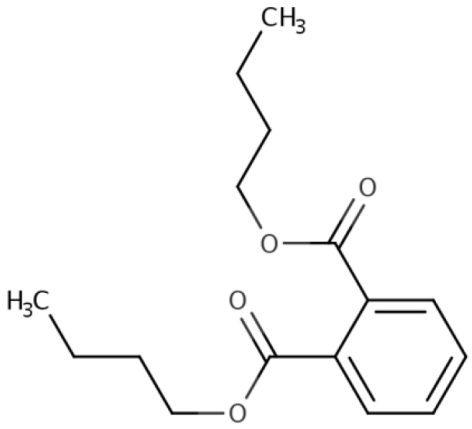
United States
Environmental Protection Agency

May 2025
Office of Chemical Safety and
Pollution Prevention

Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for Dibutyl Phthalate (DBP) (1,2-Benzenedicarboxylic acid, 1,2-dibutyl ester)

Systematic Review Support Document for the Draft Risk Evaluation

CASRN: 84-74-2



May 2025

This supplemental file contains information regarding the data quality evaluation conducted for key references identified by EPA as described in the *Draft Risk Evaluation for Dibutyl Phthalate (DBP) – 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* (referred to hereafter as the '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 Dibutyl Phthalate (DBP) – Systematic Review Protocol*.

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675949	Johnson, K. J., Hensley, J. B., Kelso, M. D., Wallace, D. G., Gaido, K. W. (2007). Mapping gene expression changes in the fetal rat testis following acute dibutyl phthalate exposure defines a complex temporal cascade of responding cell types. Biology of Reproduction 77(6):978-989.	**205**
788312	Johnson, K. J., Mcdowell, E. N., Viereck, M. P., Xia, J. Q. (2011). Species-specific dibutyl phthalate fetal testis endocrine disruption correlates with inhibition of SREBP2-dependent gene expression pathways. Toxicological Sciences 120(2):460-474.	**207**
11785000	Jr, Gray, L. E., Lambright, C. S., Evans, N., Ford, J., Conley, J. M. (2024). Using targeted fetal rat testis genomic and endocrine alterations to predict the effects of a phthalate mixture on the male reproductive tract. Current Research in Toxicology 7:100180.	**209**
1321665	Kuhl, A. J., Ross, S. M., Gaido, K. W. (2007). CCAAT/enhancer binding protein beta, but not steroidogenic factor-1, modulates the phthalate-induced dysregulation of rat fetal testicular steroidogenesis. Endocrinology 148(12):5851-5864.	**212**
61566	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.	**216**
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680063	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.	**246**
676281	Martino-Andrade, A. J., Morais, R. N., Botelho, G. G., Muller, G., Grande, S. W., Carpentieri, G. B., Leao, G. M., Dalsenter, P. R. (2008). Coadministration of active phthalates results in disruption of foetal testicular function in rats. International Journal of Andrology 32(6):704-12.	**332**
1639195	Moody, S., Goh, H., Bielanowicz, A., Rippon, P., Loveland, K. L., Itman, C. (2013). Prepubertal mouse testis growth and maturation and androgen production are acutely sensitive to di-n-butyl phthalate. Endocrinology 154(9):3460-3475.	**334**
673305	Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151.	**336**
673308	Salazar, V., Castillo, C., Ariznavarreta, C., Campón, R., Tresguerres, F., J.A. (2004). Effect of oral intake of dibutyl phthalate on reproductive parameters of Long Evans rats and pre-pubertal development of their offspring. Toxicology 205(1-2):131-137.	**347**
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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-Other (please specify below) (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:	Dibutyl Phthalate- Parent compound
HERO ID:	2219796

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Low	Test substance was identified as di-n-butyl phthalate (DBP), 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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Species:	Rat-Albino - [rat]-Female
Chemical:	Dibutyl 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

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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.
Domain 5: Exposure Methods Sensitivity				

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Domain		Metric	Rating	Comments
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	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.
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Domain 5: Exposure Methods Sensitivity				

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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):	Renal/Kidney-Kidney weight and histology-Reproductive/Developmental-Testis weight and histology-Hepatic/Liver-Liver weight and histology. Serum triglyceride and total cholesterol. Biochemical analysis of liver (cyanide-insensitive palmitoyl-CoA oxidation and protein concentration; microsomal fraction rate of lauric acid 11-hydroxylase and 12-hydroxylase activity) and ultrastructure of liver assessing peroxisome proliferation (TEM)-Mortality-Mortality
Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-24-21-day(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl 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				

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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):	Renal/Kidney-Kidney weight and histology-Reproductive/Developmental-Testis weight and histology-Hepatic/Liver-Liver weight and histology. Serum triglyceride and total cholesterol. Biochemical analysis of liver (cyanide-insensitive palmitoyl-CoA oxidation and protein concentration; microsomal fraction rate of lauric acid 11-hydroxylase and 12-hydroxylase activity) and ultrastructure of liver assessing peroxisome proliferation (TEM)-Mortality-Mortality
Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-24-21-day(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1325511 Linked HERO ID(s): 1325511, 674933, 1325463, 1325547

Domain	Metric		Rating	Comments
	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				
	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):	Other (please specify below) (Clinical signs)-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:	Dibutyl 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):	Other (please specify below) (Clinical signs)-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:	Dibutyl 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):	Nutritional/Metabolic-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:	Dibutyl 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):	Nutritional/Metabolic-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:	Dibutyl 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-Mortality
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl 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-Mortality
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl 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):	Nutritional/Metabolic-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:	Dibutyl 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):	Nutritional/Metabolic-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:	Dibutyl 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):	Other (please specify below) (Clinical signs, endocrine)-Clinical signs, adrenal gland weight-Hepatic/Liver-Liver weight, serum chemistry (cholesterol, triglyceride, total bilirubin, total protein, alkaline phosphatase, glutamate pyruvate, glutamate oxaloacetate transaminase, g-gluamyl transferase)-Renal/Kidney-Kidney weight, serum chemistry (calcium, potassium, sodium, albumin, blood urea nitrogen, creatinine, glucose), urinalysis (occult blood, pH, protein, urobilinogen, glucose, nitrite, bilirubin, ketone bodies, leukocytes, urine specific gravity)-Immune/Hematological-Spleen and thymus weights, hematology (red blood cell count, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, white blood cell count)-Lung/Respiratory-Lung weight-Cancer/Carcinogenesis-Heart weight-Thyroid-Thyroid weight
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl 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):	Other (please specify below) (Clinical signs, endocrine)-Clinical signs, adrenal gland weight-Hepatic/Liver-Liver weight, serum chemistry (cholesterol, triglyceride, total bilirubin, total protein, alkaline phosphatase, glutamate pyruvate, glutamate oxaloacetate transaminase, g-gluamyl transferase)-Renal/Kidney-Kidney weight, serum chemistry (calcium, potassium, sodium, albumin, blood urea nitrogen, creatinine, glucose), urinalysis (occult blood, pH, protein, urobilinogen, glucose, nitrite, bilirubin, ketone bodies, leukocytes, urine specific gravity)-Immune/Hematological-Spleen and thymus weights, hematology (red blood cell count, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, white blood cell count)-Lung/Respiratory-Lung weight-Cancer/Carcinogenesis-Heart weight-Thyroid-Thyroid weight
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl 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.

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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):	Other (please specify below) (Clinical signs, endocrine)-Clinical signs, adrenal gland weight-Hepatic/Liver-Liver weight, serum chemistry (cholesterol, triglyceride, total bilirubin, total protein, alkaline phosphatase, glutamate pyruvate, glutamate oxaloacetate transaminase, g-gluamyl transferase)-Renal/Kidney-Kidney weight, serum chemistry (calcium, potassium, sodium, albumin, blood urea nitrogen, creatinine, glucose), urinalysis (occult blood, pH, protein, urobilinogen, glucose, nitrite, bilirubin, ketone bodies, leukocytes, urine specific gravity)-Immune/Hematological-Spleen and thymus weights, hematology (red blood cell count, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, white blood cell count)-Lung/Respiratory-Lung weight-Cancer/Carcinogenesis-Heart weight-Thyroid-Thyroid weight
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	697382

Domain	Metric	Rating	Comments
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):	Reproductive/Developmental-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:	Dibutyl 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):	Reproductive/Developmental-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:	Dibutyl 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):	Nutritional/Metabolic-Body weight-Hepatic/Liver-Liver weight-Renal/Kidney-Kidney weight-Other (please specify below) (Endocrine)-Adrenal weight-Reproductive/Developmental-The following 5 tissues were weighed: testes, ventral prostates, combined seminal vesicles and coagulating glands, levator ani/bulbocavernosus (LABC), and Cowper's gland.Serum testosterone and luteinizing hormone
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-10-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl 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):	Nutritional/Metabolic-Body weight-Hepatic/Liver-Liver weight-Renal/Kidney-Kidney weight-Other (please specify below) (Endocrine)-Adrenal weight-Reproductive/Developmental-The following 5 tissues were weighed: testes, ventral prostates, combined seminal vesicles and coagulating glands, levator ani/bulbocavernosus (LABC), and Cowper's gland.Serum testosterone and luteinizing hormone
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-10-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl 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):	Other (please specify below) (Clinical signs)-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:	Dibutyl 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):	Other (please specify below) (Clinical signs)-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:	Dibutyl 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:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-14-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the animals and the humidity conditions.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were randomized and then assigned to dose groups, however, they do not indicate how this randomization was done and whether a computer program was used.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received undosed feed. Control responses were appropriate. A positive control group was not included and is not required. Reductions in feed consumption on Week 1 correlated with reduced body weights on Day 14. It is possible that DBP-dosed feed had decreased food palatability among the rats. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed or water was analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	Quantitative or qualitative results were provided for all outcomes described in the methods.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-14-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>99%), and storage conditions of the test substance were reported. The test substance was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. The authors reported the calculated doses (mg/kg-day) in the exposed male and female rats. The uncertainties in the exposure characterization are not expected to substantially impact the interpretation of the results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was a guideline-based dose range-finding study. Dietary exposure was conducted over a period of 14 consecutive days. The exposure timing, frequency, and duration were appropriate for the current study.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	Animals were assessed for mortality. The frequency of observations of rats was not reported. This is not expected to significantly impact the interpretation of the results. The test animals (rats) and sex (males and females) were appropriate for evaluation of the endpoints. The sample size (8 rats/sex/group) was appropriate for the study type. A wide range of doses were tested.
	Metric 9:	Results presentation	High	Study authors qualitatively stated that “during 2 weeks of treatment, no animals died.”

Additional Comments: 12.DBP Dose range-finding study in rats.

Overall Quality Determination — High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-14-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the animals and the humidity conditions.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were randomized and then assigned to dose groups, however, they do not indicate how this randomization was done and whether a computer program was used.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received undosed feed. Control responses were appropriate. A positive control group was not included and is not required. Reductions in feed consumption on Week 1 correlated with reduced body weights on Day 14. It is possible that DBP-dosed feed had decreased food palatability among the rats. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed or water was analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	Quantitative or qualitative results were provided for all outcomes described in the methods.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-14-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>99%), and storage conditions of the test substance were reported. The test substance was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. The authors reported the calculated doses (mg/kg-day) in the exposed male and female rats. The uncertainties in the exposure characterization are not expected to substantially impact the interpretation of the results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was a guideline-based dose range-finding study. Dietary exposure was conducted over a period of 14 consecutive days. The exposure timing, frequency, and duration were appropriate for the current study.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	Test animals were assessed for body weight and feed consumption The frequency of body weight and Food consumption measurements of animals were provided. Test animals were assessed for clinical signs. The frequency of clinical observations was not reported. In addition, it was not stated whether these were cage-side or in depth clinical observations. This is not expected to significantly impact the interpretation of the results. The test animals (rats) and sex (males and females) were appropriate for evaluation of the endpoints. The sample size (8 rats/sex/group) was appropriate for the study type. A wide range of doses were tested.
	Metric 9:	Results presentation	Medium	Quantitative data (mean ± SEM) was provided for body weight, body weight gain, and feed consumption. Statistical significance was provided for body weight and feed consumption. However, it is not clear if statistical comparisons were made for body weight gain. This is not expected to substantially impact the interpretation of the results. Study authors qualitatively state that "no clinical signs related to dibutyl phthalate exposure were noted." However, the authors do not provide information on the actual observed and recorded clinical signs in the mice. Sample sizes were specified. No individual animal data were provided.

Additional Comments: 12.DBP Dose range-finding study in rats.

Overall Quality Determination — Medium

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-14-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the animals and the humidity conditions.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were randomized and then assigned to dose groups, however, they do not indicate how this randomization was done and whether a computer program was used.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received undosed feed. Control responses were appropriate. A positive control group was not included and is not required. Reductions in feed consumption on Week 1 correlated with reduced body weights on Day 14. It is possible that DBP-dosed feed had decreased food palatability among the rats. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed or water was analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	Quantitative or qualitative results were provided for all outcomes described in the methods.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-14-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain		Metric	Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>99%), and storage conditions of the test substance were reported. The test substance was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. The authors reported the calculated doses (mg/kg-day) in the exposed male and female rats. The uncertainties in the exposure characterization are not expected to substantially impact the interpretation of the results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was a guideline-based dose range-finding study. Dietary exposure was conducted over a period of 14 consecutive days. The exposure timing, frequency, and duration were appropriate for the current study.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	Test animals were assessed for body weight and feed consumption The frequency of body weight and Food consumption measurements of animals were provided. Test animals were assessed for clinical signs. The frequency of clinical observations was not reported. In addition, it was not stated whether these were cage-side or in depth clinical observations. This is not expected to significantly impact the interpretation of the results. The test animals (rats) and sex (males and females) were appropriate for evaluation of the endpoints. The sample size (8 rats/sex/group) was appropriate for the study type. A wide range of doses were tested.
	Metric 9:	Results presentation	Medium	Quantitative data (mean ± SEM) was provided for body weight, body weight gain, and feed consumption. Statistical significance was provided for body weight and feed consumption. However, it is not clear if statistical comparisons were made for body weight gain. This is not expected to substantially impact the interpretation of the results. Study authors qualitatively state that "no clinical signs related to dibutyl phthalate exposure were noted." However, the authors do not provide information on the actual observed and recorded clinical signs in the mice. Sample sizes were specified. No individual animal data were provided.

Additional Comments: 12.DBP Dose range-finding study in rats.

Overall Quality Determination — Medium

Study Citation:	Srivastava, S., Singh, G. B., Srivastava, S. P., Seth, P. K. (1990). Testicular toxicity of di-n-butyl phthalate in adult rats: Effect on marker enzymes of spermatogenesis. Indian Journal of Experimental Biology 28(1):67-70.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Testes and epididymis weights, Sperm count, testes histopathology, Testes enzymes (SDH, LDH, G6PDH, gamma -GGT, acid phosphatase, beta-glucuronidase), testes protein content.
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-15-day(s)
Species:	Rat-Wistar - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	790212

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Low	The study included all critical information and most important information. The test substance was identified as Di (n-butyl) of ortho phthalic acid (DBP), purity 99%; the source was reported. Provided information included the test animals (Wistar rats) sex, source, and starting body weights. Age was not specified (adults). Animals were allowed free access to food and water. No other animal husbandry details were provided. The number of animals per cage was not specified. Details of test substance administration, number of animals per group, doses, endpoint evaluation methods, and quantitative results for at least one endpoint were provided. The missing information, particularly the animal age, could have a significant impact on the study results.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	The method of animal allocation into study groups was not specified. It is unclear if animals were normalized to body weights.
	Metric 3:	Observational Bias / Blinding Changes	Medium	The study did not specify blinding; however, the concern for bias was mitigated for most of the outcomes because they were not subjective and/or were based on based on use of automated/computer-driven systems, standard laboratory kits, simple objective measures (e.g., body or tissue weight), or screening-level evaluations of histopathology. The study did include sperm counts using a hemocytometer. This endpoint has the potential to be subjective in nature.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Uninformative	The study included an inappropriate negative control. Animals were dosed orally with the test substances dissolved in a ground nut oil vehicle. The negative control animals were administered an equivalent amount of groundnut oil intravenously. Food and water consumption were not reported in a gavage study, but the impact on results is expected to be minimal. Body weights were measured, and it was qualitatively stated that no changes from the control were observed. Insufficient animal husbandry details were included to determine confounding.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Srivastava, S., Singh, G. B., Srivastava, S. P., Seth, P. K. (1990). Testicular toxicity of di-n-butyl phthalate in adult rats: Effect on marker enzymes of spermatogenesis. Indian Journal of Experimental Biology 28(1):67-70.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Testes and epididymis weights, Sperm count, testes histopathology, Testes enzymes (SDH, LDH, G6PDH, gamma -GGT, acid phosphatase, beta-glucuronidase), testes protein content.
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-15-day(s)
Species:	Rat-Wistar - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	790212

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	High	No animals died in the study. Qualitative or quantitative results were reported for all specified outcomes. The study reported the number of animals per group; the sample size was reported in Table 1. The remaining data were representative figures. There is no evidence of animal attrition or reporting bias.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	There are no concerns regarding the source (Merk Company Ltd.) and purity (99%) of the test substance; however, the test substance was not analytically verified by the testing laboratory, and certification cannot be determined (it is unclear which product exactly was purchased from the supplier). The reported doses are presumed to be nominal. There is no indication that concentrations in the dosing solutions were measured analytically. No details on the preparation of the test solutions (including assurance of homogeneity, frequency, or stability), or storage were provided. The gavage volume was reported (0.4mL); gavage is an appropriate route of exposure for this test substance.
	Metric 7:	Exposure timing, frequency, and duration	Medium	This was a non-guideline study. Animals were exposed daily for 15 days. The study authors did not justify the exposure duration, but the duration seemed to be appropriate for the purposes of the study.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Low	The dose spacing was not explicitly justified by the study authors. Outcome assessment methodologies were sensitive to the outcomes of interest and all animals were sampled. Sufficient details on most of the outcome assessment protocols were provided. The methods did not specify that organs were weighed, but it was mentioned in the results text that no changes in organ weights were observed. Justification for the test species/strain was not provided; however, Wistar rats were an appropriate model selection. The study used 6 animals per group which were sufficient to allow for statistical analysis. Formalin was used to fix testes tissues, which is not recommended as per the updated OECD TG 407 (2008).

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Study Citation:	Srivastava, S., Singh, G. B., Srivastava, S. P., Seth, P. K. (1990). Testicular toxicity of di-n-butyl phthalate in adult rats: Effect on marker enzymes of spermatogenesis. Indian Journal of Experimental Biology 28(1):67-70.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Testes and epididymis weights, Sperm count, testes histopathology, Testes enzymes (SDH, LDH, G6PDH, gamma -GGT, acid phosphatase, beta-glucuronidase), testes protein content.
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-15-day(s)
Species:	Rat-Wistar - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	790212

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Low	Liver enzymes were reported as means ± SE. The number of animals (n) and statistical significance were reported. The statistical method (Student's T-test) was reported and was appropriate for the dataset. Sperm counts were also presented as means, and presumably, SE. The text did not specify which exposure groups were significantly different from controls, but this can be determined using the data provided and assuming an n of 6. Histopathology data were not reported in a manner allowing a clear interpretation of the study results. Representative images of histopathological lesions were shown. The text included general descriptions; however, no incidences were provided and it does not appear that the histopathology data were statistically analyzed. An independent analysis of the data cannot be conducted due to reporting limitations. At a minimum, it is reported that no histopathology was observed in the lowest dose group. Negative findings for organ weight changes were qualitatively stated in the text.

Additional Comments: None

Overall Quality Determination — Uninformative

Study Citation:	Srivastava, S., Singh, G. B., Srivastava, S. P., Seth, P. K. (1990). Testicular toxicity of di-n-butyl phthalate in adult rats: Effect on marker enzymes of spermatogenesis. Indian Journal of Experimental Biology 28(1):67-70.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weights-Mortality-Mortality
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-15-day(s)
Species:	Rat-Wistar - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	790212

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Low	The study included all critical information and most important information. The test substance was identified as Di (n-butyl) of ortho phthalic acid (DBP), purity 99%; the source was reported. Provided information included the test animals (Wistar rats) sex, source, and starting body weights. Age was not specified (adults). Animals were allowed free access to food and water. No other animal husbandry details were provided. The number of animals per cage was not specified. Details of test substance administration, number of animals per group, doses, endpoint evaluation methods, and quantitative results for at least one endpoint were provided. The missing information, particularly the animal age, could have a significant impact on the study results.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	The method of animal allocation into study groups was not specified. It is unclear if animals were normalized to body weights.
	Metric 3:	Observational Bias / Blinding Changes	Medium	The study did not specify blinding; however, the concern for bias was mitigated for these outcomes (mortality and body weights) because they were not subjective and/or were simple objective measures (e.g., body or tissue weight).
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Uninformative	The study included an inappropriate negative control. Animals were dosed orally with the test substances dissolved in a ground nut oil vehicle. The negative control animals were administered an equivalent amount of groundnut oil intravenously. Food and water consumption were not reported in a gavage study, but the impact on results is expected to be minimal. Body weights were measured, and it was qualitatively stated that no changes from the control were observed. Insufficient animal husbandry details were included to determine confounding.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	No animals died in the study. Qualitative or quantitative results were reported for all specified outcomes. The study reported the number of animals per group; the sample size was reported in Table 1. The remaining data were representative figures. There is no evidence of animal attrition or reporting bias.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Srivastava, S., Singh, G. B., Srivastava, S. P., Seth, P. K. (1990). Testicular toxicity of di-n-butyl phthalate in adult rats: Effect on marker enzymes of spermatogenesis. Indian Journal of Experimental Biology 28(1):67-70.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weights-Mortality-Mortality
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-15-day(s)
Species:	Rat-Wistar - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	790212

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	There are no concerns regarding the source (Merk Company Ltd.) and purity (99%) of the test substance; however, the test substance was not analytically verified by the testing laboratory, and certification cannot be determined (it is unclear which product exactly was purchased from the supplier). The reported doses are presumed to be nominal. There is no indication that concentrations in the dosing solutions were measured analytically. No details on the preparation of the test solutions (including assurance of homogeneity, frequency, or stability), or storage were provided. The gavage volume was reported (0.4mL); gavage is an appropriate route of exposure for this test substance.
	Metric 7:	Exposure timing, frequency, and duration	Medium	This was a non-guideline study. Animals were exposed daily for 15 days. The study authors did not justify the exposure duration, but the duration seemed to be appropriate for the purposes of the study.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	The dose spacing was not explicitly justified by the study authors. Outcome assessment methodologies were sensitive to the outcomes of interest and all animals were sampled. Sufficient details on the outcome assessment protocols were provided; body weights were recorded daily. Justification for the test species/strain was not provided; however, Wistar rats were an appropriate model selection. The study used 6 animals per group which were sufficient to allow for statistical analysis.
	Metric 9:	Results presentation	Medium	Negative findings were reported qualitatively in the text.

Additional Comments: None

Overall Quality Determination — Uninformative

Study Citation:	Srivastava, S., Singh, G. B., Srivastava, S. P., Seth, P. K. (1990). Testicular toxicity of di-n-butyl phthalate in adult rats: Effect on marker enzymes of spermatogenesis. Indian Journal of Experimental Biology 28(1):67-70.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weights-Mortality-Mortality
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-15-day(s)
Species:	Rat-Wistar - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	790212

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Low	The study included all critical information and most important information. The test substance was identified as Di (n-butyl) of ortho phthalic acid (DBP), purity 99%; the source was reported. Provided information included the test animals (Wistar rats) sex, source, and starting body weights. Age was not specified (adults). Animals were allowed free access to food and water. No other animal husbandry details were provided. The number of animals per cage was not specified. Details of test substance administration, number of animals per group, doses, endpoint evaluation methods, and quantitative results for at least one endpoint were provided. The missing information, particularly the animal age, could have a significant impact on the study results.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	The method of animal allocation into study groups was not specified. It is unclear if animals were normalized to body weights.
	Metric 3:	Observational Bias / Blinding Changes	Medium	The study did not specify blinding; however, the concern for bias was mitigated for these outcomes (mortality and body weights) because they were not subjective and/or were simple objective measures (e.g., body or tissue weight).
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Uninformative	The study included an inappropriate negative control. Animals were dosed orally with the test substances dissolved in a ground nut oil vehicle. The negative control animals were administered an equivalent amount of groundnut oil intravenously. Food and water consumption were not reported in a gavage study, but the impact on results is expected to be minimal. Body weights were measured, and it was qualitatively stated that no changes from the control were observed. Insufficient animal husbandry details were included to determine confounding.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	No animals died in the study. Qualitative or quantitative results were reported for all specified outcomes. The study reported the number of animals per group; the sample size was reported in Table 1. The remaining data were representative figures. There is no evidence of animal attrition or reporting bias.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Srivastava, S., Singh, G. B., Srivastava, S. P., Seth, P. K. (1990). Testicular toxicity of di-n-butyl phthalate in adult rats: Effect on marker enzymes of spermatogenesis. Indian Journal of Experimental Biology 28(1):67-70.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weights-Mortality-Mortality
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-15-day(s)
Species:	Rat-Wistar - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	790212

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	There are no concerns regarding the source (Merk Company Ltd.) and purity (99%) of the test substance; however, the test substance was not analytically verified by the testing laboratory, and certification cannot be determined (it is unclear which product exactly was purchased from the supplier). The reported doses are presumed to be nominal. There is no indication that concentrations in the dosing solutions were measured analytically. No details on the preparation of the test solutions (including assurance of homogeneity, frequency, or stability), or storage were provided. The gavage volume was reported (0.4mL); gavage is an appropriate route of exposure for this test substance.
	Metric 7:	Exposure timing, frequency, and duration	Medium	This was a non-guideline study. Animals were exposed daily for 15 days. The study authors did not justify the exposure duration, but the duration seemed to be appropriate for the purposes of the study.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	The dose spacing was not explicitly justified by the study authors. Outcome assessment methodologies were sensitive to the outcomes of interest and all animals were sampled. Sufficient details on the outcome assessment protocols were provided; body weights were recorded daily. Justification for the test species/strain was not provided; however, Wistar rats were an appropriate model selection. The study used 6 animals per group which were sufficient to allow for statistical analysis.
	Metric 9:	Results presentation	Medium	Negative findings were reported qualitatively in the text.

