doses in mg/kg-day were provided. The number of animals per group at each stage, and endpoint evaluation methods were clearly described, and qualitative and/or quantitative results were reported for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	The method of allocation of F0 animals into study groups was not specified. F1 litters were randomly culled to 5 pups/sex on PND4, and 3/sex/litter F1 pups were randomly selected for necropsy. F1 males at females were randomly selected to produce the F2 generation. The method of how the random selection was performed was not specified. The study did not indicate whether F0 animals were normalized for body weight.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, none of the endpoints required blinding because they were either non-subjective nature or were initial histopathology examinations.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative concurrent control group prepared in the same manner as the test diets but without adding BBP. The negative control responses were appropriate. The study did not provide quantitative food consumption and body weight data for the F0 generation, only qualitative statements were made. In the F1 generation, there were significant reductions in animal body weights, and feed consumption in F1 males was also significantly reduced at the high dose. The study's authors did not indicate there was an issue with palatability. Water intake and animal husbandry conditions were not reported. The study mentioned that food consumption of dams during the last week of lactation might be confounded by the pups self-feeding. It is unclear whether all groups were impacted. The study authors reported that reduced body weights may have "resulted in or confounded the observed delay in acquisition of vaginal patency and preputial separation, " and that the "delays in the acquisition of puberty in F1 males and females may be due to effects on steroidogenesis (especially for the males), confounded by systemic toxicity in both sexes at 11,250 ppm."

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Study Citation:	Tyl, R. W., Myers, C. B., Marr, M. C., Fail, P. A., Seely, J. C., Brine, D. R., Barter, R. A., Butala, J. H. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reproductive Toxicology 18(2):241-264.
Health Outcome(s) and Reported Health Effect(s):	Food consumption and body weights
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (10-weeks)-F0- mating-F0 - gestation-F0- lactation-F1- premating (10-weeks)-F1- mating-F1 - gestation-F1- lactation-F0- premating (10-weeks)-F0- mating-F1- premating (10-weeks)-F1- mating-F1- post-natal (necropsy at the end of female gestation period)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675462

Domain	Metric	Rating	Comments
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	The number of deaths was low, and the animals reportedly had no clinical signs of toxicity. There is no evidence of attrition based on the data provided. At a minimum, qualitative statements were made for all outcomes and there was no evidence of selective reporting. Two figures did not specify the sample sizes used to generate the data (Fig. 2 and 3). Space was likely an issue in this peer-reviewed publication, but all of the data were not provided as supplementary files.
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Low	The chemical source (Solutia) and purity (98.5%) were reported. The test article was not independently verified by the performing laboratory and cannot be identified on the source website. The study reported target doses in ppm (750, 3,750, and 11,250 ppm); the study authors justified the selected doses. Details of the diet preparation (including frequency) were provided, and stability testing was performed to verify the dosage concentrations (using GC FID). The measured values were not reported, but the desired feed concentrations were met throughout the study (and were within 90-110% of target). The authors indicated that the diet was mixed homogeneously. The authors did not report actual ingested doses or time-weighted average taking into account body weights and food intake which would likely differ between sexes and across generations. The study reported approximate equivalent doses of 50, 250, and 750 mg/kg-day for the 750, 3,750, and 11,250 ppm groups, respectively, but also noted that the ranges in these groups were 40-50, 180-760, and 590-2330 mg/kg-day. The study authors indicated that the top dose was selected as the ”positive control” based on data from a previous study. The body weight and food intake data for F0 animals were not provided precluding the ability to determine actual doses. For F1 animals, these data (showing means ± of both sexes combined) are available as figures and the information could be extracted. However, the study authors did note that pups self-feeding during the last week of lactation likely confounded the food consumption measurements for lactating dams. The dietary route of exposure was appropriate and justified by the study authors. Overall, there is substantial ambiguity regarding the actual doses, and information to determine the exact dosing was only provided for the F1 generation.
	Metric 7: Exposure timing, frequency, and duration	High	Details of exposure administration were reported, and the exposure timing, frequency, and duration were in compliance with U.S. EPA OPPTS 870.3800.
Domain 6: Outcome Measures and Results Display			