Additional Comments: None

Overall Quality Determination — Uninformative

Study Citation:	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated pathway in rats. International Journal of Toxicology 28(5):448-456.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Apical: Serum testosterone, relative organ weights (testes epididymis), testes histopathology; Mechanistic: protein and gene expression in the testes-Other (please specify below) (Endocrine)-Serum glucocorticoids, relative adrenal weight, adrenal histopathology
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676594

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The study included all critical information and most important information. The test substance was identified as Di (n-butyl phthalate) CASRN 84-74-2, purity 99.5%; the source was reported. Provided information included the test animals (Sprague-Dawley rats) sex, age, and source; initial body weights were not specified. All animal husbandry conditions were reported, including temperature, humidity, lighting, access to food and water, cage type, and the number of animals per cage. Details of test substance administration, number of animals per group, doses, endpoint evaluation methods, and quantitative results for at least one endpoint were provided.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	Animals were randomly divided into study groups according to body weight. The method of randomization was not specified.
	Metric 3:	Observational Bias / Blinding Changes	Medium	The study did not specify blinding; however, the concern for bias was mitigated because the outcomes were not subjective and/or were based on the use of automated/computer-driven systems, standard laboratory kits, simple objective measures (e.g., body or tissue weight), or screening-level evaluations of histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a concurrent negative vehicle (corn oil) control. The negative control responses were appropriate. Food and water consumption were not reported in a gavage study, but the impact on results is expected to be minimal. Body weights were measured, and it was qualitatively stated that no changes from the control were observed. Animal husbandry conditions were adequate and consistent across groups. Based on the information available, there is no evidence to suggest the presence of confounding variables.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Low	Qualitative or quantitative results were reported for all specified outcomes. The study reported the number of animals per group; the sample size was reported in only one table (Table 1), but not in any other tables or figures. The methods also did not specify sample sizes for these endpoints. Although no animals died, it is unclear whether all animals were used to generate those data. The presence or absence of reporting bias cannot be determined due to the missing information.

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Study Citation:	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated pathway in rats. International Journal of Toxicology 28(5):448-456.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Apical: Serum testosterone, relative organ weights (testes epididymis), testes histopathology; Mechanistic: protein and gene expression in the testes-Other (please specify below) (Endocrine)-Serum glucocorticoids, relative adrenal weight, adrenal histopathology
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676594

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	There are no concerns regarding the source (North Fine Chemicals Co., Ltd) and purity (99.5%) of the test substance; however, the test substance was not analytically verified by the testing laboratory, and certification cannot be determined (the supplier website could not be located). The reported doses are presumed to be nominal. There is no indication that concentrations in the dosing solutions were measured analytically. No details on the preparation of the test solutions (including assurance of homogeneity, frequency, or stability), or storage were provided. The gavage volume was not specified, although gavage is an appropriate route of exposure.
	Metric 7:	Exposure timing, frequency, and duration	Medium	Animals were exposed daily for 30 days. The study authors did not provide justification for the exposure duration, but the duration seemed to be appropriate for the purposes of the study.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Low	The dose spacing was not explicitly justified by the study authors. It was noted that because "male reproductive toxicity of DBP is based on age-dependent sensitivity," 2,000 mg/kg-day was selected as the maximum exposure in prepubertal rats. Outcome assessment methodologies for apical endpoints was mostly sensitive to the outcomes of interest; it is not clear why the epididymis was not histologically examined. Gene expression analysis was not done using quantitative RT-PCR (e.g., using Syber green or labeled probes). RT-PCR products were quantified using ethidium bromide. It is unclear why the study measured GR protein levels, but not gene expression. Typically, looking at protein concentrations is done to demonstrate functional changes downstream of changes in gene expression. Typically All animals were sampled for organ weights; however, the sampling for other endpoints (e.g., serum hormones, gene expression and specific protein quantification in testes, and histopathology) was not reported. This was not specified in the methods and only representative images from these two groups were shown in the results. Additionally, Justification for the test species/strain was not provided; however, Sprague-Dawley rats were an appropriate model selection.

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Study Citation:	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated pathway in rats. International Journal of Toxicology 28(5):448-456.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Apical: Serum testosterone, relative organ weights (testes epididymis), testes histopathology; Mechanistic: protein and gene expression in the testes-Other (please specify below) (Endocrine)-Serum glucocorticoids, relative adrenal weight, adrenal histopathology
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676594

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Low	The testes histopathology results were inadequately reported. Dose-related changes were described qualitatively in the text; however, incidences and statistical significance were not provided. Only a representative image from a control and high-dose sample was shown. A qualitative statement was made saying there were no histopathological alterations in the testes of the post-exposure group or in the adrenals. The sample size, severity, or number of slides examined were not specified. Only relative and not absolute organ weight data were reported, in the absence of terminal body weights. Relative testis weights may not be a reliable marker for testes toxicity. These data were adequately presented as means ± SD and the sample size "n" was noted. Other relevant (serum hormones and, gene expression and protein levels in the testes) were reported as bar graphs, presumably representing a mean ± SD based on information in the methods. Sample sizes were not specified. The method(s) of statistical analysis were reported and were appropriate for the apical datasets. The study authors did not sufficiently describe their criteria for considering gene expression changes to be significant.

Additional Comments: None

Overall Quality Determination Low

Study Citation:	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated pathway in rats. International Journal of Toxicology 28(5):448-456.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Apical: Serum testosterone, relative organ weights (testes epididymis), testes histopathology; Mechanistic: protein and gene expression in the testes-Other (please specify below) (Endocrine)-Serum glucocorticoids, relative adrenal weight, adrenal histopathology
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676594

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The study included all critical information and most important information. The test substance was identified as Di (n-butyl phthalate) CASRN 84-74-2, purity 99.5%; the source was reported. Provided information included the test animals (Sprague-Dawley rats) sex, age, and source; initial body weights were not specified. All animal husbandry conditions were reported, including temperature, humidity, lighting, access to food and water, cage type, and the number of animals per cage. Details of test substance administration, number of animals per group, doses, endpoint evaluation methods, and quantitative results for at least one endpoint were provided.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	Animals were randomly divided into study groups according to body weight. The method of randomization was not specified.
	Metric 3:	Observational Bias / Blinding Changes	Medium	The study did not specify blinding; however, the concern for bias was mitigated because the outcomes were not subjective and/or were based on the use of automated/computer-driven systems, standard laboratory kits, simple objective measures (e.g., body or tissue weight), or screening-level evaluations of histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a concurrent negative vehicle (corn oil) control. The negative control responses were appropriate. Food and water consumption were not reported in a gavage study, but the impact on results is expected to be minimal. Body weights were measured, and it was qualitatively stated that no changes from the control were observed. Animal husbandry conditions were adequate and consistent across groups. Based on the information available, there is no evidence to suggest the presence of confounding variables.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Low	Qualitative or quantitative results were reported for all specified outcomes. The study reported the number of animals per group; the sample size was reported in only one table (Table 1), but not in any other tables or figures. The methods also did not specify sample sizes for these endpoints. Although no animals died, it is unclear whether all animals were used to generate those data. The presence or absence of reporting bias cannot be determined due to the missing information.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated pathway in rats. International Journal of Toxicology 28(5):448-456.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Apical: Serum testosterone, relative organ weights (testes epididymis), testes histopathology; Mechanistic: protein and gene expression in the testes-Other (please specify below) (Endocrine)-Serum glucocorticoids, relative adrenal weight, adrenal histopathology
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676594

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	There are no concerns regarding the source (North Fine Chemicals Co., Ltd) and purity (99.5%) of the test substance; however, the test substance was not analytically verified by the testing laboratory, and certification cannot be determined (the supplier website could not be located). The reported doses are presumed to be nominal. There is no indication that concentrations in the dosing solutions were measured analytically. No details on the preparation of the test solutions (including assurance of homogeneity, frequency, or stability), or storage were provided. The gavage volume was not specified, although gavage is an appropriate route of exposure.
	Metric 7:	Exposure timing, frequency, and duration	Medium	Animals were exposed daily for 30 days. The study authors did not provide justification for the exposure duration, but the duration seemed to be appropriate for the purposes of the study.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Low	The dose spacing was not explicitly justified by the study authors. It was noted that because "male reproductive toxicity of DBP is based on age-dependent sensitivity," 2,000 mg/kg-day was selected as the maximum exposure in prepubertal rats. Outcome assessment methodologies for apical endpoints was mostly sensitive to the outcomes of interest; it is not clear why the epididymis was not histologically examined. Gene expression analysis was not done using quantitative RT-PCR (e.g., using Syber green or labeled probes). RT-PCR products were quantified using ethidium bromide. It is unclear why the study measured GR protein levels, but not gene expression. Typically, looking at protein concentrations is done to demonstrate functional changes downstream of changes in gene expression. Typically All animals were sampled for organ weights; however, the sampling for other endpoints (e.g., serum hormones, gene expression and specific protein quantification in testes, and histopathology) was not reported. This was not specified in the methods and only representative images from these two groups were shown in the results. Additionally, Justification for the test species/strain was not provided; however, Sprague-Dawley rats were an appropriate model selection.

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Study Citation:	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated pathway in rats. International Journal of Toxicology 28(5):448-456.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Apical: Serum testosterone, relative organ weights (testes epididymis), testes histopathology; Mechanistic: protein and gene expression in the testes-Other (please specify below) (Endocrine)-Serum glucocorticoids, relative adrenal weight, adrenal histopathology
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676594

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Low	The testes histopathology results were inadequately reported. Dose-related changes were described qualitatively in the text; however, incidences and statistical significance were not provided. Only a representative image from a control and high-dose sample was shown. A qualitative statement was made saying there were no histopathological alterations in the testes of the post-exposure group or in the adrenals. The sample size, severity, or number of slides examined were not specified. Only relative and not absolute organ weight data were reported, in the absence of terminal body weights. Relative testis weights may not be a reliable marker for testes toxicity. These data were adequately presented as means ± SD and the sample size "n" was noted. Other relevant (serum hormones and, gene expression and protein levels in the testes) were reported as bar graphs, presumably representing a mean ± SD based on information in the methods. Sample sizes were not specified. The method(s) of statistical analysis were reported and were appropriate for the apical datasets. The study authors did not sufficiently describe their criteria for considering gene expression changes to be significant.

Additional Comments: None

Overall Quality Determination Low

Study Citation:	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated pathway in rats. International Journal of Toxicology 28(5):448-456.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Nutritional/Metabolic-Body weights
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676594

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The study included all critical information and most important information. The test substance was identified as Di (n-butyl phthalate) CASRN 84-74-2, purity 99.5%; the source was reported. Provided information included the test animals (Sprague-Dawley rats) sex, age, and source; initial body weights were not specified. All animal husbandry conditions were reported, including temperature, humidity, lighting, access to food and water, cage type, and the number of animals per cage. Details of test substance administration, number of animals per group, doses, endpoint evaluation methods, and quantitative results for at least one endpoint were provided.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	Animals were randomly divided into study groups according to body weight. The method of randomization was not specified.
	Metric 3:	Observational Bias / Blinding Changes	Medium	The study did not specify blinding; however, the concern for bias was mitigated because the outcomes were not subjective and/or were based on the use of automated/computer-driven systems, standard laboratory kits, simple objective measures (e.g., body or tissue weight), or screening-level evaluations of histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a concurrent negative vehicle (corn oil) control. The negative control responses were appropriate (no animals died). Food and water consumption were not reported in a gavage study, but the impact on results is expected to be minimal. Body weights were measured, and it was qualitatively stated that no changes from the control were observed. Animal husbandry conditions were adequate and consistent across groups. Based on the information available, there is no evidence to suggest the presence of confounding variables.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Low	Qualitative or quantitative results were reported for all specified outcomes. The study reported the number of animals per group; the sample size was reported in only one table (Table 1), but not in any other tables or figures. The methods also did not specify sample sizes for these endpoints. Although no animals died, it is unclear whether all animals were used to generate those data. The presence or absence of reporting bias cannot be determined due to the missing information.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated pathway in rats. International Journal of Toxicology 28(5):448-456.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Nutritional/Metabolic-Body weights
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676594

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	There are no concerns regarding the source (North Fine Chemicals Co., Ltd) and purity (99.5%) of the test substance; however, the test substance was not analytically verified by the testing laboratory, and certification cannot be determined (the supplier website could not be located). The reported doses are presumed to be nominal. There is no indication that concentrations in the dosing solutions were measured analytically. No details on the preparation of the test solutions (including assurance of homogeneity, frequency, or stability), or storage were provided. The gavage volume was not specified, although gavage is an appropriate route of exposure.
	Metric 7:	Exposure timing, frequency, and duration	Medium	Animals were exposed daily for 30 days. The study authors did not provide justification for the exposure duration, but the duration seemed to be appropriate for the purposes of the study.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	The dose spacing was not explicitly justified by the study authors. It was noted that because "male reproductive toxicity of DBP is based on age-dependent sensitivity," 2,000 mg/kg-day was selected as the maximum exposure in prepubertal rats. The methods did not specify that animals were observed for mortality, but it was noted in the results that no animals died. Body weights were measured twice weekly. No justification for the test species/strain was provided; however, Sprague-Dawley rats were an appropriate model selection. Justification for the test species/strain was not provided; however, Sprague-Dawley rats were an appropriate model selection.
	Metric 9:	Results presentation	Medium	A qualitative description was provided for outcomes with no effects.

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated pathway in rats. International Journal of Toxicology 28(5):448-456.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Nutritional/Metabolic-Body weights
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676594

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The study included all critical information and most important information. The test substance was identified as Di (n-butyl phthalate) CASRN 84-74-2, purity 99.5%; the source was reported. Provided information included the test animals (Sprague-Dawley rats) sex, age, and source; initial body weights were not specified. All animal husbandry conditions were reported, including temperature, humidity, lighting, access to food and water, cage type, and the number of animals per cage. Details of test substance administration, number of animals per group, doses, endpoint evaluation methods, and quantitative results for at least one endpoint were provided.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	Animals were randomly divided into study groups according to body weight. The method of randomization was not specified.
	Metric 3:	Observational Bias / Blinding Changes	Medium	The study did not specify blinding; however, the concern for bias was mitigated because the outcomes were not subjective and/or were based on the use of automated/computer-driven systems, standard laboratory kits, simple objective measures (e.g., body or tissue weight), or screening-level evaluations of histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a concurrent negative vehicle (corn oil) control. The negative control responses were appropriate (no animals died). Food and water consumption were not reported in a gavage study, but the impact on results is expected to be minimal. Body weights were measured, and it was qualitatively stated that no changes from the control were observed. Animal husbandry conditions were adequate and consistent across groups. Based on the information available, there is no evidence to suggest the presence of confounding variables.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Low	Qualitative or quantitative results were reported for all specified outcomes. The study reported the number of animals per group; the sample size was reported in only one table (Table 1), but not in any other tables or figures. The methods also did not specify sample sizes for these endpoints. Although no animals died, it is unclear whether all animals were used to generate those data. The presence or absence of reporting bias cannot be determined due to the missing information.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated pathway in rats. International Journal of Toxicology 28(5):448-456.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Nutritional/Metabolic-Body weights
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676594

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	There are no concerns regarding the source (North Fine Chemicals Co., Ltd) and purity (99.5%) of the test substance; however, the test substance was not analytically verified by the testing laboratory, and certification cannot be determined (the supplier website could not be located). The reported doses are presumed to be nominal. There is no indication that concentrations in the dosing solutions were measured analytically. No details on the preparation of the test solutions (including assurance of homogeneity, frequency, or stability), or storage were provided. The gavage volume was not specified, although gavage is an appropriate route of exposure.
	Metric 7:	Exposure timing, frequency, and duration	Medium	Animals were exposed daily for 30 days. The study authors did not provide justification for the exposure duration, but the duration seemed to be appropriate for the purposes of the study.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	The dose spacing was not explicitly justified by the study authors. It was noted that because "male reproductive toxicity of DBP is based on age-dependent sensitivity," 2,000 mg/kg-day was selected as the maximum exposure in prepubertal rats. The methods did not specify that animals were observed for mortality, but it was noted in the results that no animals died. Body weights were measured twice weekly. No justification for the test species/strain was provided; however, Sprague-Dawley rats were an appropriate model selection. Justification for the test species/strain was not provided; however, Sprague-Dawley rats were an appropriate model selection.
	Metric 9:	Results presentation	Medium	A qualitative description was provided for outcomes with no effects.

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated pathway in rats. International Journal of Toxicology 28(5):448-456.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical signs)-Clinical signs (a decrease in normal activity)
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676594

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The study included all critical information and most important information. The test substance was identified as Di (n-butyl phthalate) CASRN 84-74-2, purity 99.5%; the source was reported. Provided information included the test animals (Sprague-Dawley rats) sex, age, and source; initial body weights were not specified. All animal husbandry conditions were reported, including temperature, humidity, lighting, access to food and water, cage type, and the number of animals per cage. Details of test substance administration, number of animals per group, doses, endpoint evaluation methods, and quantitative results for at least one endpoint were provided.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	Animals were randomly divided into study groups according to body weight. The method of randomization was not specified.
	Metric 3:	Observational Bias / Blinding Changes	Medium	The study did not specify the use of blinding for clinical observations.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a concurrent negative vehicle (corn oil) control. The negative control responses were appropriate (no animals died). Food and water consumption were not reported in a gavage study, but the impact on results is expected to be minimal. Body weights were measured, and it was qualitatively stated that no changes from the control were observed. Animal husbandry conditions were adequate and consistent across groups. Based on the information available, there is no evidence to suggest the presence of confounding variables.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Low	Qualitative or quantitative results were reported for all specified outcomes. The study reported the number of animals per group; the sample size was reported in only one table (Table 1), but not in any other tables or figures. The methods also did not specify sample sizes for these endpoints. Although no animals died, it is unclear whether all animals were used to generate those data. The presence or absence of reporting bias cannot be determined due to the missing information.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated pathway in rats. International Journal of Toxicology 28(5):448-456.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical signs)-Clinical signs (a decrease in normal activity)
Duration and Exposure Route:	Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676594

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	There are no concerns regarding the source (North Fine Chemicals Co., Ltd) and purity (99.5%) of the test substance; however, the test substance was not analytically verified by the testing laboratory, and certification cannot be determined (the supplier website could not be located). The reported doses are presumed to be nominal. There is no indication that concentrations in the dosing solutions were measured analytically. No details on the preparation of the test solutions (including assurance of homogeneity, frequency, or stability), or storage were provided. The gavage volume was not specified, although gavage is an appropriate route of exposure.
	Metric 7:	Exposure timing, frequency, and duration	Medium	Animals were exposed daily for 30 days. The study authors did not provide justification for the exposure duration, but the duration seemed to be appropriate for the purposes of the study.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Low	The dose spacing was not explicitly justified by the study authors. It was noted that because "male reproductive toxicity of DBP is based on age-dependent sensitivity," 2,000 mg/kg-day was selected as the maximum exposure in prepubertal rats. No outcome assessment methods were provided for this outcome. It was only noted in the results that 4 high-dose animals showed a decrease in normal activity. It is unclear how often animals were observed. No justification for the test species/strain was provided; however, Sprague-Dawley rats were an appropriate model selection. Justification for the test species/strain was not provided; however, Sprague-Dawley rats were an appropriate model selection.
	Metric 9:	Results presentation	Low	Results on this outcome were limited to a description of decreased normal activity in 4 rats at the high dose after 17 days of exposure. It was not explicitly stated that there were no observations in the controls or other dose groups. Statistical significance was not specified.

Additional Comments: None

Overall Quality Determination — Low

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
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Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination — High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination — High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
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Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination — High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination — High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
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Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
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Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have "artificially impacted the apparent reduction of triglyceride concentrations" in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Other (please specify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have “artificially impacted the apparent reduction of triglyceride concentrations” in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	High	Mortality results were quantitatively reported.
Additional Comments:	8.DBP 13-week feed study in rats			

Overall Quality Determination — High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	The study used un-dosed feed as a negative control and the negative control responses were mostly appropriate. The study authors noted that the triglyceride levels in control rats were significantly higher than control rats used for an adjoining study and this may have “artificially impacted the apparent reduction of triglyceride concentrations” in the current study. Reductions in food consumption (39% in males and 17% in females) with associated emaciation and decreased body weights occurred at the highest dose in a dietary study. No discussion of palatability issues were provided by the authors, but effects at the high dose are likely confounded by decreased food intake. No issues with food intake were observed at the other doses. Water consumption was not measured; however, the authors noted that some clinical chemistry changes (elevated albumin) was consistent with dehydration. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died. Hematological results are reported for n = 9 instead of n=10 for some dose groups; no explanation from the study authors was provided, but this is not expected to have a significant effect on the study results.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Rat-Fischer 344 - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%) and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and rationale was provided for the selected doses. A toxicity value could be determined even if the high-dose is excluded due to potential palatability issues. Methods of outcome assessment were clearly described including frequencies of observations and were generally consistent with OECD 408 guidelines. The test model and source were appropriate.
	Metric 9:	Results presentation	Low	Average feed consumption data was reported as means only with no measures of variance. Individual animal data were not provided.

Additional Comments: 8.DBP 13-week feed study in rats

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination — High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
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Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
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Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination High

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
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Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination High

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination High

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination High

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination High

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination High

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Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Immune/Hematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9).-Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9).-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9).-Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9).-Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).-Thyroid-Histopathology of thyroid (Study 8 and Study 9).-Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means ± SEM or incidences. Histopathology reports did not include severity scores. Statistical significance is shown and statistical methods were described and appropriate. Sample sizes are clearly reported. Outcomes with no effects were qualitatively reported (e.g., mortality, clinical signs, gross necropsy findings). Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain		Metric	Rating	Comments
	Metric 6:	Chemical administration and characterization	High	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.
	Metric 9:	Results presentation	High	Mortality results were quantitatively reported.
Additional Comments:	9.DBP 13-week feed study in mice			

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), source, and purity; test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); method of administration; experimental design (frequency of exposure, number of animals per study group, animal age during exposure); endpoint evaluation methods (quantitative and qualitative); and quantitative results for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a computer program.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, most endpoints were objective or simple in nature. All histology slides were reviewed and evaluated by the NTP Pathology Working Group (PWG). Citations were provided for details of the review; blinding was not specified in the current PDF.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study used un-dosed feed as a negative control and the negative control responses were appropriate. The study authors noted an issue with feed spillage in the higher male exposure groups that led to unusually high feed consumption by a few animals. It was not stated that these animals were excluded as outliers, and therefore, average feed consumption in males was increased by 3, 12, 24, 24, and 38% in the 1,250, 2,500, 5,000, 10,000, and 20,000 ppm groups, respectively. See Metric 5.1 for potential impacts on reporting of doses. Water consumption was not measured. No differences in animal husbandry conditions across groups were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantitative results were provided for all specified endpoints. No animals died.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC and confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. Doses in mg/kg-day were provided. However, the authors acknowledged that feed intake for "higher doses" were elevated due to "unusually high feed consumption by a few animals." It does not appear that these animals were excluded when determining mean feed intake, and this could influence the accuracy of the dose calculations. Individual animal data are not reported, precluding the ability to conduct an independent calculation excluding any outliers.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no particular guideline was followed; however, the study was conducted in a manner similar to OECD 408 and the methods were clearly described and sensitive to the outcomes of interest. The dose spacing was adequate for determination of toxicity values. The test model and source were appropriate.
	Metric 9:	Results presentation	Low	Average feed consumption data was reported as means only with no measures of variance. Individual animal data were not provided.

Additional Comments: 9.DBP 13-week feed study in mice

Overall Quality Determination — High

Study Citation:	Clewell, R. A., Thomas, A., Willson, G., Creasy, D. M., Andersen, M. E. (2013). A dose response study to assess effects after dietary administration of diisononyl phthalate (DINP) in gestation and lactation on male rat sexual development. Reproductive Toxicology 35(Elsevier):70-80.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, body weight gain, food consumption-Reproductive/Developmental-Number of litters; number of live pups; number of live pups/litter; male pup body weight; anogenital distance (absolute and scaled = AGD/BW^1/3); average number of nipples/areolae per male pup (based on visual identification; no histology confirmation); testis testosterone level in pups; gubernacular cord length in pups; gross necropsy of pups; examination of genital tract of pups for alterations (e.g., hypospadias, cleft phallus); examination of urogenital tract of pups; examinations for undescended testes and epididymal agenesis in pups; in situ examination of testes, epididymides, gubernacular cords, vas deferens, seminal vesicles, levator ani plus bulbocavernosus (LABC) muscles, and prostate in pups; examination of non-reproductive tissues in situ in pups; organ weights (absolute and relative to body weight) in pups for the following: testis (right and left), epididymis (right and left), seminal vesicle, ventral prostate, glans penis, LABC muscles, Cowper's glands, adrenal gland, kidney (pair), liver; histopathology of testes and epididymides in pups; metabolites of DINP in plasma collected from PND2 pups
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1325348

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information was reported. The test animal species, test article identity, dose levels tested and duration of exposure, route, quantitative or qualitative results for all endpoints examined, parity, commercial animal source, strain, age, sex, starting body weight, animal husbandry conditions (temperature, light/dark cycle, and humidity), number of animals per cage, availability of food and water, test substance source, purity, method of administration, frequency of exposure, number of animals per group, and assays and procedures used to measure endpoints were reported.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	The allocation method for the assignment of pregnant females to experimental groups is not described. There is no other mention of steps that may have been taken to balance variables, such as test animal characteristics or other modifying factors, across experimental groups when assigning animals to experimental groups.
	Metric 3:	Observational Bias / Blinding Changes	High	The study implemented methods to reduce observational bias. The study report indicates that the study methodology included "blinding of all observations to ensure objectivity and eliminate bias." The use of blinded observers (which were provided no information on treatment group) was described for specific steps of the endpoint assessment methodology, including for the determination of nipple retention and measurement of anogenital distance. Histopathological examinations of testes and epididymides were conducted using a semi-blinded method of evaluation. For this approach, the initial histopathological examinations of tissues collected from all animals were performed by a primary pathologist with knowledge of positive and negative control groups so that potential changes related to test chemical administration could be identified. The initial examinations were followed by a secondary histopathological examination of all collected tissues by a peer reviewing pathologist who was blinded to the treatment groups (no knowledge of the treatment groups). The approaches used for blinding for histopathological examinations appear to be appropriate for this study.

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Study Citation:	Clewell, R. A., Thomas, A., Willson, G., Creasy, D. M., Andersen, M. E. (2013). A dose response study to assess effects after dietary administration of diisononyl phthalate (DINP) in gestation and lactation on male rat sexual development. Reproductive Toxicology 35(Elsevier):70-80.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, body weight gain, food consumption-Reproductive/Developmental-Number of litters; number of live pups; number of live pups/litter; male pup body weight; anogenital distance (absolute and scaled = AGD/BW^1/3); average number of nipples/areolae per male pup (based on visual identification; no histology confirmation); testis testosterone level in pups; gubernacular cord length in pups; gross necropsy of pups; examination of genital tract of pups for alterations (e.g., hypospadias, cleft phallus); examination of urogenital tract of pups; examinations for undescended testes and epididymal agenesis in pups; in situ examination of testes, epididymides, gubernacular cords, vas deferens, seminal vesicles, levator ani plus bulbocavernosus (LABC) muscles, and prostate in pups; examination of non-reproductive tissues in situ in pups; organ weights (absolute and relative to body weight) in pups for the following: testis (right and left), epididymis (right and left), seminal vesicle, ventral prostate, glans penis, LABC muscles, Cowper's glands, adrenal gland, kidney (pair), liver; histopathology of testes and epididymides in pups; metabolites of DINP in plasma collected from PND2 pups
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1325348

Domain	Metric	Rating	Comments
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	No differences were observed across the study groups that could bias the results or introduce a variable not accounted for in the study analysis. No potential confounding variables were identified. Food consumption data indicated similar food consumption for the control and DBP-exposed groups. The animal husbandry conditions and test substance administration conditions were consistent for the control and DBP-exposed 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. Similarly, it is unclear if glass or plastic water bottles were used. Again, plastic bottles could leach phthalates, potentially confounding results. The negative control response was adequate for the endpoints assessed.
Domain 4: Selective Reporting and Attrition			

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Study Citation:	Clewell, R. A., Thomas, A., Willson, G., Creasy, D. M., Andersen, M. E. (2013). A dose response study to assess effects after dietary administration of diisononyl phthalate (DINP) in gestation and lactation on male rat sexual development. Reproductive Toxicology 35(Elsevier):70-80.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, body weight gain, food consumption-Reproductive/Developmental-Number of litters; number of live pups; number of live pups/litter; male pup body weight; anogenital distance (absolute and scaled = AGD/BW^1/3); average number of nipples/areolae per male pup (based on visual identification; no histology confirmation); testis testosterone level in pups; gubernacular cord length in pups; gross necropsy of pups; examination of genital tract of pups for alterations (e.g., hypospadias, cleft phallus); examination of urogenital tract of pups; examinations for undescended testes and epididymal agenesis in pups; in situ examination of testes, epididymides, gubernacular cords, vas deferens, seminal vesicles, levator ani plus bulbocavernosus (LABC) muscles, and prostate in pups; examination of non-reproductive tissues in situ in pups; organ weights (absolute and relative to body weight) in pups for the following: testis (right and left), epididymis (right and left), seminal vesicle, ventral prostate, glans penis, LABC muscles, Cowper's glands, adrenal gland, kidney (pair), liver; histopathology of testes and epididymides in pups; metabolites of DINP in plasma collected from PND2 pups
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1325348

Domain	Metric	Rating	Comments
	Metric 5: Selective Reporting and Attrition	Medium	The study reports the results for all prespecified outcomes, exposure groups, and evaluation timepoints described in the test methods. The number of animals per exposure group is not explicitly stated in the study methods; a range of 20-24 litters/treatment group is indicated in the methods. The results (e.g., Tables 1, 2, and 4, table footnotes) imply that 24 and 21 dams were treated in the control group and DBP-exposed group, respectively. There are inconsistencies in the numbers of male pups examined on PND 2 across the control group and DBP-exposed group without an explanation. The methods describe the selection of 1 male animal per litter on PND 2, but results for fewer than 24 control and 21 test substance-exposed groups are reported for some endpoints. For example, in Table 2, the number of animals was n = 19 for control animals and n = 17 for the DBP group for pup testis and epididymis weights measured on PND 2, whereas 24 control litters and 21 DBP treatment litters are reported for other endpoints. Table 2 also indicates below the table that there were n = 25 control litters "unless otherwise noted", but the number of control litters is reported as 24 in Row 1 of the table. Aside from these inconsistencies, no additional deficiencies were identified. There were no health outcomes identified (e.g., infection) that were unrelated to the exposure that would influence the outcome assessment. No other discrepancies or unexplained omissions or attrition were identified that are expected to affect the interpretation of the results of the study.

Domain 5: Exposure Methods Sensitivity

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Study Citation:	Clewell, R. A., Thomas, A., Willson, G., Creasy, D. M., Andersen, M. E. (2013). A dose response study to assess effects after dietary administration of diisononyl phthalate (DINP) in gestation and lactation on male rat sexual development. Reproductive Toxicology 35(Elsevier):70-80.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, body weight gain, food consumption-Reproductive/Developmental-Number of litters; number of live pups; number of live pups/litter; male pup body weight; anogenital distance (absolute and scaled = AGD/BW^1/3); average number of nipples/areolae per male pup (based on visual identification; no histology confirmation); testis testosterone level in pups; gubernacular cord length in pups; gross necropsy of pups; examination of genital tract of pups for alterations (e.g., hypospadias, cleft phallus); examination of urogenital tract of pups; examinations for undescended testes and epididymal agenesis in pups; in situ examination of testes, epididymides, gubernacular cords, vas deferens, seminal vesicles, levator ani plus bulbocavernosus (LABC) muscles, and prostate in pups; examination of non-reproductive tissues in situ in pups; organ weights (absolute and relative to body weight) in pups for the following: testis (right and left), epididymis (right and left), seminal vesicle, ventral prostate, glans penis, LABC muscles, Cowper's glands, adrenal gland, kidney (pair), liver; histopathology of testes and epididymides in pups; metabolites of DINP in plasma collected from PND2 pups
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1325348

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	The study report adequately characterizes the exposure and the administration methods for control and test substance-exposed groups. There are minor uncertainties in the test substance characterization and test diet preparation methods that are expected to have minimal impact on interpretation of the results. The test substance source, purity, and lot number for the test substance are reported. Test diets were prepared by adding neat test substance to rodent feed. The study report does not indicate how frequently test diets were prepared, certain conditions of methods used for mixing test substance into feed (e.g., mixing temperature), or conditions of storage of prepared test diets. However, homogeneity of test substance in prepared test diets, test substance stability in feed, and achieved concentrations of test substance in feed were analytically confirmed in samples collected from prepared feed batches. Measured concentrations of test substance in feed were within 3% of target concentrations. Test substance concentrations in samples collected from prepared feed batches at the conclusion of the study (3 months post-mixing) were within 8% of initial concentrations. Average maternal doses of test substance (in mg/kg/day) were calculated from maternal body weight and feed consumption data.
	Metric 7:	Exposure timing, frequency, and duration	High	The timing, frequency, and duration of exposure was sensitive for the outcomes of interest for this study. Methods used for exposure administration were consistent across the treatment groups. The period of exposure for this developmental toxicity study did not include exposure timing appropriate for assessing effects on implantation or organogenesis (i.e., dosing period for this study: GD 12 to PND 14; implantation in rats: GD 5; period of organogenesis in rats: GD 5-15). However, the study was designed to examine several endpoints of male rat sexual development in offspring that had been exposed during late gestation and during lactation, recognizing that other referenced studies were available which evaluated test substance-related developmental effects in rodents following exposure during a larger window of the gestational period. The exposure duration was considered appropriate for the intended purpose of this study and the failure to expose the animals during the full period of organogenesis or prior to implantation is not considered a study deficiency.

Domain 6: Outcome Measures and Results Display

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Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, body weight gain, food consumption-Reproductive/Developmental-Number of litters; number of live pups; number of live pups/litter; male pup body weight; anogenital distance (absolute and scaled = AGD/BW^1/3); average number of nipples/areolae per male pup (based on visual identification; no histology confirmation); testis testosterone level in pups; gubernacular cord length in pups; gross necropsy of pups; examination of genital tract of pups for alterations (e.g., hypospadias, cleft phallus); examination of urogenital tract of pups; examinations for undescended testes and epididymal agenesis in pups; in situ examination of testes, epididymides, gubernacular cords, vas deferens, seminal vesicles, levator ani plus bulbocavernosus (LABC) muscles, and prostate in pups; examination of non-reproductive tissues in situ in pups; organ weights (absolute and relative to body weight) in pups for the following: testis (right and left), epididymis (right and left), seminal vesicle, ventral prostate, glans penis, LABC muscles, Cowper's glands, adrenal gland, kidney (pair), liver; histopathology of testes and epididymides in pups; metabolites of DINP in plasma collected from PND2 pups
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1325348

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	Low	The procedures were sensitive and specific for evaluating the endpoints and outcomes of interest. Only one DBP dose group was tested; however, DBP served as a positive control for DINP exposures in this study. The test animals were from a commercial source and the species, strain, and sex were appropriate for the evaluation of the intended outcomes. The number of animals per study group was appropriate for the outcome analysis and consistent with studies of similar type. The selection of the DBP dose level was not explicitly justified but the dose tested appears appropriate based on the available test data on the developmental effects for this test substance cited by the study authors. The outcome assessment methodology was appropriate to address the outcomes of interest and the outcome assessment was consistent across study groups. The study authors noted that due to the large numbers of animals in the study, all animals could not be necropsied on the same day. Therefore, animals were divided into five necropsy groups, each containing four to five litters from the control group and four litters from each of the test substance exposure groups. The necropsies were divided over two days and the five necropsy groups were treated identically (including the same acclimatization, dosing, and housing conditions). All of the treatment groups were represented on each necropsy day. The approaches described for necropsy methods appear to be appropriate.
	Metric 9:	Results presentation	High	The results presentation was appropriate for the outcomes of interest and endpoints evaluated. The statistical analyses methods were clearly described and appropriate for the data sets evaluated. Quantitative data for the reported effects were reported with means and SE or SD values for continuous data and incidences were provided for categorical data (e.g., histopathology of pups) including reporting of the numbers of animals affected and the total numbers of animals examined.

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Clewell, R. A., Thomas, A., Willson, G., Creasy, D. M., Andersen, M. E. (2013). A dose response study to assess effects after dietary administration of diisononyl phthalate (DINP) in gestation and lactation on male rat sexual development. Reproductive Toxicology 35(Elsevier):70-80.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, body weight gain, food consumption-Reproductive/Developmental-Number of litters; number of live pups; number of live pups/litter; male pup body weight; anogenital distance (absolute and scaled = AGD/BW^1/3); average number of nipples/areolae per male pup (based on visual identification; no histology confirmation); testis testosterone level in pups; gubernacular cord length in pups; gross necropsy of pups; examination of genital tract of pups for alterations (e.g., hypospadias, cleft phallus); examination of urogenital tract of pups; examinations for undescended testes and epididymal agenesis in pups; in situ examination of testes, epididymides, gubernacular cords, vas deferens, seminal vesicles, levator ani plus bulbocavernosus (LABC) muscles, and prostate in pups; examination of non-reproductive tissues in situ in pups; organ weights (absolute and relative to body weight) in pups for the following: testis (right and left), epididymis (right and left), seminal vesicle, ventral prostate, glans penis, LABC muscles, Cowper's glands, adrenal gland, kidney (pair), liver; histopathology of testes and epididymides in pups; metabolites of DINP in plasma collected from PND2 pups
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1325348

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	All critical and important information was reported. The test animal species, test article identity, dose levels tested and duration of exposure, route, quantitative or qualitative results for all endpoints examined, parity, commercial animal source, strain, age, sex, starting body weight, animal husbandry conditions (temperature, light/dark cycle, and humidity), number of animals per cage, availability of food and water, test substance source, purity, method of administration, frequency of exposure, number of animals per group, and assays and procedures used to measure endpoints were reported.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	The allocation method for the assignment of pregnant females to experimental groups is not described. There is no other mention of steps that may have been taken to balance variables, such as test animal characteristics or other modifying factors, across experimental groups when assigning animals to experimental groups.
	Metric 3:	Observational Bias / Blinding Changes	High	The study implemented methods to reduce observational bias. The study report indicates that the study methodology included "blinding of all observations to ensure objectivity and eliminate bias." The use of blinded observers (which were provided no information on treatment group) was described for specific steps of the endpoint assessment methodology, including for the determination of nipple retention and measurement of anogenital distance. Histopathological examinations of testes and epididymides were conducted using a semi-blinded method of evaluation. For this approach, the initial histopathological examinations of tissues collected from all animals were performed by a primary pathologist with knowledge of positive and negative control groups so that potential changes related to test chemical administration could be identified. The initial examinations were followed by a secondary histopathological examination of all collected tissues by a peer reviewing pathologist who was blinded to the treatment groups (no knowledge of the treatment groups). The approaches used for blinding for histopathological examinations appear to be appropriate for this study.
Domain 3: Confounding / Variable Control				

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Study Citation:	Clewell, R. A., Thomas, A., Willson, G., Creasy, D. M., Andersen, M. E. (2013). A dose response study to assess effects after dietary administration of diisononyl phthalate (DINP) in gestation and lactation on male rat sexual development. Reproductive Toxicology 35(Elsevier):70-80.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, body weight gain, food consumption-Reproductive/Developmental-Number of litters; number of live pups; number of live pups/litter; male pup body weight; anogenital distance (absolute and scaled = AGD/BW^1/3); average number of nipples/areolae per male pup (based on visual identification; no histology confirmation); testis testosterone level in pups; gubernacular cord length in pups; gross necropsy of pups; examination of genital tract of pups for alterations (e.g., hypospadias, cleft phallus); examination of urogenital tract of pups; examinations for undescended testes and epididymal agenesis in pups; in situ examination of testes, epididymides, gubernacular cords, vas deferens, seminal vesicles, levator ani plus bulbocavernosus (LABC) muscles, and prostate in pups; examination of non-reproductive tissues in situ in pups; organ weights (absolute and relative to body weight) in pups for the following: testis (right and left), epididymis (right and left), seminal vesicle, ventral prostate, glans penis, LABC muscles, Cowper's glands, adrenal gland, kidney (pair), liver; histopathology of testes and epididymides in pups; metabolites of DINP in plasma collected from PND2 pups
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1325348

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	No differences were observed across the study groups that could bias the results or introduce a variable not accounted for in the study analysis. No potential confounding variables were identified. Food consumption data indicated similar food consumption for the control and DBP-exposed groups. The animal husbandry conditions and test substance administration conditions were consistent for the control and DBP-exposed 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. Similarly, it is unclear if glass or plastic water bottles were used. Again, plastic bottles could leach phthalates, potentially confounding results. The negative control response was adequate for the endpoints assessed.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Medium	The study reports the results for all prespecified outcomes, exposure groups, and evaluation timepoints described in the test methods. The number of animals per exposure group is not explicitly stated in the study methods; a range of 20-24 litters/treatment group is indicated in the methods. The results (e.g., Tables 1, 2, and 4, table footnotes) imply that 24 and 21 dams were treated in the control group and DBP-exposed group, respectively. There are inconsistencies in the numbers of male pups examined on PND 2 across the control group and DBP-exposed group without an explanation. The methods describe the selection of 1 male animal per litter on PND 2, but results for fewer than 24 control and 21 test substance-exposed groups are reported for some endpoints. For example, in Table 2, the number of animals was n = 19 for control animals and n = 17 for the DBP group for pup testis and epididymis weights measured on PND 2, whereas 24 control litters and 21 DBP treatment litters are reported for other endpoints. Table 2 also indicates below the table that there were n = 25 control litters "unless otherwise noted", but the number of control litters is reported as 24 in Row 1 of the table. Aside from these inconsistencies, no additional deficiencies were identified. There were no health outcomes identified (e.g., infection) that were unrelated to the exposure that would influence the outcome assessment. No other discrepancies or unexplained omissions or attrition were identified that are expected to affect the interpretation of the results of the study.

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Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, body weight gain, food consumption-Reproductive/Developmental-Number of litters; number of live pups; number of live pups/litter; male pup body weight; anogenital distance (absolute and scaled = AGD/BW^1/3); average number of nipples/areolae per male pup (based on visual identification; no histology confirmation); testis testosterone level in pups; gubernacular cord length in pups; gross necropsy of pups; examination of genital tract of pups for alterations (e.g., hypospadias, cleft phallus); examination of urogenital tract of pups; examinations for undescended testes and epididymal agenesis in pups; in situ examination of testes, epididymides, gubernacular cords, vas deferens, seminal vesicles, levator ani plus bulbocavernosus (LABC) muscles, and prostate in pups; examination of non-reproductive tissues in situ in pups; organ weights (absolute and relative to body weight) in pups for the following: testis (right and left), epididymis (right and left), seminal vesicle, ventral prostate, glans penis, LABC muscles, Cowper's glands, adrenal gland, kidney (pair), liver; histopathology of testes and epididymides in pups; metabolites of DINP in plasma collected from PND2 pups
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1325348

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	The study report adequately characterizes the exposure and the administration methods for control and test substance-exposed groups. There are minor uncertainties in the test substance characterization and test diet preparation methods that are expected to have minimal impact on interpretation of the results. The test substance source, purity, and lot number for the test substance are reported. Test diets were prepared by adding neat test substance to rodent feed. The study report does not indicate how frequently test diets were prepared, certain conditions of methods used for mixing test substance into feed (e.g., mixing temperature), or conditions of storage of prepared test diets. However, homogeneity of test substance in prepared test diets, test substance stability in feed, and achieved concentrations of test substance in feed were analytically confirmed in samples collected from prepared feed batches. Measured concentrations of test substance in feed were within 3% of target concentrations. Test substance concentrations in samples collected from prepared feed batches at the conclusion of the study (3 months post-mixing) were within 8% of initial concentrations. Average maternal doses of test substance (in mg/kg/day) were calculated from maternal body weight and feed consumption data.
	Metric 7:	Exposure timing, frequency, and duration	High	The timing, frequency, and duration of exposure was sensitive for the outcomes of interest for this study. Methods used for exposure administration were consistent across the treatment groups. The period of exposure for this developmental toxicity study did not include exposure timing appropriate for assessing effects on implantation or organogenesis (i.e., dosing period for this study: GD 12 to PND 14; implantation in rats: GD 5; period of organogenesis in rats: GD 5-15). However, the study was designed to examine several endpoints of male rat sexual development in offspring that had been exposed during late gestation and during lactation, recognizing that other referenced studies were available which evaluated test substance-related developmental effects in rodents following exposure during a larger window of the gestational period. The exposure duration was considered appropriate for the intended purpose of this study and the failure to expose the animals during the full period of organogenesis or prior to implantation is not considered a study deficiency.

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Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, body weight gain, food consumption-Reproductive/Developmental-Number of litters; number of live pups; number of live pups/litter; male pup body weight; anogenital distance (absolute and scaled = AGD/BW^1/3); average number of nipples/areolae per male pup (based on visual identification; no histology confirmation); testis testosterone level in pups; gubernacular cord length in pups; gross necropsy of pups; examination of genital tract of pups for alterations (e.g., hypospadias, cleft phallus); examination of urogenital tract of pups; examinations for undescended testes and epididymal agenesis in pups; in situ examination of testes, epididymides, gubernacular cords, vas deferens, seminal vesicles, levator ani plus bulbocavernosus (LABC) muscles, and prostate in pups; examination of non-reproductive tissues in situ in pups; organ weights (absolute and relative to body weight) in pups for the following: testis (right and left), epididymis (right and left), seminal vesicle, ventral prostate, glans penis, LABC muscles, Cowper's glands, adrenal gland, kidney (pair), liver; histopathology of testes and epididymides in pups; metabolites of DINP in plasma collected from PND2 pups
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1325348

Domain	Metric	Rating	Comments
Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	Low	The procedures were sensitive and specific for evaluating the endpoints and outcomes of interest. Only one DBP dose group was tested; however, DBP served as a positive control for DINP exposures in this study. The test animals were from a commercial source and the species, strain, and sex were appropriate for the evaluation of the intended outcomes. The number of animals per study group was appropriate for the outcome analysis and consistent with studies of similar type. The selection of the DBP dose level was not explicitly justified but the dose tested appears appropriate based on the available test data on the developmental effects for this test substance cited by the study authors. The outcome assessment methodology was appropriate to address the outcomes of interest and the outcome assessment was consistent across study groups. The study authors noted that due to the large numbers of animals in the study, all animals could not be necropsied on the same day. Therefore, animals were divided into five necropsy groups, each containing four to five litters from the control group and four litters from each of the test substance exposure groups. The necropsies were divided over two days and the five necropsy groups were treated identically (including the same acclimatization, dosing, and housing conditions). All of the treatment groups were represented on each necropsy day. The approaches described for necropsy methods appear to be appropriate.
	Metric 9: Results presentation	High	The results presentation was appropriate for the outcomes of interest and endpoints evaluated. The statistical analyses methods were clearly described and appropriate for the data sets evaluated. Quantitative data for the reported effects were reported with means and SE or SD values for continuous data and incidences were provided for categorical data (e.g., histopathology of pups) including reporting of the numbers of animals affected and the total numbers of animals examined.

Additional Comments: None

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):	Reproductive/Developmental-Male Reproductive - testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (GD14- GD18)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl 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 18, 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 Sigma or RTI and were 99% 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):	Reproductive/Developmental-Male Reproductive - testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (GD14- GD18)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl 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):	Reproductive/Developmental-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:	Dibutyl 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):	Reproductive/Developmental-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:	Dibutyl 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: 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):	Reproductive/Developmental-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:	Dibutyl 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):	Reproductive/Developmental-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:	Dibutyl 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 numbers of fetuses and litters used to determine testicular testosterone production (Table 6) were reported.
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, and measures were identified. Testosterone production in an ex vivo assay was measured using a commercial radioimmunoassay kit according to the manufacturer's protocols. The methods stated that both testes from the first three male fetuses were dissected and incubated individually. The data table reports results from 9 control fetuses from 3 litters, and from 12 fetuses from 4 litters for the 50, 100, 300, and 600 mg/kg-day treatment groups. These sample sizes were considered to be adequate. As a secondary test, testosterone was also extracted from both testes of 10, 2, 5, 6, 3, and 6 fetuses in the 0, 33, 50, 100, 300, and 600 mg/kg-day groups, respectively, all derived from n = 2 litters. This sample size is small and is of some concern. The authors noted that, in their hands, testosterone extraction was a "less sensitive and precise measure of phthalate inhibition of steroidogenesis than testosterone production.
	Metric 9:	Results presentation	High	All outcomes: Good. There are no notable concerns about the way the results are analyzed or presented. Additional results are provided in a supplemental file.