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Study Citation:	Tyl, R. W., Myers, C. B., Marr, M. C., Fail, P. A., Seely, J. C., Brine, D. R., Barter, R. A., Butala, J. H. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reproductive Toxicology 18(2):241-264.
Health Outcome(s) and Reported Health Effect(s):	Food consumption and body weights
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (10-weeks)-F0- mating-F0 - gestation-F0- lactation-F1- premating (10-weeks)-F1- mating-F1 - gestation-F1- lactation-F0- premating (10-weeks)-F0- mating-F1- premating (10-weeks)-F1- mating-F1- post-natal (necropsy at the end of female gestation period)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675462

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	High	The study methodology, including outcome measures followed the U.S. EPA OPPTS 870.3800 guideline. Although several methods were provided in the study text, there were some limitations on details, but the authors indicate that all facets were in compliance with the guideline. There were additional assessments performed by this study that were not required by the guideline. The number of exposure groups and spacing were justified by the authors and were appropriate. Outcome assessments were consistent across groups and sampling was adequate. The test species and strain (CD (SD) rats) were appropriate and susceptible based on a previously published study.
	Metric 9:	Results presentation	Low	Quantitative body weight data and food consumption data were not reported for F0 animals. The results for these endpoints were qualitatively described in the text and effects were observed. The significance is unclear because the text states that body weights "were reduced." However, the methods indicate statistical analysis was performed. Quantitative data for feed consumption (as grams of feed per day or per kg) for F1 adult animals was also not reported, although the intake of BBP (in mg/kg-day) was provided in a figure. F1 body weight data were reported.

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Tyl, R. W., Myers, C. B., Marr, M. C., Fail, P. A., Seely, J. C., Brine, D. R., Barter, R. A., Butala, J. H. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reproductive Toxicology 18(2):241-264.
Health Outcome(s) and Reported Health Effect(s):	Hepatic/Liver: Liver histopathology in parental animals.; Renal/Kidney: Kidney histopathology in parental animals;
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (10-weeks)-F0- mating-F0 - gestation-F0- lactation-F1- premating (10-weeks)-F1- mating-F1 - gestation-F1- lactation-F0- premating (10-weeks)-F0- mating-F1- premating (10-weeks)-F1- mating-F1- post-natal (necropsy at the end of female gestation period)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675462

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test material was commercial BBP (CASRN 85-68-7), purity 98.5%, sourced from Solutia. The test species, strain (CD(SD) rats) and source were reported. The animal age, parity, and initial body weights of F0 animals were not specified. Animal husbandry conditions were not reported, although it was specified that all facets were in compliance with OPPTS Heath Effects Test Guidelines, OPPTS 870.3800, and adhered to GLP standards as well as the NRC Guide for the Care and Use of Laboratory Animals. Animals were exposed via the diet. Doses were primarily reported as ppm in the diet, although approximate doses in mg/kg-day were provided. The number of animals per group at each stage, and endpoint evaluation methods were clearly described, and qualitative and/or quantitative results were reported for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	The method of allocation of F0 animals into study groups was not specified. F1 litters were randomly culled to 5 pups/sex on PND4, and 3/sex/litter F1 pups were randomly selected for necropsy. F1 males at females were randomly selected to produce the F2 generation. The method of how the random selection was performed was not specified. The study did not indicate whether F0 animals were normalized for body weight.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, none of the endpoints required blinding because they were either non-subjective nature or were initial histopathology examinations.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative concurrent control group prepared in the same manner as the test diets but without adding BBP. The negative control responses were appropriate. The study did not provide quantitative food consumption and body weight data for the F0 generation, only qualitative statements were made. In the F1 generation, there were significant reductions in animal body weights, and feed consumption in F1 males was also significantly reduced at the high dose. The study's authors did not indicate there was an issue with palatability. Water intake and animal husbandry conditions were not reported. The study mentioned that food consumption of dams during the last week of lactation might be confounded by the pups self-feeding. It is unclear whether all groups were impacted. The study authors reported that reduced body weights may have "resulted in or confounded the observed delay in acquisition of vaginal patency and preputial separation, " and that the "delays in the acquisition of puberty in F1 males and females may be due to effects on steroidogenesis (especially for the males), confounded by systemic toxicity in both sexes at 11,250 ppm."