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

Overall Quality Determination High

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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):	Reproductive/Developmental-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:	Dibutyl Phthalate- Parent compound
HERO ID:	675206

Domain	Metric	Rating	Comments

Study Citation:	Johnson, K. J., Hensley, J. B., Kelso, M. D., Wallace, D. G., Gaido, K. W. (2007). Mapping gene expression changes in the fetal rat testis following acute dibutyl phthalate exposure defines a complex temporal cascade of responding cell types. Biology of Reproduction 77(6):978-989.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Fetal testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (GD19)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	675949

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test substance was identified as dibutyl phthalate (DBP). The source of the test substance was identified (Aldrich Chemical Co., Milwaukee, WI). The study states that the purity and concentration of the dosing solutions were verified by gas chromatography but does not report the findings. Timed-pregnant Sprague-Dawley rats (obtained from Charles River Laboratories, Raleigh N.C.) arrived at gestation day 12 and were acclimated until use on GD 19. Age and initial body weights were not reported. Husbandry conditions (temperature, humidity, light cycle) were reported. The number of animals/cage was not reported. Food and water were available ad libitum. The frequency, duration, and route of exposure were reported. Target concentrations were reported. Endpoint evaluation methods were reported along with quantitative data. All critical information was reported; although some important information was not reported, it is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study reports ”allocation of animals to each study group was based upon body weight randomization”. No other details or method utilized was provided. Two fetuses/litter were used for analysis; the study authors do not report how the offspring were selected (if random).
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoint evaluated was not subjective in nature (measured testosterone levels).
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	A negative control group was included, and the response was appropriate. Husbandry conditions were fully reported, and no differences were identified. Animals were housed in polycarbonate cages. Polycarbonate contains BPA, which has been linked to developmental and reproductive health problems. This could potentially confound results. Similarly, it is unclear if glass or plastic water bottles were used. Again, plastic bottles could leach phthalates into the drinking water confounding results. Body weights of the dams were not reported. No information is provided on the litters (number of pups/litters, sex, weight, death), differences in these parameters may impact the results.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Johnson, K. J., Hensley, J. B., Kelso, M. D., Wallace, D. G., Gaido, K. W. (2007). Mapping gene expression changes in the fetal rat testis following acute dibutyl phthalate exposure defines a complex temporal cascade of responding cell types. Biology of Reproduction 77(6):978-989.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Fetal testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (GD19)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	675949

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Medium	The study did not report any deaths, however it is unclear if all animals were included in analysis. Quantitative data were reported for outcomes.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	Source of the test substance was reported. The purity and concentration of the dosing solutions were verified by gas chromatography; however, the study did not report these findings. Sigma Aldrich's website reports a purity of DBP as 99%, however the study took place in 2007 so it is unclear if this is the same chemical used in this study. DBP was administered in corn oil via gavage in a total volume of 1 ml/kg, which is an appropriate volume. The study did not provide any details on the preparation, stability, or storage of the test substance, however given the short duration of the study this is unlikely to substantially impact results.
	Metric 7:	Exposure timing, frequency, and duration	High	The timing, duration and frequency of exposure (single exposure on GD19) was appropriate for the study's aim.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	The test animal species was appropriate. Testis from 2 fetuses/litter/dam/group were analyzed for testosterone levels (total of 6-10 fetuses/group/timepoint). Justification was provided for the dose levels chosen (based on previous studies). The number of exposure groups and spacing was sufficient (0, 1, 10, 100, and 500 mg/kg). Outcome methodologies were described sensitive to outcome of interest. Timing of outcome assessments were clearly reported.
	Metric 9:	Results presentation	Medium	Data were reported graphically as means +/-SEM. Control testosterone levels were reported with values for mean and SEM. Statistical methods were described (one-way ANOVA and Dunnett post-hoc test), but the study did not explicitly state whether the litter was used as the statistical unit.

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

Overall Quality Determination — Medium

Study Citation:	Johnson, K. J., Mcdowell, E. N., Viereck, M. P., Xia, J. Q. (2011). Species-specific dibutyl phthalate fetal testis endocrine disruption correlates with inhibition of SREBP2-dependent gene expression pathways. Toxicological Sciences 120(2):460-474.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Fetal testosterone levels
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD12-20)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	788312

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Low	All critical and some important information was reported. Reported information included information on the test substance (name and source), the test model (species, strain, sex, and source), animal husbandry details (food and water availability), exposure methods, experimental design, endpoint evaluations, and presentation of results.Missing information included the purity of the test substance, test animal age, initial body weights, parity, additional animal husbandry details, and number of animals per cage.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	Rats were “weight-randomized” into study groups. Further details of the randomization method were not specified.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not specified but the outcome was measured using a standard laboratory kit.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	A negative corn oil control group was included. Consistency of other potentially confounding factors (e.g., animal husbandry conditions, body weights, food or water intake) was not reported. The study did not report taking measures to minimize the exposure to other plasticizers. Animals were housed in polycarbonate cages with pine bedding. Food, tap water, and bedding were not tested for contaminates, and the materials used to dispense water to the animals were not specified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Medium	The total number of dams included in each test group was not specified in the methods. The data figure indicated that there were at least 6 control and 5 dams/treatment group. There were no effects on maternal or pup body weights. The study did not provide enough information to determine attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Johnson, K. J., Mcdowell, E. N., Viereck, M. P., Xia, J. Q. (2011). Species-specific dibutyl phthalate fetal testis endocrine disruption correlates with inhibition of SREBP2-dependent gene expression pathways. Toxicological Sciences 120(2):460-474.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Fetal testosterone levels
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD12-20)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	788312

Domain		Metric	Rating	Comments
	Metric 6:	Chemical administration and characterization	Low	The test material source (Sigma) was reported. The purity was not specified and no certificate of analysis was provided in the study report. Purity and certificates of analysis would have been available on the supplier's website and the time of purchase. There is no indication that the test substance was verified by the performing laboratory. No details on the preparation, storage, or stability of the test solutions were provided. Animals were dosed via gavage in corn oil and the gavage volume (1 mL/kg) was appropriate. Dosing occurred at the same time each day. Doses were reported in mg/kg-day. It was not specified whether the doses were adjusted daily based on dam body weight. Doses were not analytically verified.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were exposed from GD12-20. This exposure covers the period of post-implantation embryonic development and the critical windows of organogenesis and male sexual differentiation.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	There are no major concerns regarding the specificity and validity of the protocol for measuring testosterone production. Testosterone levels were measured using an ELISA assay on pooled homogenized testes from 2 fetuses (when possible) per litter from 6 control and 5 DBP-treated litters. The study included only two dose groups plus a control; the spacing was adequate to identify a NOAEL and LOAEL for this endpoint. The doses were justified by the study authors. The test species and strain were appropriate for the study type.
	Metric 9:	Results presentation	Low	Results were reported in a figure (bar graph) showing means ± SD. Statistical significance and sample sizes were noted. There is no indication that the litter was used as the experimental unit. Individual animal data were not provided.

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

Overall Quality Determination — Medium

Study Citation:	Jr, Gray, L. E., Lambright, C. S., Evans, N., Ford, J., Conley, J. M. (2024). Using targeted fetal rat testis genomic and endocrine alterations to predict the effects of a phthalate mixture on the male reproductive tract. Current Research in Toxicology 7:100180.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Ex vivo fetal testicular testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD14-18)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	11785000

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	This study is considered High for Domain 1. All critical and most important information was reported. The test animals' species, chemical name, doses, duration of exposure, and route of exposure were clearly reported, and quantitative results were provided for at least one endpoint. The test animal source, strain, age, sex, and starting body weight were reported. Parity status was not reported. Information on animal husbandry was reported, including temperature, humidity, light/dark cycle, diet, water availability, and number of animals per cage. The test substance source and purity and the method of administration were reported. The frequency of exposure, number of animals per study group, animal age and life stage during exposure and at endpoint/outcome evaluation were also reported. Assays used to evaluate the outcome of interest were also reported. The only missing piece of important information was the parity status of the animals; however, this is not expected to substantially impact the study evaluation.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	This study is considered High for Domain 2.1. The dams were weight-ranked and randomly assigned to treatment groups using experimental design software.
	Metric 3:	Observational Bias / Blinding Changes	Medium	This study is considered Medium for Domain 2.2. Measures to reduce observational bias were not described, but the potential concern for bias was mitigated because the outcomes were not subjective and based on the use of automated/computer-driven systems (LC-MS).
Domain 3: Confounding / Variable Control				

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Study Citation:	Jr, Gray, L. E., Lambright, C. S., Evans, N., Ford, J., Conley, J. M. (2024). Using targeted fetal rat testis genomic and endocrine alterations to predict the effects of a phthalate mixture on the male reproductive tract. Current Research in Toxicology 7:100180.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Ex vivo fetal testicular testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD14-18)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	11785000

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Low	This study is considered Low for Domain 3. The negative control group was exposed to corn oil vehicle only in the same manner as the treated groups (via gavage). A positive control group was not included and is not required. The animals were randomized based on body weight at the beginning of the study, so there is no concern for differences in initial body weight. Food/water intake was not reported; however, there were no statistically significant differences in body weight or weight gain between the treated and control groups. Palatability is also not an issue, as the test substance was administered via gavage. Animal husbandry conditions were well-described and uniform across all groups; however, the animals were housed in polycarbonate cages. There was also no indication of whether test animal bedding, food, and water were analyzed for the presence of contaminants, such as phthalates, which might impact the results and validity of the study. Food and water dispensing containers were not described. The potential for co-exposure to plasticizers is a major confounding factor.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	This study is considered High for Domain 4. The number of animals in the control and treatment groups were identified as n=7-8 per group. Although survival was not explicitly stated, the individual data were available in the supplemental materials. Additionally, although it was not explicitly stated in the results that 3 testis per litter per treatment group were collected (as per the methods section), the individual data were available in the supplemental materials, confirming there was no attrition.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	This study is considered Medium for Domain 5.1. The test substance and vehicle were identified and the source and lot of each were provided. The purity of the test substances was reported (DBP= 99.9% and DINP=99%) There was no indication that the test substance was verified by the performing laboratory. Gavage volume was reported to be 2.5 ml/kg-body weight. Dosing occurred at the same time each day. Doses were reported in mg/kg-day. It was not specified whether the doses were adjusted daily based on dam body weight. The test substance was prepared in corn oil, but no other details were provided (how solutions were mixed, frequency solutions were made). No details on the storage or stability of the test solutions were provided. Although some details in reporting are lacking, there is no indication that these omissions are likely to have a substantial impact on the study evaluation.

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Study Citation:	Jr, Gray, L. E., Lambright, C. S., Evans, N., Ford, J., Conley, J. M. (2024). Using targeted fetal rat testis genomic and endocrine alterations to predict the effects of a phthalate mixture on the male reproductive tract. Current Research in Toxicology 7:100180.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Ex vivo fetal testicular testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD14-18)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	11785000

Domain	Metric		Rating	Comments
	Metric 7:	Exposure timing, frequency, and duration	Medium	This study is considered Medium for Domain 5.2. The purpose of this study was to measure fetal testicular testosterone; however, animals were dosed from GD 14-GD 18 and sacrificed on GD 18. Fetal testicular testosterone is produced between GD 14-GD 21, so the early sacrifice may not have captured the true fetal testicular testosterone level. However, as the exposure covered most of the critical window, and the control animals were also sacrificed at GD 18, the early sacrifice is considered a minor limitation. The route and frequency (daily gavage exposure between 0700 and 0900 EST) were appropriate for the study type and outcome of interest.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	The study is considered Medium for Domain 6.1. The doses were justified by the authors, but only one dose per chemical was used. Outcome assessment methodologies were sensitive for the outcomes of interest and were consistently assessed across groups. The test animals selected were appropriate. The sample size (n=7 pregnant females/group) is slightly lower for the DBP and DINP groups than what is recommended by OECD for a reproductive study (n=8 pregnant females/group).
	Metric 9:	Results presentation	High	The study is considered High for Domain 6.2 for the reproductive/developmental endpoint. Data were analyzed and presented appropriately and included statistical significance. Individual animal data were provided in the supplemental file. Each litter was considered the experimental unit.

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Kuhl, A. J., Ross, S. M., Gaido, K. W. (2007). CCAAT/enhancer binding protein beta, but not steroidogenic factor-1, modulates the phthalate-induced dysregulation of rat fetal testicular steroidogenesis. Endocrinology 148(12):5851-5864.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Male Reproductive - testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 18)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1321665

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	Adequate. All critical information and some important information were reported. The test animal species, test article identity (identified by name), dose levels tested, duration of exposure, exposure route, method of administration, exposure frequency and duration, and qualitative or quantitative results were reported. Test animal characteristics, including commercial source, strain, sex, and gestation day at test initiation (GD 18) were reported. Cage type, bedding type, number of animals per cage, food and water type, and temperature, humidity, and light/dark cycle were reported. Food and water were provided ad libitum. The number of animals per study group and assays and procedures used to measure the endpoints of interest were reported. Test substance purity, test animal age and starting body weight at test initiation, and parity (i.e., the number of times maternal animal has given birth previously) were not reported.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	Adequate. Animals were assigned to study groups by body weight randomization using the program Provantis; however, the specific methods used were not described.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Adequate. Measures to reduce observational bias were not reported; however, this is not expected to impact the results for fetal testosterone analysis because the endpoints are relatively objective (e.g., quantitative measurement of fetal testosterone concentrations using radioimmunoassay, RIA, analysis).
Domain 3: Confounding / Variable Control				

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Study Citation:	Kuhl, A. J., Ross, S. M., Gaido, K. W. (2007). CCAAT/enhancer binding protein beta, but not steroidogenic factor-1, modulates the phthalate-induced dysregulation of rat fetal testicular steroidogenesis. Endocrinology 148(12):5851-5864.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Male Reproductive - testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 18)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1321665

Domain	Metric		Rating	Comments
	Metric 4:	Confounding / Variable Control	Medium	Adequate. An appropriate negative control was included in the study. Negative controls were included for the vehicle (corn oil) and for another phthalate (diethyl phthalate, DEP). Justification for use of DEP as a negative control was provided (i.e., DEP induced no developmental abnormalities in the male fetus after a 750 mg/kg/day dosage from GD 14 to postnatal day 3). The vehicle (corn oil, source provided; grade not specified) and gavage volume were the same for the control and treatment groups. There was no indication that experimental conditions, including husbandry, differed across the study groups. However, the study report did not indicate whether approaches were used to reduce exposure of test animals to plasticizers. There was also no indication of whether test animal bedding, food, and water were analyzed for the presence of contaminants, such as phthalates, which might impact the results and validity of the study. Body weights of maternal animals at initiation or during the study were not reported. Polycarbonate cages were used instead of wire cages. Food and water dispensing containers were not described.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Low	Deficient. Sample size is not reported for the testosterone concentration results. Results are presented in Figure 1 for fetal testosterone concentration measurements by RIA and described qualitatively in the text. It is unknown if the results presented in Figure 1 are representative of all eight replicate testes sampled per treatment group. One pair of testes was collected from eight replicate pups per group for testosterone concentration determination. Data are presented as a bar graph with error bars (mean +/- SEM, without N values). Neither the results text nor the Figure text indicates the N per group for the testosterone data presented in Figure 1. Therefore, it is unknown if all sampled replicates per group are accounted for in the results. It is unknown if there was any attrition among the test groups because no information is presented on maternal animals (N = 10/control and test concentration).
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	Deficient. Purity was not reported. Test substance was prepared in the vehicle, corn oil, for dosing via gavage. No information was provided on the preparation methods, storage, or stability of the test substance and dosing solutions although there was presumably only one test concentration preparation day since animals were dosed only once in this study. The study report states that purity and concentrations of all doses were verified with gas chromatography. Due to the lack of information on test substance purity and preparation methods, this metric is rated as low.

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Study Citation:	Kuhl, A. J., Ross, S. M., Gaido, K. W. (2007). CCAAT/enhancer binding protein beta, but not steroidogenic factor-1, modulates the phthalate-induced dysregulation of rat fetal testicular steroidogenesis. Endocrinology 148(12):5851-5864.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Male Reproductive - testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 18)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1321665

Domain	Metric		Rating	Comments
	Metric 7:	Exposure timing, frequency, and duration	Medium	Adequate. Animals were treated once on GD 18. The exposure does not cover the entire period of organogenesis or male sexual differentiation, but the exposure was appropriate for detecting the endpoints of interest identified by the study authors (fetal testosterone concentrations and mechanistic endpoints related to the regulation of testosterone synthesis). The selection of GD 18 corresponds with the time frame of production of "steadily increasing testosterone levels" by Leydig cells during normal development of the male reproductive tract (i.e., GD 17-20; as discussed on p. 5851 of the study report). A justification for administration only on GD 18 is not provided.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	Adequate. No concerns were identified regarding the specificity and validity of the protocol used for measuring fetal testosterone concentrations. Testosterone was measured based on an assay method published previously (multiple reports cited) and using a commercial radioimmunoassay kit according to the manufacturer's instructions. Timing of endpoint analysis (24 hours after control or test substance treatment) appears to be appropriate for the endpoints of interest. There are multiple concerns related to sampling and sample size. Although there were 10 maternal animals/group, only 8 pups were sampled (both testes collected from each replicate pup). It is unclear whether replicate pups selected from each treatment group were from different litters. Additionally, it is unclear if the results are based on all eight replicates per treatment group (N is not reported in text results or Figure 1); however, there was sufficient power to statistically detect differences in testosterone concentrations (results in Figure 1). It appears dose concentration spacing was appropriate but there were only two DBP dose groups (100 and 500 mg/kg/day).
	Metric 9:	Results presentation	Low	Deficient. Although testosterone concentrations are presented for each control and treatment group in Figure 1 as mean values +/- SEM (shown as error bars), N values are not reported. The methods section states that eight replicate pups were sampled from each group for measurement of testosterone concentrations but the N value for each group is not reported in the results (Figure 1), so it is unknown if all eight replicate pups sampled per group are represented in the results. Individual values are not reported. Additionally, it was not reported if replicate pups were selected from different litters or the same litters. There is no indication that the litter was used as the experimental unit. Individual animal data were not provided.

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

Overall Quality Determination — Low

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Study Citation:	Kuhl, A. J., Ross, S. M., Gaido, K. W. (2007). CCAAT/enhancer binding protein beta, but not steroidogenic factor-1, modulates the phthalate-induced dysregulation of rat fetal testicular steroidogenesis. Endocrinology 148(12):5851-5864.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Male Reproductive - testosterone
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 18)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1321665

Domain	Metric	Rating	Comments

Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Organ weight (testis, epididymis, prostate, seminal vesicles, ovaries including the oviducts, uterus); Histopathology (testis, epididymis, prostate, seminal vesicles, ovary, oviduct, uterus, and vagina);Sperm parameters (percent of motile sperm, concentration and percentage of abnormal sperm);Mating and fertility indices (copulatory plug, number of fertile pairs/number cohabitated, litter/pair);F1: live pup body weight, sex ratio, proportion of pups born alive, number of live pups/litter
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The chemical was identified by name (CASRN was not provided). The source and purity (>99%) were reported. Test animal species, strain, sex, age, and source were reported. It was not specified if mice were virgins. Initial body weights were not reported. Husbandry conditions (temperature, light cycle, number of animals/cage) were reported; humidity was not reported. Cage type and bedding type were reported. Food and water were provided ad libitum. Route of exposure was reported. Doses were reported as % in food. Target concentrations were reported, and analytical concentrations were reportedly within 86-107% of target concentration for DEHP and 96- 107% for DBP. Duration of exposure was reported. Endpoint evaluation methods were reported along with quantitative data.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	Animals were allocated to groups by stratified randomization procedure based on body weights.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, endpoints evaluated were either not subjective in nature or consisted of clinical signs or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	Body weight and food intake were not sufficiently reported in this dietary exposure study to determine confounding. Food intake was reported to be similar between the groups, however the study did not distinguish between when mice were pregnant vs non-pregnant or male/female difference. A negative control group was included (Purina certified chow) and responses were appropriate. Housing conditions that were specified seemed to be consistent across groups (humidity was not reported). The study report did not indicate whether approaches were used to reduce exposure of test animals to plasticizers. There was also no indication of whether test animal bedding, food, and water were analyzed for the presence of contaminants, such as phthalates, which might impact the results and validity of the study. Body weights of maternal animals at initiation or during the study were not reported. Polycarbonate cages were used instead of wire cages. Food and water dispensing containers were not described.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Organ weight (testis, epididymis, prostate, seminal vesicles, ovaries including the oviducts, uterus); Histopathology (testis, epididymis, prostate, seminal vesicles, ovary, oviduct, uterus, and vagina);Sperm parameters (percent of motile sperm, concentration and percentage of abnormal sperm);Mating and fertility indices (copulatory plug, number of fertile pairs/number cohabitated, litter/pair);F1: live pup body weight, sex ratio, proportion of pups born alive, number of live pups/litter
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Medium	Data were reported for most outcomes in tabular form or within text. Most animals were accounted for the results. Methods stated that pups were assessed for sex ratio but results were not reported for this endpoint. Overall, the omissions and attrition are not explained but they are not expected to significantly impact the interpretation of the results. Sample size was stated in the methods and the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	The source of the test substance was reported. The purity of the test substance was independently verified by chromatography and spectrometric analysis to be 99%. Test substance formulations were mixed separately every week, stored at -20°C until used, and tested every 6 weeks by Midwest Research Institute for referee analysis. The compound was reportedly stable in room air and light for 7 days. Target test concentrations were reported (%); data in mg/kg/day was not provided. Feed intake and body weights were not reported. Study authors stated that because pairs were cohabiting that it was not possible to accurately determine relative dose in mg/kg.
	Metric 7:	Exposure timing, frequency, and duration	Low	Doses were selected to ensure no severe systemic toxicity at the highest dose and lesser or no toxicity at the two lower doses; however, it was unclear if this was based on previous toxicity studies. Animals were exposed for a 7-day premating period, paired, and then exposed an additional 98 days. Pairs were then separated and exposed for 21 days. Exposure was consistent across study groups. Groups were treated concurrently. The OECD 422 and 443 Guidelines which examine similar endpoints suggest a premating period of 14 days as opposed to 7 days. This shortened pre-mating period may not have allowed females to have completed enough oestrous cycles to sufficiently detect adverse effects or for males to have adequate time for the maturing of spermatozoa.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	No guideline was specified. The number of animals/group was appropriate as group sizes were large enough to yield at least 20 pregnant females/group and sufficient for statistical analysis. Three treated groups and one control group were utilized which was appropriate. The OECD guidelines recommend using doses that are two to four-fold increase intervals apart. While the study authors used doses with ten-fold intervals, excessive death was not observed at the highest dose and adverse effects were not observed at the lowest dose. Outcome methodologies were reported and considered sensitive for most endpoints. Necropsy and histopathology were performed only on the highest dose group and control group.

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Organ weight (testis, epididymis, prostate, seminal vesicles, ovaries including the oviducts, uterus); Histopathology (testis, epididymis, prostate, seminal vesicles, ovary, oviduct, uterus, and vagina);Sperm parameters (percent of motile sperm, concentration and percentage of abnormal sperm);Mating and fertility indices (copulatory plug, number of fertile pairs/number cohabitated, litter/pair);F1: live pup body weight, sex ratio, proportion of pups born alive, number of live pups/litter
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Low	Results were described in the text and data were presented in tables as means ± standard error. Statistical analysis methods were reported. The study used the pup instead of the litter as the unit of statistical analysis, this has the potential to overestimate statistical significance of experimental findings (Dishaw et al. 2020). Individual animal data was not reported.

Additional Comments: None

Overall Quality Determination Low

Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Hepatic/Liver-Liver weight-Neurological/Behavioral-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The chemical was identified by name (CASRN was not provided). The source and purity (>99%) were reported. Test animal species, strain, sex, age, and source were reported. It was not specified if mice were virgins. Initial body weights were not reported. Husbandry conditions (temperature, light cycle, number of animals/cage) were reported; humidity was not reported. Cage type and bedding type were reported. Food and water were provided ad libitum. Route of exposure was reported. Doses were reported as % in food. Target concentrations were reported, and analytical concentrations were reportedly within 86-107% of target concentration for DEHP and 96- 107% for DBP. Duration of exposure was reported. Endpoint evaluation methods were reported along with quantitative data.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	Animals were allocated to groups by stratified randomization procedure based on body weights.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, endpoints evaluated were either not subjective in nature or consisted of clinical signs or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	Body weight and food intake were not sufficiently reported in this dietary exposure study to determine confounding. Food intake was reported to be similar between the groups, however the study did not distinguish between when mice were pregnant vs non-pregnant or male/female difference. A negative control group was included (Purina certified chow) and responses were appropriate. Housing conditions that were specified seemed to be consistent across groups (humidity was not reported). The study report did not indicate whether approaches were used to reduce exposure of test animals to plasticizers. There was also no indication of whether test animal bedding, food, and water were analyzed for the presence of contaminants, such as phthalates, which might impact the results and validity of the study. Body weights of maternal animals at initiation or during the study were not reported. Polycarbonate cages were used instead of wire cages. Food and water dispensing containers were not described.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Hepatic/Liver-Liver weight-Neurological/Behavioral-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Medium	Data were reported for most outcomes in tabular form or within text. Most animals were accounted for the results. Methods stated that pups were assessed for sex ratio but results were not reported for this endpoint. Overall, the omissions and attrition are not explained but they are not expected to significantly impact the interpretation of the results. Sample size was stated in the methods and the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	The source of the test substance was reported. The purity of the test substance was independently verified by chromatography and spectrometric analysis to be 99%. Test substance formulations were mixed separately every week, stored at -20°C until used, and tested every 6 weeks by Midwest Research Institute for referee analysis. The compound was reportedly stable in room air and light for 7 days. Target test concentrations were reported (%); data in mg/kg/day was not provided. Feed intake and body weights were not reported. Study authors stated that because pairs were cohabiting that it was not possible to accurately determine relative dose in mg/kg.
	Metric 7:	Exposure timing, frequency, and duration	Low	Doses were selected to ensure no severe systemic toxicity at the highest dose and lesser or no toxicity at the two lower doses; however, it was unclear if this was based on previous toxicity studies. Animals were exposed for a 7-day premating period, paired, and then exposed an additional 98 days. Pairs were then separated and exposed for 21 days. Exposure was consistent across study groups. Groups were treated concurrently. The OECD 422 and 443 Guidelines which examine similar endpoints suggest a premating period of 14 days as opposed to 7 days. This shortened pre-mating period may not have allowed females to have completed enough oestrous cycles to sufficiently detect adverse effects or for males to have adequate time for the maturing of spermatozoa.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	No guideline was specified. The number of animals/group was appropriate as group sizes were large enough to yield at least 20 pregnant females/group and sufficient for statistical analysis. Three treated groups and one control group were utilized which was appropriate. The OECD guidelines recommend using doses that are two to four-fold increase intervals apart. While the study authors used doses with ten-fold intervals, excessive death was not observed at the highest dose and adverse effects were not observed at the lowest dose. Outcome methodologies were reported and considered sensitive for most endpoints. Necropsy and histopathology were performed only on the highest dose group and control group.

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Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	High	Data for mortality and organ weights were fully reported. Organ weights were reported as means +/- SE along with number of animals. Statistical methods were reported and appropriate.

Additional Comments: None

Overall Quality Determination Medium

Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Hepatic/Liver-Liver weight-Neurological/Behavioral-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The chemical was identified by name (CASRN was not provided). The source and purity (>99%) were reported. Test animal species, strain, sex, age, and source were reported. It was not specified if mice were virgins. Initial body weights were not reported. Husbandry conditions (temperature, light cycle, number of animals/cage) were reported; humidity was not reported. Cage type and bedding type were reported. Food and water were provided ad libitum. Route of exposure was reported. Doses were reported as % in food. Target concentrations were reported, and analytical concentrations were reportedly within 86-107% of target concentration for DEHP and 96- 107% for DBP. Duration of exposure was reported. Endpoint evaluation methods were reported along with quantitative data.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	Animals were allocated to groups by stratified randomization procedure based on body weights.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, endpoints evaluated were either not subjective in nature or consisted of clinical signs or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	Body weight and food intake were not sufficiently reported in this dietary exposure study to determine confounding. Food intake was reported to be similar between the groups, however the study did not distinguish between when mice were pregnant vs non-pregnant or male/female difference. A negative control group was included (Purina certified chow) and responses were appropriate. Housing conditions that were specified seemed to be consistent across groups (humidity was not reported). The study report did not indicate whether approaches were used to reduce exposure of test animals to plasticizers. There was also no indication of whether test animal bedding, food, and water were analyzed for the presence of contaminants, such as phthalates, which might impact the results and validity of the study. Body weights of maternal animals at initiation or during the study were not reported. Polycarbonate cages were used instead of wire cages. Food and water dispensing containers were not described.
Domain 4: Selective Reporting and Attrition				

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Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Hepatic/Liver-Liver weight-Neurological/Behavioral-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Medium	Data were reported for most outcomes in tabular form or within text. Most animals were accounted for the results. Methods stated that pups were assessed for sex ratio but results were not reported for this endpoint. Overall, the omissions and attrition are not explained but they are not expected to significantly impact the interpretation of the results. Sample size was stated in the methods and the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	The source of the test substance was reported. The purity of the test substance was independently verified by chromatography and spectrometric analysis to be 99%. Test substance formulations were mixed separately every week, stored at -20°C until used, and tested every 6 weeks by Midwest Research Institute for referee analysis. The compound was reportedly stable in room air and light for 7 days. Target test concentrations were reported (%); data in mg/kg/day was not provided. Feed intake and body weights were not reported. Study authors stated that because pairs were cohabiting that it was not possible to accurately determine relative dose in mg/kg.
	Metric 7:	Exposure timing, frequency, and duration	Low	Doses were selected to ensure no severe systemic toxicity at the highest dose and lesser or no toxicity at the two lower doses; however, it was unclear if this was based on previous toxicity studies. Animals were exposed for a 7-day premating period, paired, and then exposed an additional 98 days. Pairs were then separated and exposed for 21 days. Exposure was consistent across study groups. Groups were treated concurrently. The OECD 422 and 443 Guidelines which examine similar endpoints suggest a premating period of 14 days as opposed to 7 days. This shortened pre-mating period may not have allowed females to have completed enough oestrous cycles to sufficiently detect adverse effects or for males to have adequate time for the maturing of spermatozoa.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	No guideline was specified. The number of animals/group was appropriate as group sizes were large enough to yield at least 20 pregnant females/group and sufficient for statistical analysis. Three treated groups and one control group were utilized which was appropriate. The OECD guidelines recommend using doses that are two to four-fold increase intervals apart. While the study authors used doses with ten-fold intervals, excessive death was not observed at the highest dose and adverse effects were not observed at the lowest dose. Outcome methodologies were reported and considered sensitive for most endpoints. Necropsy and histopathology were performed only on the highest dose group and control group.

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Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
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Domain	Metric	Rating	Comments
	Metric 9: Results presentation	High	Data for mortality and organ weights were fully reported. Organ weights were reported as means +/- SE along with number of animals. Statistical methods were reported and appropriate.

Additional Comments: None

Overall Quality Determination Medium

Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
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Domain 4: Selective Reporting and Attrition				

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	Metric 7:	Exposure timing, frequency, and duration	Low	Doses were selected to ensure no severe systemic toxicity at the highest dose and lesser or no toxicity at the two lower doses; however, it was unclear if this was based on previous toxicity studies. Animals were exposed for a 7-day premating period, paired, and then exposed an additional 98 days. Pairs were then separated and exposed for 21 days. Exposure was consistent across study groups. Groups were treated concurrently. The OECD 422 and 443 Guidelines which examine similar endpoints suggest a premating period of 14 days as opposed to 7 days. This shortened pre-mating period may not have allowed females to have completed enough oestrous cycles to sufficiently detect adverse effects or for males to have adequate time for the maturing of spermatozoa.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	No guideline was specified. The number of animals/group was appropriate as group sizes were large enough to yield at least 20 pregnant females/group and sufficient for statistical analysis. Three treated groups and one control group were utilized which was appropriate. The OECD guidelines recommend using doses that are two to four-fold increase intervals apart. While the study authors used doses with ten-fold intervals, excessive death was not observed at the highest dose and adverse effects were not observed at the lowest dose. Outcome methodologies were reported and considered sensitive for most endpoints. Necropsy and histopathology were performed only on the highest dose group and control group.

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Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Hepatic/Liver-Liver weight-Neurological/Behavioral-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	High	Data for mortality and organ weights were fully reported. Organ weights were reported as means +/- SE along with number of animals. Statistical methods were reported and appropriate.

Additional Comments: None

Overall Quality Determination Medium

Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Hepatic/Liver-Liver weight-Neurological/Behavioral-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The chemical was identified by name (CASRN was not provided). The source and purity (>99%) were reported. Test animal species, strain, sex, age, and source were reported. It was not specified if mice were virgins. Initial body weights were not reported. Husbandry conditions (temperature, light cycle, number of animals/cage) were reported; humidity was not reported. Cage type and bedding type were reported. Food and water were provided ad libitum. Route of exposure was reported. Doses were reported as % in food. Target concentrations were reported, and analytical concentrations were reportedly within 86-107% of target concentration for DEHP and 96- 107% for DBP. Duration of exposure was reported. Endpoint evaluation methods were reported along with quantitative data.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	Animals were allocated to groups by stratified randomization procedure based on body weights.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, endpoints evaluated were either not subjective in nature or consisted of clinical signs or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	Body weight and food intake were not sufficiently reported in this dietary exposure study to determine confounding. Food intake was reported to be similar between the groups, however the study did not distinguish between when mice were pregnant vs non-pregnant or male/female difference. A negative control group was included (Purina certified chow) and responses were appropriate. Housing conditions that were specified seemed to be consistent across groups (humidity was not reported). The study report did not indicate whether approaches were used to reduce exposure of test animals to plasticizers. There was also no indication of whether test animal bedding, food, and water were analyzed for the presence of contaminants, such as phthalates, which might impact the results and validity of the study. Body weights of maternal animals at initiation or during the study were not reported. Polycarbonate cages were used instead of wire cages. Food and water dispensing containers were not described.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Hepatic/Liver-Liver weight-Neurological/Behavioral-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Medium	Data were reported for most outcomes in tabular form or within text. Most animals were accounted for the results. Methods stated that pups were assessed for sex ratio but results were not reported for this endpoint. Overall, the omissions and attrition are not explained but they are not expected to significantly impact the interpretation of the results. Sample size was stated in the methods and the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	The source of the test substance was reported. The purity of the test substance was independently verified by chromatography and spectrometric analysis to be 99%. Test substance formulations were mixed separately every week, stored at -20°C until used, and tested every 6 weeks by Midwest Research Institute for referee analysis. The compound was reportedly stable in room air and light for 7 days. Target test concentrations were reported (%); data in mg/kg/day was not provided. Feed intake and body weights were not reported. Study authors stated that because pairs were cohabiting that it was not possible to accurately determine relative dose in mg/kg.
	Metric 7:	Exposure timing, frequency, and duration	Low	Doses were selected to ensure no severe systemic toxicity at the highest dose and lesser or no toxicity at the two lower doses; however, it was unclear if this was based on previous toxicity studies. Animals were exposed for a 7-day premating period, paired, and then exposed an additional 98 days. Pairs were then separated and exposed for 21 days. Exposure was consistent across study groups. Groups were treated concurrently. The OECD 422 and 443 Guidelines which examine similar endpoints suggest a premating period of 14 days as opposed to 7 days. This shortened pre-mating period may not have allowed females to have completed enough oestrous cycles to sufficiently detect adverse effects or for males to have adequate time for the maturing of spermatozoa.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	No guideline was specified. The number of animals/group was appropriate as group sizes were large enough to yield at least 20 pregnant females/group and sufficient for statistical analysis. Three treated groups and one control group were utilized which was appropriate. The OECD guidelines recommend using doses that are two to four-fold increase intervals apart. While the study authors used doses with ten-fold intervals, excessive death was not observed at the highest dose and adverse effects were not observed at the lowest dose. Outcome methodologies were reported and considered sensitive for most endpoints. Necropsy and histopathology were performed only on the highest dose group and control group.

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Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Hepatic/Liver-Liver weight-Neurological/Behavioral-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	High	Data for mortality and organ weights were fully reported. Organ weights were reported as means +/- SE along with number of animals. Statistical methods were reported and appropriate.

Additional Comments: None

Overall Quality Determination Medium

Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical signs)-Clinical signs of toxicity
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The chemical was identified by name (CASRN was not provided). The source and purity (>99%) were reported. Test animal species, strain, sex, age, and source were reported. It was not specified if mice were virgins. Initial body weights were not reported. Husbandry conditions (temperature, light cycle, number of animals/cage) were reported; humidity was not reported. Cage type and bedding type were reported. Food and water were provided ad libitum. Route of exposure was reported. Doses were reported as % in food. Target concentrations were reported, and analytical concentrations were reportedly within 86-107% of target concentration for DEHP and 96- 107% for DBP. Duration of exposure was reported. Endpoint evaluation methods were reported along with quantitative data.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	Animals were allocated to groups by stratified randomization procedure based on body weights.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, endpoints evaluated were either not subjective in nature or consisted of clinical signs or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	Body weight and food intake were not sufficiently reported in this dietary exposure study to determine confounding. Food intake was reported to be similar between the groups, however the study did not distinguish between when mice were pregnant vs non-pregnant or male/female difference. A negative control group was included (Purina certified chow) and responses were appropriate. Housing conditions that were specified seemed to be consistent across groups (humidity was not reported). The study report did not indicate whether approaches were used to reduce exposure of test animals to plasticizers. There was also no indication of whether test animal bedding, food, and water were analyzed for the presence of contaminants, such as phthalates, which might impact the results and validity of the study. Body weights of maternal animals at initiation or during the study were not reported. Polycarbonate cages were used instead of wire cages. Food and water dispensing containers were not described.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical signs)-Clinical signs of toxicity
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Medium	Data were reported for most outcomes in tabular form or within text. Most animals were accounted for the results. Methods stated that pups were assessed for sex ratio but results were not reported for this endpoint. Overall, the omissions and attrition are not explained but they are not expected to significantly impact the interpretation of the results. Sample size was stated in the methods and the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	The source of the test substance was reported. The purity of the test substance was independently verified by chromatography and spectrometric analysis to be 99%. Test substance formulations were mixed separately every week, stored at -20°C until used, and tested every 6 weeks by Midwest Research Institute for referee analysis. The compound was reportedly stable in room air and light for 7 days. Target test concentrations were reported (%); data in mg/kg/day was not provided. Feed intake and body weights were not reported. Study authors stated that because pairs were cohabiting that it was not possible to accurately determine relative dose in mg/kg.
	Metric 7:	Exposure timing, frequency, and duration	Low	Doses were selected to ensure no severe systemic toxicity at the highest dose and lesser or no toxicity at the two lower doses; however, it was unclear if this was based on previous toxicity studies. Animals were exposed for a 7-day premating period, paired, and then exposed an additional 98 days. Pairs were then separated and exposed for 21 days. Exposure was consistent across study groups. Groups were treated concurrently. The OECD 422 and 443 Guidelines which examine similar endpoints suggest a premating period of 14 days as opposed to 7 days. This shortened pre-mating period may not have allowed females to have completed enough oestrous cycles to sufficiently detect adverse effects or for males to have adequate time for the maturing of spermatozoa.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	No guideline was specified. The number of animals/group was appropriate as group sizes were large enough to yield at least 20 pregnant females/group and sufficient for statistical analysis. Three treated groups and one control group were utilized which was appropriate. The OECD guidelines recommend using doses that are two to four-fold increase intervals apart. While the study authors used doses with ten-fold intervals, excessive death was not observed at the highest dose and adverse effects were not observed at the lowest dose. Outcome methodologies for assessing clinical signs were not reported (frequency, detailed or cage-side observations).
	Metric 9:	Results presentation	Medium	Clinical signs were reported as negative in text.

Additional Comments: None

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Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical signs)-Clinical signs of toxicity
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

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

Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight and food intake
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The chemical was identified by name (CASRN was not provided). The source and purity (>99%) were reported. Test animal species, strain, sex, age, and source were reported. It was not specified if mice were virgins. Initial body weights were not reported. Husbandry conditions (temperature, light cycle, number of animals/cage) were reported; humidity was not reported. Cage type and bedding type were reported. Food and water were provided ad libitum. Route of exposure was reported. Doses were reported as % in food. Target concentrations were reported, and analytical concentrations were reportedly within 86-107% of target concentration for DEHP and 96- 107% for DBP. Duration of exposure was reported. Endpoint evaluation methods were reported along with quantitative data.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	Animals were allocated to groups by stratified randomization procedure based on body weights.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported; however, endpoints evaluated were either not subjective in nature or consisted of clinical signs or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	Body weight and food intake were not sufficiently reported in this dietary exposure study to determine confounding. Food intake was reported to be similar between the groups, however the study did not distinguish between when mice were pregnant vs non-pregnant or male/female difference. A negative control group was included (Purina certified chow) and responses were appropriate. Housing conditions that were specified seemed to be consistent across groups (humidity was not reported). The study report did not indicate whether approaches were used to reduce exposure of test animals to plasticizers. There was also no indication of whether test animal bedding, food, and water were analyzed for the presence of contaminants, such as phthalates, which might impact the results and validity of the study. Body weights of maternal animals at initiation or during the study were not reported. Polycarbonate cages were used instead of wire cages. Food and water dispensing containers were not described.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight and food intake
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Medium	Data were reported for most outcomes in tabular form or within text. Most animals were accounted for the results. Methods stated that pups were assessed for sex ratio but results were not reported for this endpoint. Overall, the omissions and attrition are not explained but they are not expected to significantly impact the interpretation of the results. Sample size was stated in the methods and the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	The source of the test substance was reported. The purity of the test substance was independently verified by chromatography and spectrometric analysis to be 99%. Test substance formulations were mixed separately every week, stored at -20°C until used, and tested every 6 weeks by Midwest Research Institute for referee analysis. The compound was reportedly stable in room air and light for 7 days. Target test concentrations were reported (%); data in mg/kg/day was not provided. Feed intake and body weights were not reported. Study authors stated that because pairs were cohabiting that it was not possible to accurately determine relative dose in mg/kg.
	Metric 7:	Exposure timing, frequency, and duration	Low	Doses were selected to ensure no severe systemic toxicity at the highest dose and lesser or no toxicity at the two lower doses; however, it was unclear if this was based on previous toxicity studies. Animals were exposed for a 7-day premating period, paired, and then exposed an additional 98 days. Pairs were then separated and exposed for 21 days. Exposure was consistent across study groups. Groups were treated concurrently. The OECD 422 and 443 Guidelines which examine similar endpoints suggest a premating period of 14 days as opposed to 7 days. This shortened pre-mating period may not have allowed females to have completed enough oestrous cycles to sufficiently detect adverse effects or for males to have adequate time for the maturing of spermatozoa.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	No guideline was specified. The number of animals/group was appropriate as group sizes were large enough to yield at least 20 pregnant females/group and sufficient for statistical analysis. Three treated groups and one control group were utilized which was appropriate. The OECD guidelines recommend using doses that are two to four-fold increase intervals apart. While the study authors used doses with ten-fold intervals, excessive death was not observed at the highest dose and adverse effects were not observed at the lowest dose. Outcome methodologies were not adequately reported. Timing of measurements for food intake and body weights were not reported.

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Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied Pharmacology 88(2):255-269.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight and food intake
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating (98 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	61566

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Necropsy body weights were reported as means +/- SE for control and high dose groups. Statistical analysis was reported and appropriate. Body weights at 1 and 13 weeks are not fully reported (SE not included, only high-dose and control group reported). Food intake was reported in text as similar between the groups.

Additional Comments: None

Overall Quality Determination Low

Study Citation:	Lee, K. Y., Shibutani, M., Takagi, H., Kato, N., Takigami, S., Uneyama, C., Hirose, M. (2004). Diverse developmental toxicity of di-n-butyl phthalate in both sexes of rat offspring after maternal exposure during the period from late gestation through lactation. Toxicology 203(1-3):221-238.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Number of pups, body weights, sex ratio, anogenital distance, number of nipples/areolae, day of vaginal opening, day of preputial separation, estrous cyclicity. Organs weighed: brain, liver, kidneys, adrenals, testes, epidiymides, ovaries and uterus; in addition, pituitary, ventral lobe of the prostate and seminal vesicles were weight at PNW 11 and PNW 20. Histopathology was performed on the following tissues: brain, pituitary, thyroid glands, liver, kidneys, adrenals, testes, epidiymides, prostate, seminal vesicles, ovaries, uterus, vagina, and mammary glands. Immunohistochemistry was performed on the pituitary gland on offspring sacrificed on PND 21 and PNW 11 for luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin.
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-F0 - gestation (GD15 to delivery)-F0- lactation (until weaning (PND21))
Species:	Rat-Other (CD (SD) IGS)-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676278

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	Test substance was identified as di-n-butyl phthalate, CAS no 84-74-2; >98% pure. The supplier was reported. Dose levels in food were reported (0, 20, 200, 2000, and 10000 ppm). Food consumption and DBP intake were reported (split up in GD 15-20; PND 2-10; PND 10-21), 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. 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	Medium	Study states animals weighing 320-330 g were randomized into study groups. There is no indication what method was 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., body weight, organ weights, developmental milestones) or consisted of either an initial histopathology review, and no secondary histopathology review was conducted.
Domain 3: Confounding / Variable Control				

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Study Citation:	Lee, K. Y., Shibutani, M., Takagi, H., Kato, N., Takigami, S., Uneyama, C., Hirose, M. (2004). Diverse developmental toxicity of di-n-butyl phthalate in both sexes of rat offspring after maternal exposure during the period from late gestation through lactation. Toxicology 203(1-3):221-238.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Number of pups, body weights, sex ratio, anogenital distance, number of nipples/areolae, day of vaginal opening, day of preputial separation, estrous cyclicity. Organs weighed: brain, liver, kidneys, adrenals, testes, epidiymides, ovaries and uterus; in addition, pituitary, ventral lobe of the prostate and seminal vesicles were weight at PNW 11 and PNW 20. Histopathology was performed on the following tissues: brain, pituitary, thyroid glands, liver, kidneys, adrenals, testes, epidiymides, prostate, seminal vesicles, ovaries, uterus, vagina, and mammary glands. Immunohistochemistry was performed on the pituitary gland on offspring sacrificed on PND 21 and PNW 11 for luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin.
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-F0 - gestation (GD15 to delivery)-F0- lactation (until weaning (PND21))
Species:	Rat-Other (CD (SD) IGS)-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676278

Domain	Metric		Rating	Comments
	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. The test substance was delivered via diet. Food consumption was reported and did not differ significantly between the groups, suggesting palatability of the diet was not a concern. Although there were points when body weight gain differed in some groups (GD 15-20 for the lowest and highest dose), overall differences in body weights was not considered a confounding variable. Husbandry conditions were consistent between the groups. A concurrent negative control group was included, and the response was appropriate. The study took into consideration potential confounding variables in the diet, feeding the dams a soy-free diet with phytoestrogen below the detection limit (<0.05 mg/100g diet) and coumestrol present at 0.3 mg/100 g. Weaned pups were fed a normal rodent diet to avoid the potential changes in development due to long-term use of a soy-free diet.
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				
	Metric 6:	Chemical administration and characterization	Low	Animals were fed a soy-free diet containing DBP (>98% pure) at various concentrations. The study does not describe how the diet was prepared or how often. Information on stability of test substance in the diet was not provided. The study only reported nominal concentrations and not analytical, so there is uncertainty if the concentration reported is accurate. The study did report food intake and calculated DBP intake at three intervals (GD 15-20; PND 2-10; and PND 10-21), however given the uncertainty of the actual concentration in the food, and stability of test substance in the food, the calculated concentrations may not be accurate.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure timing and frequency, and duration were appropriate for the study's aim (GD15- PND 21). The study stated they wanted to focus on effects of test chemical on offspring when exposed from late gestation through lactation.
Domain 6: Outcome Measures and Results Display				

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Study Citation:	Lee, K. Y., Shibutani, M., Takagi, H., Kato, N., Takigami, S., Uneyama, C., Hirose, M. (2004). Diverse developmental toxicity of di-n-butyl phthalate in both sexes of rat offspring after maternal exposure during the period from late gestation through lactation. Toxicology 203(1-3):221-238.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Number of pups, body weights, sex ratio, anogenital distance, number of nipples/areolae, day of vaginal opening, day of preputial separation, estrous cyclicity. Organs weighed: brain, liver, kidneys, adrenals, testes, epidiymides, ovaries and uterus; in addition, pituitary, ventral lobe of the prostate and seminal vesicles were weight at PNW 11 and PNW 20. Histopathology was performed on the following tissues: brain, pituitary, thyroid glands, liver, kidneys, adrenals, testes, epidiymides, prostate, seminal vesicles, ovaries, uterus, vagina, and mammary glands. Immunohistochemistry was performed on the pituitary gland on offspring sacrificed on PND 21 and PNW 11 for luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin.
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-F0 - gestation (GD15 to delivery)-F0- lactation (until weaning (PND21))
Species:	Rat-Other (CD (SD) IGS)-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676278

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	Medium	The selected concentration (20-10000 ppm in food) were based on a preliminary study, "the highest dose was selected as the level to maintain pregnancy, delivery and lactation (data not shown)". The endpoints selected were sensitive to assess development, particularly sexual development in males and females. A NOAEL was not established. The lowest dose tested was reported by authors as the LOAEL for developmental toxicity. Endpoints were assessed consistently and sensitive to outcomes of interest.
	Metric 9:	Results presentation	Low	Data were presented fully for most endpoints. However, there were significant effects on absolute organ weights (testis on PND 21; prostate weight at PNW 11; kidney PNW 20) and data were not shown. Since effects on sexual development is an endpoint of interest, fully reporting testis and prostate absolute weight is important.

Additional Comments: None

Overall Quality Determination Medium

Study Citation:	Lee, K. Y., Shibutani, M., Takagi, H., Kato, N., Takigami, S., Uneyama, C., Hirose, M. (2004). Diverse developmental toxicity of di-n-butyl phthalate in both sexes of rat offspring after maternal exposure during the period from late gestation through lactation. Toxicology 203(1-3):221-238.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight and food intake of pregnant dams
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-F0 - gestation (GD15 to delivery)-F0- lactation (until weaning (PND21))
Species:	Rat-Other (CD (SD) IGS)-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676278

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	Test substance was identified as di-n-butyl phthalate, CAS no 84-74-2; >98% pure. The supplier was reported. Dose levels in food were reported (0, 20, 200, 2000, and 10000 ppm). Food consumption and DBP intake were reported (split up in GD 15-20; PND 2-10; PND 10-21), 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. 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	Medium	Study states animals weighing 320-330 g were randomized into study groups. There is no indication what method was 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., body weight, food intake).
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. The test substance was delivered via diet. Food consumption was reported and did not differ significantly between the groups, suggesting palatability of the diet was not a concern. Although there were points when body weight gain differed in some groups (GD 15-20 for the lowest and highest dose), overall differences in body weights was not considered a confounding variable. Husbandry conditions were consistent between the groups. A concurrent negative control group was included, and the response was appropriate. The study took into consideration potential confounding variables in the diet, feeding the dams a soy-free diet with phytoestrogen below the detection limit (<0.05 mg/100g diet) and coumestrol present at 0.3 mg/100 g. Weaned pups were fed a normal rodent diet to avoid the potential changes in development due to long-term use of a soy-free diet.
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.