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Health Outcome(s) and Reported Health Effect(s):	Hepatic/Liver: Liver histopathology in parental animals.; Renal/Kidney: Kidney histopathology in parental animals;
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (10-weeks)-F0- mating-F0 - gestation-F0- lactation-F1- premating (10-weeks)-F1- mating-F1 - gestation-F1- lactation-F0- premating (10-weeks)-F0- mating-F1- premating (10-weeks)-F1- mating-F1- post-natal (necropsy at the end of female gestation period)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675462

Domain	Metric	Rating	Comments
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	The number of deaths was low, and the animals reportedly had no clinical signs of toxicity. There is no evidence of attrition based on the data provided. At a minimum, qualitative statements were made for all outcomes and there was no evidence of selective reporting. Two figures did not specify the sample sizes used to generate the data (Fig. 2 and 3). Space was likely an issue in this peer-reviewed publication, but all of the data were not provided as supplementary files.
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Low	The chemical source (Solutia) and purity (98.5%) were reported. The test article was not independently verified by the performing laboratory and cannot be identified on the source website. The study reported target doses in ppm (750, 3,750, and 11,250 ppm); the study authors justified the selected doses. Details of the diet preparation (including frequency) were provided, and stability testing was performed to verify the dosage concentrations (using GC FID). The measured values were not reported, but the desired feed concentrations were met throughout the study (and were within 90-110% of target). The authors indicated that the diet was mixed homogeneously. The authors did not report actual ingested doses or time-weighted average taking into account body weights and food intake which would likely differ between sexes and across generations. The study reported approximate equivalent doses of 50, 250, and 750 mg/kg-day for the 750, 3,750, and 11,250 ppm groups, respectively, but also noted that the ranges in these groups were 40-50, 180-760, and 590-2330 mg/kg-day. The study authors indicated that the top dose was selected as the ”positive control” based on data from a previous study. The body weight and food intake data for F0 animals were not provided precluding the ability to determine actual doses. For F1 animals, these data (showing means ± of both sexes combined) are available as figures and the information could be extracted. However, the study authors did note that pups self-feeding during the last week of lactation likely confounded the food consumption measurements for lactating dams. The dietary route of exposure was appropriate and justified by the study authors. Overall, there is substantial ambiguity regarding the actual doses, and information to determine the exact dosing was only provided for the F1 generation.
	Metric 7: Exposure timing, frequency, and duration	High	Details of exposure administration were reported, and the exposure timing, frequency, and duration were in compliance with U.S. EPA OPPTS 870.3800.
Domain 6: Outcome Measures and Results Display			

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Health Outcome(s) and Reported Health Effect(s):	Hepatic/Liver: Liver histopathology in parental animals.; Renal/Kidney: Kidney histopathology in parental animals;
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (10-weeks)-F0- mating-F0 - gestation-F0- lactation-F1- premating (10-weeks)-F1- mating-F1 - gestation-F1- lactation-F0- premating (10-weeks)-F0- mating-F1- premating (10-weeks)-F1- mating-F1- post-natal (necropsy at the end of female gestation period)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675462

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	High	The study methodology, including outcome measures followed the U.S. EPA OPPTS 870.3800 guideline. Although several methods were provided in the study text, there were some limitations on details, but the authors indicate that all facets were in compliance with the guideline. There were additional assessments performed by this study that were not required by the guideline. The number of exposure groups and spacing were justified by the authors and were appropriate. Outcome assessments were consistent across groups and sampling was adequate. The test species and strain (CD (SD) rats) were appropriate and susceptible based on a previously published study.
	Metric 9:	Results presentation	Medium	Some absolute and relative organ weight data were adequately reported as means; a measure of variance was provided, but Table 1 did not specify whether it was SD or SEM. The sample size was provided. The data were statistically analyzed, and the statistical methods were adequately reported. Incidences of microscopic lesions in the liver were provided in a data table. The incidence purportedly included a spectrum of histologic changes generally described as minimal hepatic cytologic alterations. The incidences of each type of lesion were not provided. No histopathological changes for other organs was qualitative described in the text. Raw or individual animal data were not available for independent analysis.