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Study Citation:	Lee, K. Y., Shibutani, M., Takagi, H., Kato, N., Takigami, S., Uneyama, C., Hirose, M. (2004). Diverse developmental toxicity of di-n-butyl phthalate in both sexes of rat offspring after maternal exposure during the period from late gestation through lactation. Toxicology 203(1-3):221-238.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight and food intake of pregnant dams
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-F0 - gestation (GD15 to delivery)-F0- lactation (until weaning (PND21))
Species:	Rat-Other (CD (SD) IGS)-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676278

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	Animals were fed a soy-free diet containing DBP (>98% pure) at various concentrations. The study does not describe how the diet was prepared or how often. Information on stability of test substance in the diet was not provided. The study only reported nominal concentrations and not analytical, so there is uncertainty if the concentration reported is accurate. The study did report food intake and calculated DBP intake at three intervals (GD 15-20; PND 2-10; and PND 10-21), however given the uncertainty of the actual concentration in the food, and stability of test substance in the food, the calculated concentrations may not be accurate.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure timing and frequency, and duration were appropriate for the study's aim (GD15- PND 21). The study stated they wanted to focus on effects of test chemical on offspring when exposed from late gestation through lactation.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	The selected concentration (20-10000 ppm in food) were based on a preliminary study, "the highest dose was selected as the level to maintain pregnancy, delivery and lactation (data not shown)". The endpoints selected were sensitive to assess development, particularly sexual development in males and females. A NOAEL was not established. The lowest dose tested was reported by authors as the LOAEL for developmental toxicity. Endpoints were assessed consistently and sensitive to outcomes of interest.
	Metric 9:	Results presentation	High	Body weight gain and food intake were reported as means +/- SD broken down from GD 15-20, PND 2-10 and PND 10-21 (times when females were exposed).

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Lehmann, K. P., Phillips, S., Sar, M., Foster, D., P.M., Gaido, K. W. (2004). Dose-dependent alterations in gene expression and testosterone synthesis in the fetal testes of male rats exposed to di (n-butyl) phthalate. Toxicological Sciences 81(1):60-68.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Testicular levels of testosterone (radioimmunoassay) and lipid content (oil red O staining)Gene and protein expression of genes and proteins involved in cholesterol transport and steroidogenesis (RT-PCR, Western Blot, and immunohistochemistry)
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-19)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	674382

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 di (n-butyl) phthalate (DBP). The source was reported (Aldrich Chemical Co., Milwaukee, WI). Purity was not reported. Test animal species, strain, sex, age and source were reported. Initial body weight of the animals was not reported. Husbandry conditions (temperature, humidity, and light cycle) were reported. Diet and water were provided ad libitum. Animals were housed individually. The concentration 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	High	Pregnant dams were assigned to a treatment group by body weight randomization using Provantis.
	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., testosterone levels, body weight).
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	A concurrent negative control group was included. Husbandry conditions were reported and similar between the groups. Body weight changes and food consumption were not reported, which could potentially confound results. Animals were housed in polycarbonate cages. Polycarbonate contains BPA, which have been linking to developmental and reproductive health problems. Similarly, it is unclear if glass or plastic water bottles were used. Again, plastic bottles could leach phthalates that could confound results. This could potentially confound results, although if control animals were exposed to the same levels, this may not substantially impact interpretation of results.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Low	Sample size was not clearly reported in method or results. It is not clear if any animals may have died during treatment.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Lehmann, K. P., Phillips, S., Sar, M., Foster, D., P.M., Gaido, K. W. (2004). Dose-dependent alterations in gene expression and testosterone synthesis in the fetal testes of male rats exposed to di (n-butyl) phthalate. Toxicological Sciences 81(1):60-68.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Testicular levels of testosterone (radioimmunoassay) and lipid content (oil red O staining)Gene and protein expression of genes and proteins involved in cholesterol transport and steroidogenesis (RT-PCR, Western Blot, and immunohistochemistry)
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-19)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	674382

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	Purity and concentration of all doses were verified using a Hewlett Packard 5890 gas chromatograph; however the study does not report what the purity was. The highest dose level was chosen based on our previous studies showing that 500 mg/kg/day produced significant changes in gene expression in the male offspring without maternal toxicity or fetal death (Barlow and Foster, 2003; Shultz et al., 2001). The lowest dose level was selected based on current estimates for human exposure, which reach as high as 0.113 mg/kg/day (Blount et al., 2000; Kohn et al., 2000). A NOAEL and LOAEL were determined. The gavage volume was appropriate (did not exceed 0.1 ml/10 g body weight).
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency, timing and duration were appropriate for the study's aim (GD 12-19).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Low	Study only reported testicular testosterone levels via radioimmunoassay. No histological examination was performed, or any other apical endpoint evaluated. Detail regarding sampling of testosterone levels are not fully reported. The study reports 3-4 separate rat fetuses from 1-4 dams per treatment group were assess. That means there could be a large discrepancy of the number of fetuses assessed (potentially from 3 to 16) between groups. This large range of animals evaluated could substantially impact results.
	Metric 9:	Results presentation	Low	Data were presented as mean +/- SEM from 3-4 separate rat fetuses from 1-4 dams per treatment group. The presentation of offspring data as means of individual animals, rather than as litter means, has the potential to overestimate the statistical significance of experimental findings.

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Lehmann, K. P., Phillips, S., Sar, M., Foster, D., P.M., Gaido, K. W. (2004). Dose-dependent alterations in gene expression and testosterone synthesis in the fetal testes of male rats exposed to di (n-butyl) phthalate. Toxicological Sciences 81(1):60-68.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight of dams
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-19)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	674382

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 di (n-butyl) phthalate (DBP). The source was reported (Aldrich Chemical Co., Milwaukee, WI). Purity was not reported. Test animal species, strain, sex, age and source were reported. Initial body weight of the animals was not reported. Husbandry conditions (temperature, humidity, and light cycle) were reported. Diet and water were provided ad libitum. Animals were housed individually. The concentration 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	High	Pregnant dams were assigned to a treatment group by body weight randomization using Provantis.
	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 (body weight).
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	A concurrent negative control group was included. Husbandry conditions were reported and similar between the groups. Body weight changes and food consumption were not reported, which could potentially confound results. Animals were housed in polycarbonate cages. Polycarbonate contains BPA, which have been linking to developmental and reproductive health problems. Similarly, it is unclear if glass or plastic water bottles were used. Again, plastic bottles could leach phthalates that could confound results. This could potentially confound results, although if control animals were exposed to the same levels, this may not substantially impact interpretation of results.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Low	Sample size was not clearly reported in method or results. It is not clear if any animals may have died during treatment.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Lehmann, K. P., Phillips, S., Sar, M., Foster, D., P.M., Gaido, K. W. (2004). Dose-dependent alterations in gene expression and testosterone synthesis in the fetal testes of male rats exposed to di (n-butyl) phthalate. Toxicological Sciences 81(1):60-68.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight of dams
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-19)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	674382

Domain		Metric	Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	Purity and concentration of all doses were verified using a Hewlett Packard 5890 gas chromatograph; however the study does not report what the purity was. The highest dose level was chosen based on our previous studies showing that 500 mg/kg/day produced significant changes in gene expression in the male offspring without maternal toxicity or fetal death (Barlow and Foster, 2003; Shultz et al., 2001). The lowest dose level was selected based on current estimates for human exposure, which reach as high as 0.113 mg/kg/day (Blount et al., 2000; Kohn et al., 2000). A NOAEL and LOAEL were determined. The gavage volume was appropriate (did not exceed 0.1 ml/10 g body weight).
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency, timing and duration were appropriate for the study's aim (GD 12-19).
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Low	Body weights of dams were measured daily from GD 4-GD 19.
	Metric 9:	Results presentation	Uninformative	No data were reported or information on body weights were provided.

Additional Comments: None

Overall Quality Determination — Uninformative

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information was reported in this study. The study included identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (temperature, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). The study lacked the starting body weights of the dams and did not report parity. 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 or selection of animals for endpoint evaluations was provided. No other methods to control for modifying factors across groups were noted by the study authors. In addition, for this experiment, two female rats were paired with one male rat to form a breeding group. For each dose level, there were 5 breeding groups formed (10 female rats/group). However, for prenatal developmental toxicity studies (OECD guideline 414) it is recommended that females inseminated by the same male should be evenly distributed across the study groups. It is unclear if this occurred in this study. This could potentially substantially impact the interpretation of the results.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	The study included a negative control group, which received un-dosed feed. A positive control group was not included and is not required. The study authors did not measure food consumption among the dams in a dietary study. It is unclear whether there were issues with palatability or if any differences in food consumption influenced the study results. Decreased body weights were observed.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Medium	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods (comments on clinical signs were not present in the results section). Overall, this is not expected to notably impact the interpretation of the results. There is no indication of animal attrition.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	In this study, test animals were exposed to DBP-dosed feed. The purity (>99%) and storage conditions of the test substance were reported. The stability of the DBP feed mixtures were tested at different temperatures using gas chromatography. It was found that DBP mixtures were stable for 3 weeks when stored in the dark at -20 degrees and for 1 week when stored under animal room conditions. The route and method of exposure were suited to the test substance. The study reported the concentrations of the test material as ppm in food. The authors do not report the calculated dose in mg/kg-animal/day. In addition, they do not provide sufficient information to independently calculate doses from concentrations in feed as they do not provide dam body weight at the start of or throughout the study period, or feed consumption. This uncertainty in the exposure characterization is expected to impact the interpretation of the results.
	Metric 7:	Exposure timing, frequency, and duration	Medium	For this study, the route, frequency, and duration of exposure were appropriate for the study type and endpoints of interest; however, it is unclear whether the duration of exposure was consistent; animals were dosed for "up to 20 days." The study text suggests groups of animals were sacrificed starting on GD17.
Domain 6: Outcome Measures and Results Display				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	Low	This was an in-utero developmental exposure study, designed as a supplement to larger NTP studies. This study tested limited endpoints, with a focus on evaluating hepatic peroxisome activity. The outcome methods were sensitive to the outcomes of interest for this study; however, there are some concerns with the timing of outcome assessment. The methods state that "during the interval between GDs17-20, maternal livers and pooled fetal livers were weighed for all rats and 5 control rats per evaluation day (a total of 15 control rats)." It is unclear if the timing of the outcome assessment was consistent across groups. There are discrepancies between the study methods and data tables. The study methods states that "groups of 5 pregnant females" [per group] were dosed. However, the data table says that the "data for dams and fetuses are….. averages of two dams per breeding group." And an n =5 breeding groups was reported. There are similar discrepancies in the number of control rats used. The test model, including the source and strain were appropriate for the evaluation of the endpoints. Dose spacing was adequate for determination of NOAEL/LOAEL values.
	Metric 9:	Results presentation	Medium	Quantitative data (mean ± SEM) were provided for the endpoints specified for each dose group. Statistical methods were described and were appropriate. The sample sizes are not clearly specified in the data tables for each endpoint. The study text states "For breeding groups in which one female was used for the maximum perinatal exposure determination study, only data for the dam in the in utero exposure study are included." No "exposure determination study" was mentioned for this chemical, it is possible this statement is in error. Relative liver weights were not reported.

Additional Comments: 3.DBP Supp study in utero in rats

Overall Quality Determination Low

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information was reported in this study. The study included identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (temperature, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). The study lacked the starting body weights of the dams and did not report parity. 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 or selection of animals for endpoint evaluations was provided. No other methods to control for modifying factors across groups were noted by the study authors. In addition, for this experiment, two female rats were paired with one male rat to form a breeding group. For each dose level, there were 5 breeding groups formed (10 female rats/group). However, for prenatal developmental toxicity studies (OECD guideline 414) it is recommended that females inseminated by the same male should be evenly distributed across the study groups. It is unclear if this occurred in this study. This could potentially substantially impact the interpretation of the results.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	The study included a negative control group, which received un-dosed feed. A positive control group was not included and is not required. The study authors did not measure food consumption among the dams in a dietary study. It is unclear whether there were issues with palatability or if any differences in food consumption influenced the study results. Decreased body weights were observed.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Medium	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods (comments on clinical signs were not present in the results section). Overall, this is not expected to notably impact the interpretation of the results. There is no indication of animal attrition.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	In this study, test animals were exposed to DBP-dosed feed. The purity (>99%) and storage conditions of the test substance were reported. The stability of the DBP feed mixtures were tested at different temperatures using gas chromatography. It was found that DBP mixtures were stable for 3 weeks when stored in the dark at -20 degrees and for 1 week when stored under animal room conditions. The route and method of exposure were suited to the test substance. The study reported the concentrations of the test material as ppm in food. The authors do not report the calculated dose in mg/kg-animal/day. In addition, they do not provide sufficient information to independently calculate doses from concentrations in feed as they do not provide dam body weight at the start of or throughout the study period, or feed consumption. This uncertainty in the exposure characterization is expected to impact the interpretation of the results.
	Metric 7:	Exposure timing, frequency, and duration	Medium	For this study, the route, frequency, and duration of exposure were appropriate for the study type and endpoints of interest; however, it is unclear whether the duration of exposure was consistent; animals were dosed for "up to 20 days." The study text suggests groups of animals were sacrificed starting on GD17.
Domain 6: Outcome Measures and Results Display				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	Low	This was an in-utero developmental exposure study, designed as a supplement to larger NTP studies. This study tested limited endpoints, with a focus on evaluating hepatic peroxisome activity. The outcome methods were sensitive to the outcomes of interest for this study; however, there are some concerns with the timing of outcome assessment. The methods state that "during the interval between GDs17-20, maternal livers and pooled fetal livers were weighed for all rats and 5 control rats per evaluation day (a total of 15 control rats)." It is unclear if the timing of the outcome assessment was consistent across groups. There are discrepancies between the study methods and data tables. The study methods states that "groups of 5 pregnant females" [per group] were dosed. However, the data table says that the "data for dams and fetuses are..... averages of two dams per breeding group." And an n =5 breeding groups was reported. There are similar discrepancies in the number of control rats used. The test model, including the source and strain were appropriate for the evaluation of the endpoints. Dose spacing was adequate for determination of NOAEL/LOAEL values.
	Metric 9:	Results presentation	Medium	Quantitative data (mean ± SEM) were provided for the endpoints specified for each dose group. Statistical methods were described and were appropriate. The sample sizes are not clearly specified in the data tables for each endpoint. The study text states "For breeding groups in which one female was used for the maximum perinatal exposure determination study, only data for the dam in the in utero exposure study are included." No "exposure determination study" was mentioned for this chemical, it is possible this statement is in error. Relative liver weights were not reported.

Additional Comments: 3.DBP Supp study in utero in rats

Overall Quality Determination Low

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information was reported in this study. The study included identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (temperature, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). The study lacked the starting body weights of the dams and did not report parity. 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 or selection of animals for endpoint evaluations was provided. No other methods to control for modifying factors across groups were noted by the study authors. In addition, for this experiment, two female rats were paired with one male rat to form a breeding group. For each dose level, there were 5 breeding groups formed (10 female rats/group). However, for prenatal developmental toxicity studies (OECD guideline 414) it is recommended that females inseminated by the same male should be evenly distributed across the study groups. It is unclear if this occurred in this study. This could potentially substantially impact the interpretation of the results.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	The study included a negative control group, which received un-dosed feed. A positive control group was not included and is not required. The study authors did not measure food consumption among the dams in a dietary study. It is unclear whether there were issues with palatability or if any differences in food consumption influenced the study results. Decreased body weights were observed.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Medium	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods (comments on clinical signs were not present in the results section). Overall, this is not expected to notably impact the interpretation of the results. There is no indication of animal attrition.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	In this study, test animals were exposed to DBP-dosed feed. The purity (>99%) and storage conditions of the test substance were reported. The stability of the DBP feed mixtures were tested at different temperatures using gas chromatography. It was found that DBP mixtures were stable for 3 weeks when stored in the dark at -20 degrees and for 1 week when stored under animal room conditions. The route and method of exposure were suited to the test substance. The study reported the concentrations of the test material as ppm in food. The authors do not report the calculated dose in mg/kg-animal/day. In addition, they do not provide sufficient information to independently calculate doses from concentrations in feed as they do not provide dam body weight at the start of or throughout the study period, or feed consumption. This uncertainty in the exposure characterization is expected to impact the interpretation of the results.
	Metric 7:	Exposure timing, frequency, and duration	Medium	For this study, the route, frequency, and duration of exposure were appropriate for the study type and endpoints of interest; however, it is unclear whether the duration of exposure was consistent; animals were dosed for "up to 20 days." The study text suggests groups of animals were sacrificed starting on GD17.
Domain 6: Outcome Measures and Results Display				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	Low	This was an in-utero developmental exposure study, designed as a supplement to larger NTP studies. This study tested limited endpoints, with a focus on evaluating hepatic peroxisome activity. The outcome methods were sensitive to the outcomes of interest for this study; however, there are some concerns with the timing of outcome assessment. The methods state that "during the interval between GDs17-20, maternal livers and pooled fetal livers were weighed for all rats and 5 control rats per evaluation day (a total of 15 control rats)." It is unclear if the timing of the outcome assessment was consistent across groups. There are discrepancies between the study methods and data tables. The study methods states that "groups of 5 pregnant females" [per group] were dosed. However, the data table says that the "data for dams and fetuses are….. averages of two dams per breeding group." And an n =5 breeding groups was reported. There are similar discrepancies in the number of control rats used. The test model, including the source and strain were appropriate for the evaluation of the endpoints. Dose spacing was adequate for determination of NOAEL/LOAEL values.
	Metric 9:	Results presentation	Medium	Quantitative data (mean ± SEM) were provided for the endpoints specified for each dose group. Statistical methods were described and were appropriate. The sample sizes are not clearly specified in the data tables for each endpoint. The study text states "For breeding groups in which one female was used for the maximum perinatal exposure determination study, only data for the dam in the in utero exposure study are included." No "exposure determination study" was mentioned for this chemical, it is possible this statement is in error. Relative liver weights were not reported.

Additional Comments: 3.DBP Supp study in utero in rats

Overall Quality Determination Low

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical and most important information was reported in this study. The study included identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (temperature, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). The study lacked the starting body weights of the dams and did not report parity. 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 or selection of animals for endpoint evaluations was provided. No other methods to control for modifying factors across groups were noted by the study authors. In addition, for this experiment, two female rats were paired with one male rat to form a breeding group. For each dose level, there were 5 breeding groups formed (10 female rats/group). However, for prenatal developmental toxicity studies (OECD guideline 414) it is recommended that females inseminated by the same male should be evenly distributed across the study groups. It is unclear if this occurred in this study. This could potentially substantially impact the interpretation of the results.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	The study included a negative control group, which received un-dosed feed. A positive control group was not included and is not required. The study authors did not measure food consumption among the dams in a dietary study. It is unclear whether there were issues with palatability or if any differences in food consumption influenced the study results. Decreased body weights were observed.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods (comments on clinical signs were not present in the results section). Overall, this is not expected to notably impact the interpretation of the results. There is no indication of animal attrition.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	In this study, test animals were exposed to DBP-dosed feed. The purity (>99%) and storage conditions of the test substance were reported. The stability of the DBP feed mixtures were tested at different temperatures using gas chromatography. It was found that DBP mixtures were stable for 3 weeks when stored in the dark at -20 degrees and for 1 week when stored under animal room conditions. The route and method of exposure were suited to the test substance. The study reported the concentrations of the test material as ppm in food. The authors do not report the calculated dose in mg/kg-animal/day. In addition, they do not provide sufficient information to independently calculate doses from concentrations in feed as they do not provide dam body weight at the start of or throughout the study period, or feed consumption. This uncertainty in the exposure characterization is expected to impact the interpretation of the results.
	Metric 7:	Exposure timing, frequency, and duration	Medium	For this study, the route, frequency, and duration of exposure were appropriate for the study type and endpoints of interest; however, it is unclear whether the duration of exposure was consistent; animals were dosed for "up to 20 days." The study text suggests groups of animals were sacrificed starting on GD17.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	This was an in utero developmental exposure study and dams were observed for clinical signs. The frequency of observations was reported, and it was specified that results were recorded "as needed." The test model, including the source and strain were appropriate for the evaluation of the endpoints. The sample size (10 pregnant females/group) was small, but sufficient for performing statistics.
	Metric 9:	Results presentation	Uninformative	Neither quantitative nor qualitative data were provided for clinical signs.

Additional Comments: 3.DBP Supp study in utero in rats

Overall Quality Determination — Uninformative

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information was reported in this study. The study included identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (temperature, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). The study lacked the starting body weights of the dams and did not report parity. 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 or selection of animals for interim sacrifices was provided. No other methods to control for modifying factors across groups were noted by the study authors.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	The study included a negative control group, which received un-dosed feed. A positive control group was not included and is not required. The study authors did not measure food consumption among the dams in a dietary study. It is unclear whether there were issues with palatability or if any differences in food consumption influenced the study results. Decreased body weights were observed. The authors did not specify whether measures were taken to reduce exposure to plasticizers and the test substance is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for only some outcomes described in the methods. The following results were not reported: Sex and number of pups and litter weights on LD0 and 1; number, sex, and individual body weights on LD4, or results of observations for clinical signs. The study methods reported dosing 12 female rats/group; however, female data were only reported for 6 females per group (and 18 for controls). The 10,000 ppm group had an n of 5 for palmitoyl-CoA oxidase activity in dams. No explanation was provided. The methods state there should have been data for 24 controls. There is no indication of animal attrition.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	In this study, test animals were exposed to DBP-dosed feed. The purity (>98%) and storage conditions of the test substance were reported. The stability of the DBP feed mixtures were tested at different temperatures using gas chromatography. It was found that DBP mixtures were stable for 3 weeks when stored in the dark at -20°C and for 1 weeks when stored under animal room conditions. The route and method of exposure were suited to the test substance. The study reported the concentrations of the test material as ppm in food. The authors do not report the calculated dose in mg/kg-animal/day. In addition, they do not provide sufficient information to independently calculate doses from concentrations in feed as they do not provide dam body weight at the start of or throughout the study period, or feed consumption. This uncertainty in the exposure characterization is expected to impact the interpretation of the results.
	Metric 7:	Exposure timing, frequency, and duration	High	The window of exposure (days 1-22 of lactation) differs from standard developmental studies; however, the authors justified this exposure window which was appropriate for this study and the endpoints of interest.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	This was a lactational exposure study. The outcome assessment methods were clearly described and were appropriate and sensitive for the outcomes of interest and goals of the study. The test model, including the source and strain were appropriate for the evaluation of the endpoints. Dose spacing was adequate for determination of NOAEL/LOAEL values. The sample sizes were sufficient for conducting statistical analysis.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Medium	Quantitative data (mean ± SEM) were provided for the endpoints Day 0 litter weight, individual pup body weight (Day 7, 14, 21), pup absolute liver weight, palmitoyl-CoA oxidase activity in livers of pups, absolute liver weights of dams, palmitoyl-CoA oxidase activity in dam livers, and terminal body weights of dams. Statistical significance was provided for these endpoints. In addition, the study groups were clearly provided/indicated. It should be noted that the day of parturition and day of lactation varied between the exposure groups. As a result, two sets of analyses were performed for each day of evaluation. Data for the following endpoints: sex and number of pups and litter weights on LD0 and 1; number, sex, and individual pup body weights on LD4, were not provided.

Additional Comments: 4.DBP Supp study lactational in rats

Overall Quality Determination Low

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information was reported in this study. The study included identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (temperature, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). The study lacked the starting body weights of the dams and did not report parity. 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 or selection of animals for interim sacrifices was provided. No other methods to control for modifying factors across groups were noted by the study authors.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	The study included a negative control group, which received un-dosed feed. A positive control group was not included and is not required. The study authors did not measure food consumption among the dams in a dietary study. It is unclear whether there were issues with palatability or if any differences in food consumption influenced the study results. Decreased body weights were observed. The authors did not specify whether measures were taken to reduce exposure to plasticizers and the test substance is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for only some outcomes described in the methods. The following results were not reported: Sex and number of pups and litter weights on LD0 and 1; number, sex, and individual body weights on LD4, or results of observations for clinical signs. The study methods reported dosing 12 female rats/group; however, female data were only reported for 6 females per group (and 18 for controls). The 10,000 ppm group had an n of 5 for palmitoyl-CoA oxidase activity in dams. No explanation was provided. The methods state there should have been data for 24 controls. There is no indication of animal attrition.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	In this study, test animals were exposed to DBP-dosed feed. The purity (>98%) and storage conditions of the test substance were reported. The stability of the DBP feed mixtures were tested at different temperatures using gas chromatography. It was found that DBP mixtures were stable for 3 weeks when stored in the dark at -20°C and for 1 weeks when stored under animal room conditions. The route and method of exposure were suited to the test substance. The study reported the concentrations of the test material as ppm in food. The authors do not report the calculated dose in mg/kg-animal/day. In addition, they do not provide sufficient information to independently calculate doses from concentrations in feed as they do not provide dam body weight at the start of or throughout the study period, or feed consumption. This uncertainty in the exposure characterization is expected to impact the interpretation of the results.
	Metric 7:	Exposure timing, frequency, and duration	High	The window of exposure (days 1-22 of lactation) differs from standard developmental studies; however, the authors justified this exposure window which was appropriate for this study and the endpoints of interest.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	This was a lactational exposure study. The outcome assessment methods were clearly described and were appropriate and sensitive for the outcomes of interest and goals of the study. The test model, including the source and strain were appropriate for the evaluation of the endpoints. Dose spacing was adequate for determination of NOAEL/LOAEL values. The sample sizes were sufficient for conducting statistical analysis.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 9:	Results presentation	Medium	Quantitative data (mean ± SEM) were provided for the endpoints Day 0 litter weight, individual pup body weight (Day 7, 14, 21), pup absolute liver weight, palmitoyl-CoA oxidase activity in livers of pups, absolute liver weights of dams, palmitoyl-CoA oxidase activity in dam livers, and terminal body weights of dams. Statistical significance was provided for these endpoints. In addition, the study groups were clearly provided/indicated. It should be noted that the day of parturition and day of lactation varied between the exposure groups. As a result, two sets of analyses were performed for each day of evaluation. Data for the following endpoints: sex and number of pups and litter weights on LD0 and 1; number, sex, and individual pup body weights on LD4, were not provided.

Additional Comments: 4.DBP Supp study lactational in rats

Overall Quality Determination Low

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information was reported in this study. The study included identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (temperature, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). The study lacked the starting body weights of the dams and did not report parity. 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 or selection of animals for interim sacrifices was provided. No other methods to control for modifying factors across groups were noted by the study authors.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	The study included a negative control group, which received un-dosed feed. A positive control group was not included and is not required. The study authors did not measure food consumption among the dams in a dietary study. It is unclear whether there were issues with palatability or if any differences in food consumption influenced the study results. Decreased body weights were observed. The authors did not specify whether measures were taken to reduce exposure to plasticizers and the test substance is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for only some outcomes described in the methods. The following results were not reported: Sex and number of pups and litter weights on LD0 and 1; number, sex, and individual body weights on LD4, or results of observations for clinical signs. The study methods reported dosing 12 female rats/group; however, female data were only reported for 6 females per group (and 18 for controls). The 10,000 ppm group had an n of 5 for palmitoyl-CoA oxidase activity in dams. No explanation was provided. The methods state there should have been data for 24 controls. There is no indication of animal attrition.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	In this study, test animals were exposed to DBP-dosed feed. The purity (>98%) and storage conditions of the test substance were reported. The stability of the DBP feed mixtures were tested at different temperatures using gas chromatography. It was found that DBP mixtures were stable for 3 weeks when stored in the dark at -20°C and for 1 weeks when stored under animal room conditions. The route and method of exposure were suited to the test substance. The study reported the concentrations of the test material as ppm in food. The authors do not report the calculated dose in mg/kg-animal/day. In addition, they do not provide sufficient information to independently calculate doses from concentrations in feed as they do not provide dam body weight at the start of or throughout the study period, or feed consumption. This uncertainty in the exposure characterization is expected to impact the interpretation of the results.
	Metric 7:	Exposure timing, frequency, and duration	High	The window of exposure (days 1-22 of lactation) differs from standard developmental studies; however, the authors justified this exposure window which was appropriate for this study and the endpoints of interest.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	This was a lactational exposure study. The outcome assessment methods were clearly described and were appropriate and sensitive for the outcomes of interest and goals of the study. The test model, including the source and strain were appropriate for the evaluation of the endpoints. Dose spacing was adequate for determination of NOAEL/LOAEL values. The sample sizes were sufficient for conducting statistical analysis.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 9:	Results presentation	Medium	Quantitative data (mean ± SEM) were provided for the endpoints Day 0 litter weight, individual pup body weight (Day 7, 14, 21), pup absolute liver weight, palmitoyl-CoA oxidase activity in livers of pups, absolute liver weights of dams, palmitoyl-CoA oxidase activity in dam livers, and terminal body weights of dams. Statistical significance was provided for these endpoints. In addition, the study groups were clearly provided/indicated. It should be noted that the day of parturition and day of lactation varied between the exposure groups. As a result, two sets of analyses were performed for each day of evaluation. Data for the following endpoints: sex and number of pups and litter weights on LD0 and 1; number, sex, and individual pup body weights on LD4, were not provided.

Additional Comments: 4.DBP Supp study lactational in rats

Overall Quality Determination Low

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical and most important information was reported in this study. The study included identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (temperature, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). The study lacked the starting body weights of the dams and did not report parity. 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 or selection of animals for interim sacrifices was provided. No other methods to control for modifying factors across groups were noted by the study authors.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	The study included a negative control group, which received un-dosed feed. A positive control group was not included and is not required. The study authors did not measure food consumption among the dams in a dietary study. It is unclear whether there were issues with palatability or if any differences in food consumption influenced the study results. Decreased body weights were observed. The authors did not specify whether measures were taken to reduce exposure to plasticizers and the test substance is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for only some outcomes described in the methods. The following results were not reported: Sex and number of pups and litter weights on LD0 and 1; number, sex, and individual body weights on LD4, or results of observations for clinical signs. The study methods reported dosing 12 female rats/group; however, female data were only reported for 6 females per group (and 18 for controls). The 10,000 ppm group had an n of 5 for palmitoyl-CoA oxidase activity in dams. No explanation was provided. The methods state there should have been data for 24 controls. There is no indication of animal attrition.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	In this study, test animals were exposed to DBP-dosed feed. The purity (>98%) and storage conditions of the test substance were reported. The stability of the DBP feed mixtures were tested at different temperatures using gas chromatography. It was found that DBP mixtures were stable for 3 weeks when stored in the dark at -20°C and for 1 weeks when stored under animal room conditions. The route and method of exposure were suited to the test substance. The study reported the concentrations of the test material as ppm in food. The authors do not report the calculated dose in mg/kg-animal/day. In addition, they do not provide sufficient information to independently calculate doses from concentrations in feed as they do not provide dam body weight at the start of or throughout the study period, or feed consumption. This uncertainty in the exposure characterization is expected to impact the interpretation of the results.
	Metric 7:	Exposure timing, frequency, and duration	High	The window of exposure (days 1-22 of lactation) differs from standard developmental studies; however, the authors justified this exposure window which was appropriate for this study and the endpoints of interest.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	This was a lactational exposure study. The outcome assessment methods were clearly described and were appropriate and sensitive for the outcomes of interest and goals of the study. The test model, including the source and strain were appropriate for the evaluation of the endpoints. Dose spacing was adequate for determination of NOAEL/LOAEL values. The sample sizes were sufficient for conducting statistical analysis.
	Metric 9:	Results presentation	Uninformative	Neither quantitative nor qualitative data were provided for clinical signs.

Additional Comments: 4.DBP Supp study lactational in rats

Overall Quality Determination — Uninformative

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the dams used in the study.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a computer program. Litters were randomly culled; however, the method was not reported.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received un-dosed feed. Control responses were appropriate. A positive control group was not included and is not required. Food consumption was reported for offspring, but not dams in a dietary exposure study. It is unclear whether reductions in dam body weights or weight gain were related to altered food consumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed, water, or bedding was analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods. The methods state that there were up to 24 females per treatment group which differs from what is reported in the data tables (18-19 sperm positive females per group). The methods also state that there were 48 animals in the control group, but data are reported from 30 sperm positive controls). There are large variations across groups in the sample sizes used for certain dam endpoints. For example, no dams died, however, dam body weights for some groups were derived from 9 or 11 dams, when there were more dams in those groups. In another example, in the 20,000 ppm group, dam body weights on PND 0 were from only 2 dams but at the same period (PND 0) the number of live pups per litter was reported to be from 7 dams and litters. No explanation for the exclusion of some animals is provided by the authors, although it was stated in the methods that "animals suspected of being sick due to causes other than treatment, and values that the study laboratory personnel indicated as being inadequate due to technical problems were eliminated from the analysis." It is unclear how many animals, or which groups, this applies to. Control data for only some (18 dams/17 litters) were used for most endpoints, despite there being 28 control females that delivered. It was not specified why some control animals were excluded. Overall, there appears to be selective reporting and this is expected to notably impact the interpretation of the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. However, the authors do not report the calculated dose (mg/kg-day) in the exposed dams. Food consumption data for dams were not provided. Default values would need to be used to calculate approximate doses in mg/kg-day. The study authors do report the calculated doses (mg/kg-day) for the male and female F1 offspring. The uncertainties in the exposure characterization of dams could influence interpretation of the study results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was an extended exposure study. Exposure was conducted in utero (from GD 0) through lactation, and for 4 weeks after weaning as part of a collection of studies assessing the potential for DBP reproductive and developmental toxicity. The exposure timing, frequency, and duration were appropriate for the study type and endpoint(s) of interest.
Domain 6: Outcome Measures and Results Display				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	High	Dams were assessed for mortality. The frequency of observations of dams was reported. The test animals (rats) and sex (females) were appropriate for evaluation of the end-points. The sample size (18-19 sperm positive dams/treatment group; 30 sperm positive dams/control group) was appropriate for this endpoint. A wide range of doses were tested.
	Metric 9:	Results presentation	High	The study authors qualitatively stated that ”all females survived until the pups were weaned.”

Additional Comments: 5.DBP MPE Determination study in rats

Overall Quality Determination Medium

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the dams used in the study.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a computer program. Litters were randomly culled; however, the method was not reported.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received un-dosed feed. Control responses were appropriate. A positive control group was not included and is not required. Food consumption was reported for offspring, but not dams in a dietary exposure study. It is unclear whether reductions in dam body weights or weight gain were related to altered food consumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed, water, or bedding was analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods. The methods state that there were up to 24 females per treatment group which differs from what is reported in the data tables (18-19 sperm positive females per group). The methods also state that there were 48 animals in the control group, but data are reported from 30 sperm positive controls). There are large variations across groups in the sample sizes used for certain dam endpoints. For example, no dams died, however, dam body weights for some groups were derived from 9 or 11 dams, when there were more dams in those groups. In another example, in the 20,000 ppm group, dam body weights on PND 0 were from only 2 dams but at the same period (PND 0) the number of live pups per litter was reported to be from 7 dams and litters. No explanation for the exclusion of some animals is provided by the authors, although it was stated in the methods that "animals suspected of being sick due to causes other than treatment, and values that the study laboratory personnel indicated as being inadequate due to technical problems were eliminated from the analysis." It is unclear how many animals, or which groups, this applies to. Control data for only some (18 dams/17 litters) were used for most endpoints, despite there being 28 control females that delivered. It was not specified why some control animals were excluded. Overall, there appears to be selective reporting and this is expected to notably impact the interpretation of the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. However, the authors do not report the calculated dose (mg/kg-day) in the exposed dams. Food consumption data for dams were not provided. Default values would need to be used to calculate approximate doses in mg/kg-day. The study authors do report the calculated doses (mg/kg-day) for the male and female F1 offspring. The uncertainties in the exposure characterization of dams could influence interpretation of the study results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was an extended exposure study. Exposure was conducted in utero (from GD 0) through lactation, and for 4 weeks after weaning as part of a collection of studies assessing the potential for DBP reproductive and developmental toxicity. The exposure timing, frequency, and duration were appropriate for the study type and endpoint(s) of interest.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	Medium	This study was conducted to identify the maximum prenatal exposure (MPE) concentration to be used in further studies. Dams were assessed for body weight and feed consumption. The frequency of body weight and food consumption measurements of dams were provided. Dams and pups were assessed for select Reproductive / Developmental endpoints. The frequency of clinical observations of offspring was reported, but no other details were provided. For instance, it was not stated whether these were cage-side or in depth clinical observations. Some endpoints typically included in developmental studies were not included (e.g., AGD, no assessment of sexual maturation). In addition, it is unclear how much time elapsed between the end of treatment (28 days on feed) and necropsy of F1 animals. The test animals (rats) and sex (females) were appropriate for evaluation of the endpoints. The original sample size (18-19 sperm positive dams/treatment group) is slightly less than the preferred 20 pregnant dams/group for most developmental studies. For some endpoints, there were unexplained inconsistencies in sample sizes (see Metric 4). The sample size of F1s that continued treatment (10/sex) was appropriate. A wide range of doses were tested allowing for a determination of a NOAEL and a LOAEL.
	Metric 9: Results presentation	Low	Quantitative data (mean ± SEM) were provided for most of the specified endpoints. Statistical methods were described. Statistical significance was provided for these endpoints. Sample sizes were specified. It was not explicitly stated whether the litter was used as the experimental unit. There may be an error in the body weight gain during lactation value reported for the 1,250 ppm group. Neither quantitative nor qualitative data were provided for the endpoint dam feed consumption during gestation and lactation. This is expected to substantially impact the interpretation of the results. Pup body weights were the combined means of both male and female pups. Qualitative statements were provided for the endpoints pup clinical observations, necropsy, and histologic examinations on >30 organs/tissues and gross lesions in pups. Neither quantitative nor qualitative data were provided for the endpoints pups/sex/litter, litter weights (PND 0 & 1), and number of implantation sites in the uteri of female rats exposed to DBP that did not litter. Additionally, no individual animal data were provided.

Additional Comments: 5.DBP MPE Determination study in rats

Overall Quality Determination Medium

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the dams used in the study.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a computer program. Litters were randomly culled; however, the method was not reported.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received un-dosed feed. Control responses were appropriate. A positive control group was not included and is not required. Food consumption was reported for offspring, but not dams in a dietary exposure study. It is unclear whether reductions in dam body weights or weight gain were related to altered food consumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed, water, or bedding was analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods. The methods state that there were up to 24 females per treatment group which differs from what is reported in the data tables (18-19 sperm positive females per group). The methods also state that there were 48 animals in the control group, but data are reported from 30 sperm positive controls). There are large variations across groups in the sample sizes used for certain dam endpoints. For example, no dams died, however, dam body weights for some groups were derived from 9 or 11 dams, when there were more dams in those groups. In another example, in the 20,000 ppm group, dam body weights on PND 0 were from only 2 dams but at the same period (PND 0) the number of live pups per litter was reported to be from 7 dams and litters. No explanation for the exclusion of some animals is provided by the authors, although it was stated in the methods that "animals suspected of being sick due to causes other than treatment, and values that the study laboratory personnel indicated as being inadequate due to technical problems were eliminated from the analysis." It is unclear how many animals, or which groups, this applies to. Control data for only some (18 dams/17 litters) were used for most endpoints, despite there being 28 control females that delivered. It was not specified why some control animals were excluded. Overall, there appears to be selective reporting and this is expected to notably impact the interpretation of the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. However, the authors do not report the calculated dose (mg/kg-day) in the exposed dams. Food consumption data for dams were not provided. Default values would need to be used to calculate approximate doses in mg/kg-day. The study authors do report the calculated doses (mg/kg-day) for the male and female F1 offspring. The uncertainties in the exposure characterization of dams could influence interpretation of the study results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was an extended exposure study. Exposure was conducted in utero (from GD 0) through lactation, and for 4 weeks after weaning as part of a collection of studies assessing the potential for DBP reproductive and developmental toxicity. The exposure timing, frequency, and duration were appropriate for the study type and endpoint(s) of interest.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	Medium	This study was conducted to identify the maximum prenatal exposure (MPE) concentration to be used in further studies. Dams were assessed for body weight and feed consumption. The frequency of body weight and food consumption measurements of dams were provided. Dams and pups were assessed for select Reproductive / Developmental endpoints. The frequency of clinical observations of offspring was reported, but no other details were provided. For instance, it was not stated whether these were cage-side or in depth clinical observations. Some endpoints typically included in developmental studies were not included (e.g., AGD, no assessment of sexual maturation). In addition, it is unclear how much time elapsed between the end of treatment (28 days on feed) and necropsy of F1 animals. The test animals (rats) and sex (females) were appropriate for evaluation of the endpoints. The original sample size (18-19 sperm positive dams/treatment group) is slightly less than the preferred 20 pregnant dams/group for most developmental studies. For some endpoints, there were unexplained inconsistencies in sample sizes (see Metric 4). The sample size of F1s that continued treatment (10/sex) was appropriate. A wide range of doses were tested allowing for a determination of a NOAEL and a LOAEL.
	Metric 9: Results presentation	Low	Quantitative data (mean ± SEM) were provided for most of the specified endpoints. Statistical methods were described. Statistical significance was provided for these endpoints. Sample sizes were specified. It was not explicitly stated whether the litter was used as the experimental unit. There may be an error in the body weight gain during lactation value reported for the 1,250 ppm group. Neither quantitative nor qualitative data were provided for the endpoint dam feed consumption during gestation and lactation. This is expected to substantially impact the interpretation of the results. Pup body weights were the combined means of both male and female pups. Qualitative statements were provided for the endpoints pup clinical observations, necropsy, and histologic examinations on >30 organs/tissues and gross lesions in pups. Neither quantitative nor qualitative data were provided for the endpoints pups/sex/litter, litter weights (PND 0 & 1), and number of implantation sites in the uteri of female rats exposed to DBP that did not litter. Additionally, no individual animal data were provided.

Additional Comments: 5.DBP MPE Determination study in rats

Overall Quality Determination — Medium

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the dams used in the study.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a computer program. Litters were randomly culled; however, the method was not reported.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received un-dosed feed. Control responses were appropriate. A positive control group was not included and is not required. Food consumption was reported for offspring, but not dams in a dietary exposure study. It is unclear whether reductions in dam body weights or weight gain were related to altered food consumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed, water, or bedding was analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods. The methods state that there were up to 24 females per treatment group which differs from what is reported in the data tables (18-19 sperm positive females per group). The methods also state that there were 48 animals in the control group, but data are reported from 30 sperm positive controls). There are large variations across groups in the sample sizes used for certain dam endpoints. For example, no dams died, however, dam body weights for some groups were derived from 9 or 11 dams, when there were more dams in those groups. In another example, in the 20,000 ppm group, dam body weights on PND 0 were from only 2 dams but at the same period (PND 0) the number of live pups per litter was reported to be from 7 dams and litters. No explanation for the exclusion of some animals is provided by the authors, although it was stated in the methods that "animals suspected of being sick due to causes other than treatment, and values that the study laboratory personnel indicated as being inadequate due to technical problems were eliminated from the analysis." It is unclear how many animals, or which groups, this applies to. Control data for only some (18 dams/17 litters) were used for most endpoints, despite there being 28 control females that delivered. It was not specified why some control animals were excluded. Overall, there appears to be selective reporting and this is expected to notably impact the interpretation of the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. However, the authors do not report the calculated dose (mg/kg-day) in the exposed dams. Food consumption data for dams were not provided. Default values would need to be used to calculate approximate doses in mg/kg-day. The study authors do report the calculated doses (mg/kg-day) for the male and female F1 offspring. The uncertainties in the exposure characterization of dams could influence interpretation of the study results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was an extended exposure study. Exposure was conducted in utero (from GD 0) through lactation, and for 4 weeks after weaning as part of a collection of studies assessing the potential for DBP reproductive and developmental toxicity. The exposure timing, frequency, and duration were appropriate for the study type and endpoint(s) of interest.
Domain 6: Outcome Measures and Results Display				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	Medium	Dams were assessed for clinical signs. The frequency of clinical observations was reported, but no other details were provided. For instance, it was not stated whether these were cage-side or in-depth clinical observations. This is not expected to significantly impact the interpretation of the results. The test animals (rats) and sex (females) were appropriate for evaluation of the endpoints. The sample size (18-19 dams/treatment group; 30 dams/control group) was appropriate for the study type. A wide range of doses were tested.
	Metric 9:	Results presentation	Medium	Study authors qualitatively state that ”no clinical signs in the dams were considered related to DBP administration.” However, they do not provide information on the actual observed and recorded clinical signs in these rats and individual animal data were not provided.

Additional Comments: 5.DBP MPE Determination study in rats

Overall Quality Determination Medium

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Mouse-B6C3F1 - [mouse]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the dams used in this study.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a computer program. Litters were randomly culled; however, the method was not reported.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	The study included a negative control group, which received undosed feed. Control responses were appropriate. A positive control group was not included and is not required. Food consumption was reported for offspring, but not dams in a dietary exposure study. Dams in all study groups, except for the 10,000 ppm group, lost weight during lactation. The authors do not provide an explanation for why these dams lost weight during lactation. It is unclear whether reductions in dam body weights or weight gain were related to altered food consumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed, water, or bedding was analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Mouse-B6C3F1 - [mouse]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods. The methods state that there were up to 20 females per group which differs from what is reported in the data tables (18-20 sperm positive females per group). There are large variations across groups in the sample sizes used for certain dam endpoints. For example, dam body weights for some groups were derived from only 9 or 10 dams, when there were more dams in those study groups. No explanation for the exclusion of some animals is provided by the authors, although it was stated in the methods that "animals suspected of being sick due to causes other than treatment, and values that the study laboratory personnel indicated as being inadequate due to technical problems were eliminated from the analysis." It is unclear how many animals, or which groups, this applies to. Overall, there appears to be selective reporting and this is expected to notably impact the interpretation of the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. However, the authors do not report the calculated dose (mg/kg-day) in the exposed dams. Food consumption data for dams were not provided. Default values would need to be used to calculate approximate doses in mg/kg-day. The study authors do report the calculated doses (mg/kg-day) for the male and female F1 offspring. The uncertainties in the exposure characterization of dams could influence interpretation of the study results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was an extended exposure study. Exposure was conducted in utero (from GD 0) through lactation, and for 4 weeks after weaning as part of a collection of studies assessing the potential for DBP reproductive and developmental toxicity. The exposure timing, frequency, and duration were appropriate for the current study.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dams were assessed for mortality. The frequency of observations of dams was reported, but no other details were provided. This is not expected to significantly impact the interpretation of the results. The test animals (mice) and sex (females) were appropriate for evaluation of the endpoints. The original sample size (18-20 sperm positive dams/treatment group; 20 dams/control group) was appropriate for the study type. A wide range of doses were tested.

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Mouse-B6C3F1 - [mouse]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	High	Study authors qualitatively stated that “one female in each of the 0, 5,000, and 7,500 ppm groups died during the gestation period.”

Additional Comments: 6.DBP MPE Determination study in mice

Overall Quality Determination Medium

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Mouse-B6C3F1 - [mouse]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the dams used in this study.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a computer program. Litters were randomly culled; however, the method was not reported.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	LOW: The study included a negative control group, which received undosed feed. Control responses were appropriate. A positive control group was not included and is not required. Food consumption was reported for offspring, but not dams in a dietary exposure study. Dams in all study groups, except for the 10,000 ppm group, lost weight during lactation. The authors do not provide an explanation for why these dams lost weight during lactation. It is unclear whether reductions in dam body weights or weight gain were related to altered food consumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed, water, or bedding was analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Mouse-B6C3F1 - [mouse]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods. The methods state that there were up to 20 females per group which differs from what is reported in the data tables (18-20 sperm positive females per group). There are large variations across groups in the sample sizes used for certain dam endpoints. For example, dam body weights for some groups were derived from only 9 or 10 dams, when there were more dams in those study groups. No explanation for the exclusion of some animals is provided by the authors, although it was stated in the methods that "animals suspected of being sick due to causes other than treatment, and values that the study laboratory personnel indicated as being inadequate due to technical problems were eliminated from the analysis." It is unclear how many animals, or which groups, this applies to. Overall, there appears to be selective reporting and this is expected to notably impact the interpretation of the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. However, the authors do not report the calculated dose (mg/kg-day) in the exposed dams. Food consumption data for dams were not provided. Default values would need to be used to calculate approximate doses in mg/kg-day. The study authors do report the calculated doses (mg/kg-day) for the male and female F1 offspring. The uncertainties in the exposure characterization are not expected to substantially impact the interpretation of the results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was an extended exposure study. Exposure was conducted in utero (from GD 0) through lactation, and for 4 weeks after weaning as part of a collection of studies assessing the potential for DBP reproductive and developmental toxicity. The exposure timing, frequency, and duration were appropriate for the current study.
Domain 6: Outcome Measures and Results Display				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Mouse-B6C3F1 - [mouse]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	Low	This study conducted to identify the maximum perinatal exposure (MPE) concentration to be used in further studies. Dams were assessed for body weight and feed consumption. The frequency of body weight and food consumption measurements of dams were provided. Dams and pups were assessed for select Reproductive/Developmental endpoints. The frequency of clinical observations of offspring was reported, but no other details were provided. For instance, it was not stated whether these were cage-side or in depth clinical observations. Some endpoints typically included in developmental studies were not included (e.g., AGD, no assessment of sexual maturation). In addition, it is unclear how much time elapsed between the end of treatment (28 days on feed) and necropsy of F1 animals. The test animals (mice) and sex (females) were appropriate for evaluation of the endpoints. The original sample size (18-20 sperm positive dams/treatment group) is slightly less than the preferred 20 pregnant dams/group for most developmental studies. The sample size of F1s that continued treatment (10/sex) was appropriate and large enough to perform statistics for most groups. However, the F1 male 3,804 mg/kg-day group only contained one animal, which was not enough to perform statistics. A wide range of doses were tested.
	Metric 9:	Results presentation	Low	Quantitative data (mean ± SEM) were provided for most of the specified endpoints. Statistical methods were described. Statistical significance was provided for these endpoints. It was not explicitly stated whether the litter was used as the experimental unit. Sample sizes were specified. Neither quantitative nor qualitative data were provided for the endpoint dam feed consumption during gestation and lactation. This is expected to substantially impact the interpretation of the results. Pup body weights were the combined means of both male and female pups. There may be an error in the value reported as the number of live pups per litter on PND 0 in the 7,500 ppm group. The authors do not provide an explanation for how the number of live pups per litter could increase from PND 0 to PND 1 in this group. Qualitative statements were provided for the endpoint pup clinical observations, necropsy, and histologic examinations on >30 organs/tissues and gross lesions in pups. Neither quantitative nor qualitative data were provided for the endpoints pups/sex/litter, litter weights (PND 0 & 1), and number of implantation sites in the uteri of female mice exposed to DBP that did not litter. Additionally, no individual animal data were provided.