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Tyl, R. W., Myers, C. B., Marr, M. C., Fail, P. A., Seely, J. C., Brine, D. R., Barter, R. A., Butala, J. H. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reproductive Toxicology 18(2):241-264.
Health Outcome(s) and Reported Health Effect(s):	Clinical signs: Unspecified clinical signs of toxicity; Thyroid: Thyroid histopathology in parental animals; Endocrine: Adrenal histopathology in parental animals; Immune/Hematological: Spleen, thymus organ weights and histopathology;
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (10-weeks)-F0- mating-F0 - gestation-F0- lactation-F1- premating (10-weeks)-F1- mating-F1 - gestation-F1- lactation-F0- premating (10-weeks)-F0- mating-F1- premating (10-weeks)-F1- mating-F1- post-natal (necropsy at the end of female gestation period)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675462

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test material was commercial BBP (CASRN 85-68-7), purity 98.5%, sourced from Solutia. The test species, strain (CD(SD) rats) and source were reported. The animal age, parity, and initial body weights of F0 animals were not specified. Animal husbandry conditions were not reported, although it was specified that all facets were in compliance with OPPTS Heath Effects Test Guidelines, OPPTS 870.3800, and adhered to GLP standards as well as the NRC Guide for the Care and Use of Laboratory Animals. Animals were exposed via the diet. Doses were primarily reported as ppm in the diet, although approximate doses in mg/kg-day were provided. The number of animals per group at each stage, and endpoint evaluation methods were clearly described, and qualitative and/or quantitative results were reported for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	The method of allocation of F0 animals into study groups was not specified. F1 litters were randomly culled to 5 pups/sex on PND4, and 3/sex/litter F1 pups were randomly selected for necropsy. F1 males at females were randomly selected to produce the F2 generation. The method of how the random selection was performed was not specified. The study did not indicate whether F0 animals were normalized for body weight.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, none of the endpoints required blinding because they were either non-subjective nature or were initial histopathology examinations. Blinding was not reported for clinical signs.
Domain 3: Confounding / Variable Control				

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Study Citation:	Tyl, R. W., Myers, C. B., Marr, M. C., Fail, P. A., Seely, J. C., Brine, D. R., Barter, R. A., Butala, J. H. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reproductive Toxicology 18(2):241-264.
Health Outcome(s) and Reported Health Effect(s):	Clinical signs: Unspecified clinical signs of toxicity; Thyroid: Thyroid histopathology in parental animals; Endocrine: Adrenal histopathology in parental animals; Immune/Hematological: Spleen, thymus organ weights and histopathology;
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (10-weeks)-F0- mating-F0 - gestation-F0- lactation-F1- premating (10-weeks)-F1- mating-F1 - gestation-F1- lactation-F0- premating (10-weeks)-F0- mating-F1- premating (10-weeks)-F1- mating-F1- post-natal (necropsy at the end of female gestation period)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675462

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative concurrent control group prepared in the same manner as the test diets but without adding BBP. The negative control responses were appropriate. The study did not provide quantitative food consumption and body weight data for the F0 generation, only qualitative statements were made. In the F1 generation, there were significant reductions in animal body weights, and feed consumption in F1 males was also significantly reduced at the high dose. The study's authors did not indicate there was an issue with palatability. Water intake and animal husbandry conditions were not reported. The study mentioned that food consumption of dams during the last week of lactation might be confounded by the pups self-feeding. It is unclear whether all groups were impacted. The study authors reported that reduced body weights may have "resulted in or confounded the observed delay in acquisition of vaginal patency and preputial separation, " and that the "delays in the acquisition of puberty in F1 males and females may be due to effects on steroidogenesis (especially for the males), confounded by systemic toxicity in both sexes at 11,250 ppm."
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Medium	The number of deaths was low, and the animals reportedly had no clinical signs of toxicity. There is no evidence of attrition based on the data provided. At a minimum, qualitative statements were made for all outcomes and there was no evidence of selective reporting. Two figures did not specify the sample sizes used to generate the data (Fig. 2 and 3). Space was likely an issue in this peer-reviewed publication, but all of the data were not provided as supplementary files.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Tyl, R. W., Myers, C. B., Marr, M. C., Fail, P. A., Seely, J. C., Brine, D. R., Barter, R. A., Butala, J. H. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reproductive Toxicology 18(2):241-264.
Health Outcome(s) and Reported Health Effect(s):	Clinical signs: Unspecified clinical signs of toxicity; Thyroid: Thyroid histopathology in parental animals; Endocrine: Adrenal histopathology in parental animals; Immune/Hematological: Spleen, thymus organ weights and histopathology;
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (10-weeks)-F0- mating-F0 - gestation-F0- lactation-F1- premating (10-weeks)-F1- mating-F1 - gestation-F1- lactation-F0- premating (10-weeks)-F0- mating-F1- premating (10-weeks)-F1- mating-F1- post-natal (necropsy at the end of female gestation period)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675462

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	The chemical source (Solutia) and purity (98.5%) were reported. The test article was not independently verified by the performing laboratory and cannot be identified on the source website. The study reported target doses in ppm (750, 3,750, and 11,250 ppm); the study authors justified the selected doses. Details of the diet preparation (including frequency) were provided, and stability testing was performed to verify the dosage concentrations (using GC FID). The measured values were not reported, but the desired feed concentrations were met throughout the study (and were within 90-110% of target). The authors indicated that the diet was mixed homogeneously. The authors did not report actual ingested doses or time-weighted average taking into account body weights and food intake which would likely differ between sexes and across generations. The study reported approximate equivalent doses of 50, 250, and 750 mg/kg-day for the 750, 3,750, and 11,250 ppm groups, respectively, but also noted that the ranges in these groups were 40-50, 180-760, and 590-2330 mg/kg-day. The study authors indicated that the top dose was selected as the "positive control" based on data from a previous study. The body weight and food intake data for F0 animals were not provided precluding the ability to determine actual doses. For F1 animals, these data (showing means ± of both sexes combined) are available as figures and the information could be extracted. However, the study authors did note that pups self-feeding during the last week of lactation likely confounded the food consumption measurements for lactating dams. The dietary route of exposure was appropriate and justified by the study authors. Overall, there is substantial ambiguity regarding the actual doses, and information to determine the exact dosing was only provided for the F1 generation.
	Metric 7:	Exposure timing, frequency, and duration	High	Details of exposure administration were reported, and the exposure timing, frequency, and duration were in compliance with U.S. EPA OPPTS 870.3800.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	The study methodology, including outcome measures followed the U.S. EPA OPPTS 870.3800 guideline. Although several methods were provided in the study text, there were some limitations on details, but the authors indicate that all facets were in compliance with the guideline. There were additional assessments performed by this study that were not required by the guideline. The number of exposure groups and spacing were justified by the authors and were appropriate. Outcome assessments were consistent across groups. Outcomes with no effects were qualitatively reported in the text and the exact sample sizes were not included. Histopathology of these organs was performed on animals from the control and high-dose groups only. The test species and strain (CD (SD) rats) were appropriate and susceptible based on a previously published study.

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Study Citation:	Tyl, R. W., Myers, C. B., Marr, M. C., Fail, P. A., Seely, J. C., Brine, D. R., Barter, R. A., Butala, J. H. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reproductive Toxicology 18(2):241-264.
Health Outcome(s) and Reported Health Effect(s):	Clinical signs: Unspecified clinical signs of toxicity; Thyroid: Thyroid histopathology in parental animals; Endocrine: Adrenal histopathology in parental animals; Immune/Hematological: Spleen, thymus organ weights and histopathology;
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (10-weeks)-F0- mating-F0 - gestation-F0- lactation-F1- premating (10-weeks)-F1- mating-F1 - gestation-F1- lactation-F0- premating (10-weeks)-F0- mating-F1- premating (10-weeks)-F1- mating-F1- post-natal (necropsy at the end of female gestation period)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Butyl benzyl phthalate- Parent compound
HERO ID:	675462

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Data for clinical signs, organ weight relevant to this outcome of interest, and histopathology of these organs without effects were not quantitatively reported; qualitative descriptions were provided for outcomes with no effects.

Additional Comments: None

Overall Quality Determination Medium