Additional Comments: 6.DBP MPE Determination study in mice

Overall Quality Determination Low

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Mouse-B6C3F1 - [mouse]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the dams used in this study.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a computer program. Litters were randomly culled; however, the method was not reported.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	LOW: The study included a negative control group, which received undosed feed. Control responses were appropriate. A positive control group was not included and is not required. Food consumption was reported for offspring, but not dams in a dietary exposure study. Dams in all study groups, except for the 10,000 ppm group, lost weight during lactation. The authors do not provide an explanation for why these dams lost weight during lactation. It is unclear whether reductions in dam body weights or weight gain were related to altered food consumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed, water, or bedding was analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Mouse-B6C3F1 - [mouse]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods. The methods state that there were up to 20 females per group which differs from what is reported in the data tables (18-20 sperm positive females per group). There are large variations across groups in the sample sizes used for certain dam endpoints. For example, dam body weights for some groups were derived from only 9 or 10 dams, when there were more dams in those study groups. No explanation for the exclusion of some animals is provided by the authors, although it was stated in the methods that "animals suspected of being sick due to causes other than treatment, and values that the study laboratory personnel indicated as being inadequate due to technical problems were eliminated from the analysis." It is unclear how many animals, or which groups, this applies to. Overall, there appears to be selective reporting and this is expected to notably impact the interpretation of the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. However, the authors do not report the calculated dose (mg/kg-day) in the exposed dams. Food consumption data for dams were not provided. Default values would need to be used to calculate approximate doses in mg/kg-day. The study authors do report the calculated doses (mg/kg-day) for the male and female F1 offspring. The uncertainties in the exposure characterization are not expected to substantially impact the interpretation of the results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was an extended exposure study. Exposure was conducted in utero (from GD 0) through lactation, and for 4 weeks after weaning as part of a collection of studies assessing the potential for DBP reproductive and developmental toxicity. The exposure timing, frequency, and duration were appropriate for the current study.
Domain 6: Outcome Measures and Results Display				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Mouse-B6C3F1 - [mouse]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	Low	This study conducted to identify the maximum perinatal exposure (MPE) concentration to be used in further studies. Dams were assessed for body weight and feed consumption. The frequency of body weight and food consumption measurements of dams were provided. Dams and pups were assessed for select Reproductive/Developmental endpoints. The frequency of clinical observations of offspring was reported, but no other details were provided. For instance, it was not stated whether these were cage-side or in depth clinical observations. Some endpoints typically included in developmental studies were not included (e.g., AGD, no assessment of sexual maturation). In addition, it is unclear how much time elapsed between the end of treatment (28 days on feed) and necropsy of F1 animals. The test animals (mice) and sex (females) were appropriate for evaluation of the endpoints. The original sample size (18-20 sperm positive dams/treatment group) is slightly less than the preferred 20 pregnant dams/group for most developmental studies. The sample size of F1s that continued treatment (10/sex) was appropriate and large enough to perform statistics for most groups. However, the F1 male 3,804 mg/kg-day group only contained one animal, which was not enough to perform statistics. A wide range of doses were tested.
	Metric 9:	Results presentation	Low	Quantitative data (mean ± SEM) were provided for most of the specified endpoints. Statistical methods were described. Statistical significance was provided for these endpoints. It was not explicitly stated whether the litter was used as the experimental unit. Sample sizes were specified. Neither quantitative nor qualitative data were provided for the endpoint dam feed consumption during gestation and lactation. This is expected to substantially impact the interpretation of the results. Pup body weights were the combined means of both male and female pups. There may be an error in the value reported as the number of live pups per litter on PND 0 in the 7,500 ppm group. The authors do not provide an explanation for how the number of live pups per litter could increase from PND 0 to PND 1 in this group. Qualitative statements were provided for the endpoint pup clinical observations, necropsy, and histologic examinations on >30 organs/tissues and gross lesions in pups. Neither quantitative nor qualitative data were provided for the endpoints pups/sex/litter, litter weights (PND 0 & 1), and number of implantation sites in the uteri of female mice exposed to DBP that did not litter. Additionally, no individual animal data were provided.

Additional Comments: 6.DBP MPE Determination study in mice

Overall Quality Determination Low

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Mouse-B6C3F1 - [mouse]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the dams used in this study.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a computer program. Litters were randomly culled; however, the method was not reported.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	The study included a negative control group, which received undosed feed. Control responses were appropriate. A positive control group was not included and is not required. Food consumption was reported for offspring, but not dams in a dietary exposure study. Dams in all study groups, except for the 10,000 ppm group, lost weight during lactation. The authors do not provide an explanation for why these dams lost weight during lactation. It is unclear whether reductions in dam body weights or weight gain were related to altered food consumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed, water, or bedding was analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Mouse-B6C3F1 - [mouse]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods. The methods state that there were up to 20 females per group which differs from what is reported in the data tables (18-20 sperm positive females per group). There are large variations across groups in the sample sizes used for certain dam endpoints. For example, dam body weights for some groups were derived from only 9 or 10 dams, when there were more dams in those study groups. No explanation for the exclusion of some animals is provided by the authors, although it was stated in the methods that "animals suspected of being sick due to causes other than treatment, and values that the study laboratory personnel indicated as being inadequate due to technical problems were eliminated from the analysis." It is unclear how many animals, or which groups, this applies to. Overall, there appears to be selective reporting and this is expected to notably impact the interpretation of the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. However, the authors do not report the calculated dose (mg/kg-day) in the exposed dams. Food consumption data for dams were not provided. Default values would need to be used to calculate approximate doses in mg/kg-day. The study authors do report the calculated doses (mg/kg-day) for the male and female F1 offspring. The uncertainties in the exposure characterization of dams could influence interpretation of the study results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was an extended exposure study. Exposure was conducted in utero (from GD 0) through lactation, and for 4 weeks after weaning as part of a collection of studies assessing the potential for DBP reproductive and developmental toxicity. The exposure timing, frequency, and duration were appropriate for the current study.
Domain 6: Outcome Measures and Results Display				

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Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Species:	Mouse-B6C3F1 - [mouse]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	Medium	Dams were assessed for clinical signs. The frequency of clinical observations was reported, but no other details were provided. For instance, it was not stated whether these were cage-side or in depth clinical observations. This is not expected to significantly impact the interpretation of the results. The test animals (mice) and sex (females) were appropriate for evaluation of the endpoints. The sample size (18-20 sperm positive dams/treatment group; 20 dams/control group) was appropriate for the study type. A wide range of doses were tested.
	Metric 9:	Results presentation	Medium	Study authors qualitatively state that “the incidence of cannibalization of pups was greater in the 7,500 and 10,000 ppm groups than in the controls. No other clinical signs in pups or dams were considered related to dibutyl phthalate administration.” The incidence values for cannibalization of pups were not provided. In addition, the authors do not provide information on the actual observed and recorded clinical signs in the mice. In addition, individual animal data were not provided.

Additional Comments: 6.DBP MPE Determination study in mice

Overall Quality Determination Medium

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the dams used in this study.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a computer program. Litters were randomly culled; however, the method was not reported.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received undosed feed. Control responses were appropriate. A positive control group was not included and is not required. Food consumption was reported for offspring, but not dams in a dietary exposure study. It is unclear whether reductions in dam body weights were related to altered food consumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed, water, or bedding were analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods. The methods state that 72 females were administered 10,000 ppm DBP in feed throughout gestation and lactation, which differs from what is reported in data tables (71 sperm positive females in the 10,000 ppm group). In some instances, animals were missing from the data tables. For example, absolute and relative right testis weights and testis zinc concentrations were only provided for 9/10 F1 males in the 1,262 mg/kg-day group. In addition, hematology results were provided for only 6 F1 males in the 1,262 mg/kg-day group, as opposed to the 10 that were reported in the methods section. No explanation for the exclusion of some animals is provided by the authors, although it was stated in the methods that "animals suspected of being sick due to causes other than treatment, and values that the study laboratory personnel indicated as being inadequate due to technical problems were eliminated from the analysis." It is unclear how many animals, or which groups, this applies to. Overall, there appears to be selective reporting and this is expected to notably impact the interpretation of the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. However, the authors do not report the calculated dose (mg/kg-day) in the exposed dams. Food consumption data for dams were not provided. Default values would need to be used to calculate approximate doses in mg/kg-day. The study authors do report the calculated doses (mg/kg-day) for the male and female F1 offspring. The uncertainties in the exposure characterization of dams could influence interpretation of the study results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was a developmental and extended exposure study. Exposure was conducted in utero (from GD 0) through lactation, for 4 weeks after weaning, and then for another 13 weeks after the 4-week exposure period as part of a collection of studies assessing the potential for DBP reproductive and developmental toxicity. The exposure timing, frequency, and duration were appropriate for the current study.
Domain 6: Outcome Measures and Results Display				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	Medium	Dams were assessed for mortality. The frequency of observations of dams was reported, but no other details were provided. This is not expected to significantly impact the interpretation of the results. The test animals (rats) and sex (females) were appropriate for evaluation of the endpoints. The sample size (71 sperm positive dams in the 10,000 ppm group; 12 sperm positive dams in the control group) was appropriate for the study type. Dosing was limited as dams were only exposed to one dose of DBP. This is not expected to substantially impact the interpretation of the results.
	Metric 9:	Results presentation	High	Study authors qualitatively stated that “all dams survived until the scheduled termination.”

Additional Comments: 7.DBP 13-week feed study w/ perinatal in rats

Overall Quality Determination Medium

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the dams used in this study.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a computer program. Litters were randomly culled; however, the method was not reported.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received undosed feed. Control responses were appropriate. A positive control group was not included and is not required. Food consumption was reported for offspring, but not dams in a dietary exposure study. It is unclear whether reductions in dam body weights were related to altered food consumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed, water, or bedding were analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods. The methods state that 72 females were administered 10,000 ppm DBP in feed throughout gestation and lactation, which differs from what is reported in data tables (71 sperm positive females in the 10,000 ppm group). In some instances, animals were missing from the data tables. For example, absolute and relative right testis weights and testis zinc concentrations were only provided for 9/10 F1 males in the 1,262 mg/kg-day group. In addition, hematology results were provided for only 6 F1 males in the 1,262 mg/kg-day group, as opposed to the 10 that were reported in the methods section. No explanation for the exclusion of some animals is provided by the authors, although it was stated in the methods that "animals suspected of being sick due to causes other than treatment, and values that the study laboratory personnel indicated as being inadequate due to technical problems were eliminated from the analysis." It is unclear how many animals, or which groups, this applies to. Overall, there appears to be selective reporting and this is expected to notably impact the interpretation of the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. However, the authors do not report the calculated dose (mg/kg-day) in the exposed dams. Food consumption data for dams were not provided. Default values would need to be used to calculate approximate doses in mg/kg-day. The study authors do report the calculated doses (mg/kg-day) for the male and female F1 offspring. The uncertainties in the exposure characterization of dams could influence interpretation of the study results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was a developmental and extended exposure study. Exposure was conducted in utero (from GD 0) through lactation, for 4 weeks after weaning, and then for another 13 weeks after the 4-week exposure period as part of a collection of studies assessing the potential for DBP reproductive and developmental toxicity. The exposure timing, frequency, and duration were appropriate for the current study.
Domain 6: Outcome Measures and Results Display				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	Medium	Dams were assessed for body weight and feed consumption. The frequency of body weight and food consumption measurements of dams were provided. The test animals (rats) and sex (females) were appropriate for evaluation of the endpoints. The sample sizes (71 sperm positive dams in the 10,000 ppm group; 12 sperm positive dams in the control group) were sufficient to allow for statistical analysis. Dosing was limited as dams were only exposed to one dose of DBP. This is not expected to substantially impact the interpretation of the results.
	Metric 9:	Results presentation	Low	Quantitative data (mean ± SEM) and sample sizes were provided for dam body weights and total dam weight gain during gestation and lactation. Statistical significance was provided for these endpoints. Sample sizes were specified. Neither quantitative nor qualitative data were provided for the endpoint dam feed consumption during gestation and lactation. This is expected to substantially impact the interpretation of the results. Additionally, no individual animal data were provided.

Additional Comments: 7.DBP 13-week feed study w/ perinatal in rats

Overall Quality Determination Medium

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the dams used in this study.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a computer program. Litters were randomly culled; however, the method was not reported.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received undosed feed. Control responses were appropriate. A positive control group was not included and is not required. Food consumption was reported for offspring, but not dams in a dietary exposure study. It is unclear whether reductions in dam body weights were related to altered food consumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed, water, or bedding were analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods. The methods state that 72 females were administered 10,000 ppm DBP in feed throughout gestation and lactation, which differs from what is reported in data tables (71 sperm positive females in the 10,000 ppm group). In some instances, animals were missing from the data tables. For example, absolute and relative right testis weights and testis zinc concentrations were only provided for 9/10 F1 males in the 1,262 mg/kg-day group. In addition, hematology results were provided for only 6 F1 males in the 1,262 mg/kg-day group, as opposed to the 10 that were reported in the methods section. No explanation for the exclusion of some animals is provided by the authors, although it was stated in the methods that "animals suspected of being sick due to causes other than treatment, and values that the study laboratory personnel indicated as being inadequate due to technical problems were eliminated from the analysis." It is unclear how many animals, or which groups, this applies to. Overall, there appears to be selective reporting and this is expected to notably impact the interpretation of the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. However, the authors do not report the calculated dose (mg/kg-day) in the exposed dams. Food consumption data for dams were not provided. Default values would need to be used to calculate approximate doses in mg/kg-day. The study authors do report the calculated doses (mg/kg-day) for the male and female F1 offspring. The uncertainties in the exposure characterization of dams could influence interpretation of the study results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was a developmental and extended exposure study. Exposure was conducted in utero (from GD 0) through lactation, for 4 weeks after weaning, and then for another 13 weeks after the 4-week exposure period as part of a collection of studies assessing the potential for DBP reproductive and developmental toxicity. The exposure timing, frequency, and duration were appropriate for the current study.
Domain 6: Outcome Measures and Results Display				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	Medium	This was a developmental and extended exposure study. Dams and pups were assessed for select Reproductive/Developmental endpoints. The frequency of clinical observations of offspring was reported, but no other details were provided. For instance, it was not stated whether these were cage-side or in depth clinical observations. Some endpoints typically included in developmental studies were not included (e.g., AGD, no assessment of sexual maturation). In addition, it is unclear how much time elapsed between the end of treatment (13-week exposure period) and necropsy of F1 animals. The test animals (rats) and sex (females) were appropriate for evaluation of the endpoints. The sample sizes (71 sperm positive dams in the 10,000 ppm group; 12 sperm positive dams in the control group) were appropriate, however, the 12 control dams was slightly less than the preferred 20 pregnant dams/group for most developmental studies. The sample size of F1s that continued treatment (10/sex/group) was appropriate and large enough to perform statistics for most groups. Dosing was limited as dams were only exposed to one dose of DBP. This is not expected to substantially impact the interpretation of the results.
	Metric 9:	Results presentation	Low	Quantitative data (mean ± SEM) were provided for most of the specified endpoints. Statistical methods were described. It was not explicitly stated whether the litter was used as the experimental unit. Pup body weights were the combined means of both male and female pups. There may be an error in the value reported as the number of live pups per litter on PND 0 in the 7,500 ppm group. The authors do not provide an explanation for how the number of live pups per litter could increase from PND 0 to PND 1 in this group. Qualitative statements were provided for the endpoint pup clinical observations, necropsy, and histologic examinations on >30 organs/tissues and gross lesions in pups. Neither quantitative nor qualitative data were provided for the endpoints pups/sex/litter, litter weights (PND 0 & 1), and number of implantation sites in the uteri of female mice exposed to DBP that did not litter. Individual animal data were not provided.

Additional Comments: 7.DBP 13-week feed study w/ perinatal in rats

Overall Quality Determination — Medium

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Chem Central); test animal characteristics (source, strain, age, sex, starting body weight); general animal husbandry conditions (temperature, humidity, light/dark cycle, diet, water availability, number of animals/cage); exposure methods (test substance source, purity, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). Missing important information included the parity of the dams used in this study.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a computer program. Litters were randomly culled; however, the method was not reported.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received undosed feed. Control responses were appropriate. A positive control group was not included and is not required. Food consumption was reported for offspring, but not dams in a dietary exposure study. It is unclear whether reductions in dam body weights were related to altered food consumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry conditions were consistent across groups. The study did not indicate whether feed, water, or bedding were analyzed for the presence of plasticizers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods. The methods state that 72 females were administered 10,000 ppm DBP in feed throughout gestation and lactation, which differs from what is reported in data tables (71 sperm positive females in the 10,000 ppm group). In some instances, animals were missing from the data tables. For example, absolute and relative right testis weights and testis zinc concentrations were only provided for 9/10 F1 males in the 1,262 mg/kg-day group. In addition, hematology results were provided for only 6 F1 males in the 1,262 mg/kg-day group, as opposed to the 10 that were reported in the methods section. No explanation for the exclusion of some animals is provided by the authors, although it was stated in the methods that "animals suspected of being sick due to causes other than treatment, and values that the study laboratory personnel indicated as being inadequate due to technical problems were eliminated from the analysis." It is unclear how many animals, or which groups, this applies to. Overall, there appears to be selective reporting and this is expected to notably impact the interpretation of the results.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number, purity (>98%), and storage conditions of the test substance were reported. The test substance identity was analytically verified using NMR and GC; all impurities were reported. Homogeneity, stability, and storage of the feed mixtures was reported. Periodic analysis of the dosed feed mixtures by HPLC confirmed that the dose formulations were within 10% of the theoretical concentrations. The route and method of exposure were suited to the test substance. However, the authors do not report the calculated dose (mg/kg-day) in the exposed dams. Food consumption data for dams were not provided. Default values would need to be used to calculate approximate doses in mg/kg-day. The study authors do report the calculated doses (mg/kg-day) for the male and female F1 offspring. The uncertainties in the exposure characterization of dams could influence interpretation of the study results.
	Metric 7:	Exposure timing, frequency, and duration	High	This was a developmental and extended exposure study. Exposure was conducted in utero (from GD 0) through lactation, for 4 weeks after weaning, and then for another 13 weeks after the 4-week exposure period as part of a collection of studies assessing the potential for DBP reproductive and developmental toxicity. The exposure timing, frequency, and duration were appropriate for the current study.
Domain 6: Outcome Measures and Results Display				

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Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical observations)-Clinical Observations
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	Medium	Dams were assessed for clinical signs. The frequency of clinical observations was reported, but no other details were provided. For instance, it was not stated whether these were cage-side or in depth clinical observations. This is not expected to significantly impact the interpretation of the results. The test animals (rats) and sex (females) were appropriate for evaluation of the endpoints. The sample size (71 sperm positive dams in the 10,000 ppm group; 12 sperm positive dams in the control group) was appropriate for the study type. Dosing was limited as dams were only exposed to one dose of DBP. This is not expected to substantially impact the interpretation of the results.
	Metric 9:	Results presentation	Medium	Study authors qualitatively state that “All male and female rats that received 40,000 ppm as adults were emaciated. Males in the 40,000 ppm group also had abnormal posture and ruffled fur and appeared hypoactive during Week 2 through Week 4, and males in this group had a higher incidence of nasal discharge (8/10) than the controls (2/10) or the MPE:0 ppm group (3/10).” The incidence values for abnormal posture, ruffled fur, and hypoactivity were not provided. In addition, the authors do not provide information on the actual observed and recorded clinical signs in the mice. In addition, individual animal data were not provided.

Additional Comments: 7.DBP 13-week feed study w/ perinatal in rats

Overall Quality Determination Medium

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (1 week)-F0- mating-F0 - gestation (3 weeks)-F0- lactation (4 weeks (F1e litter only))-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test chemical was identified as DBP; the purity, source and lot/batch number was provided. Animal husbandry (photoperiod, temperature, cage materials, food and water availability), the test model (species, strain, source), exposure details (doses, duration, route), number of animals per group, endpoint evaluation methods, and quantitative results for all endpoints. Missing information included humidity, animal age, and parity.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	No method of animal allocation into study groups was provided.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were not subjective or were simple measures or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropriate. A positive control was not required for the study type. Animal husbandry conditions were consistent across groups. Animals were housed in polypropylene cages, and it was not reported whether authors took measures to limit exposure to other plasticizers from food, bedding, or water. No other potentially confounding factors were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative results for all endpoints (also see HERO 1333020 and 673328). All deaths or early sacrifices were clearly reported and were not expected to have an impact on the study results. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (1 week)-F0- mating-F0 - gestation (3 weeks)-F0- lactation (4 weeks (F1e litter only))-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analytically verified using GC. Preparation and storage details of the test formulations were provided. Stability was reported. Concentrations in feed were also analytically validated at several points throughout the study and were with 99 to 106% of the target. Estimated doses in mg/kg-day at different stages of the study were reported in HERO 133020.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dosing and dose spacing were based on the literature and a dose-range-finding study and were justified by the study authors. There are no concerns about the sensitivity or consistency of the outcome assessment methodologies. The test animals and sample sizes were appropriate.
	Metric 9:	Results presentation	High	Data were quantitatively reported as means ± SEM. Sample sizes were specified. Statistical significance was shown and detailed statistical methods were provided. The litter was used as the statistical unit of analysis where appropriate. Individual animal data are provided in HERO 1333020.

Additional Comments: 10.DBP Continuous breeding study in rats

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (1 week)-F0- mating-F0 - gestation (3 weeks)-F0- lactation (4 weeks (F1e litter only))-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test chemical was identified as DBP; the purity, source and lot/batch number was provided. Animal husbandry (photoperiod, temperature, cage materials, food and water availability), the test model (species, strain, source), exposure details (doses, duration, route), number of animals per group, endpoint evaluation methods, and quantitative results for all endpoints. Missing information included humidity, animal age, and parity.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	No method of animal allocation into study groups was provided.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were not subjective or were simple measures or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropriate. A positive control was not required for the study type. Animal husbandry conditions were consistent across groups. Animals were housed in polypropylene cages, and it was not reported whether authors took measures to limit exposure to other plasticizers from food, bedding, or water. No other potentially confounding factors were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative results for all endpoints (also see HERO 1333020 and 673328). All deaths or early sacrifices were clearly reported and were not expected to have an impact on the study results. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (1 week)-F0- mating-F0 - gestation (3 weeks)-F0- lactation (4 weeks (F1e litter only))-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analytically verified using GC. Preparation and storage details of the test formulations were provided. Stability was reported. Concentrations in feed were also analytically validated at several points throughout the study and were with 99 to 106% of the target. Estimated doses in mg/kg-day at different stages of the study were reported in HERO 133020.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dosing and dose spacing were based on the literature and a dose-range-finding study and were justified by the study authors. There are no concerns about the sensitivity or consistency of the outcome assessment methodologies. The test animals and sample sizes were appropriate.
	Metric 9:	Results presentation	High	Data were quantitatively reported as means ± SEM. Sample sizes were specified. Statistical significance was shown and detailed statistical methods were provided. The litter was used as the statistical unit of analysis where appropriate. Individual animal data are provided in HERO 1333020.

Additional Comments: 10.DBP Continuous breeding study in rats

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
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Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test chemical was identified as DBP; the purity, source and lot/batch number was provided. Animal husbandry (photoperiod, temperature, cage materials, food and water availability), the test model (species, strain, source), exposure details (doses, duration, route), number of animals per group, endpoint evaluation methods, and quantitative results for all endpoints. Missing information included humidity, animal age, and parity.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	No method of animal allocation into study groups was provided.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were not subjective or were simple measures or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropriate. A positive control was not required for the study type. Animal husbandry conditions were consistent across groups. Animals were housed in polypropylene cages, and it was not reported whether authors took measures to limit exposure to other plasticizers from food, bedding, or water. No other potentially confounding factors were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative results for all endpoints (also see HERO 1333020 and 673328). All deaths or early sacrifices were clearly reported and were not expected to have an impact on the study results. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (1 week)-F0- mating-F0 - gestation (3 weeks)-F0- lactation (4 weeks (F1e litter only))-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analytically verified using GC. Preparation and storage details of the test formulations were provided. Stability was reported. Concentrations in feed were also analytically validated at several points throughout the study and were with 99 to 106% of the target. Estimated doses in mg/kg-day at different stages of the study were reported in HERO 133020.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dosing and dose spacing were based on the literature and a dose-range-finding study and were justified by the study authors. There are no concerns about the sensitivity or consistency of the outcome assessment methodologies. The test animals and sample sizes were appropriate.
	Metric 9:	Results presentation	High	Data were quantitatively reported as means ± SEM. Sample sizes were specified. Statistical significance was shown and detailed statistical methods were provided. The litter was used as the statistical unit of analysis where appropriate. Individual animal data are provided in HERO 1333020.

Additional Comments: 10.DBP Continuous breeding study in rats

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
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Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (1 week)-F0- mating-F0 - gestation (3 weeks)-F0- lactation (4 weeks (F1e litter only))-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test chemical was identified as DBP; the purity, source and lot/batch number was provided. Animal husbandry (photoperiod, temperature, cage materials, food and water availability), the test model (species, strain, source), exposure details (doses, duration, route), number of animals per group, endpoint evaluation methods, and quantitative results for all endpoints. Missing information included humidity, animal age, and parity.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	No method of animal allocation into study groups was provided.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were not subjective or were simple measures or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropriate. A positive control was not required for the study type. Animal husbandry conditions were consistent across groups. Animals were housed in polypropylene cages, and it was not reported whether authors took measures to limit exposure to other plasticizers from food, bedding, or water. No other potentially confounding factors were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative results for all endpoints (also see HERO 1333020 and 673328). All deaths or early sacrifices were clearly reported and were not expected to have an impact on the study results. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (1 week)-F0- mating-F0 - gestation (3 weeks)-F0- lactation (4 weeks (F1e litter only))-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analytically verified using GC. Preparation and storage details of the test formulations were provided. Stability was reported. Concentrations in feed were also analytically validated at several points throughout the study and were with 99 to 106% of the target. Estimated doses in mg/kg-day at different stages of the study were reported in HERO 133020.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dosing and dose spacing were based on the literature and a dose-range-finding study and were justified by the study authors. There are no concerns about the sensitivity or consistency of the outcome assessment methodologies. The test animals and sample sizes were appropriate.
	Metric 9:	Results presentation	High	Data were quantitatively reported as means ± SEM. Sample sizes were specified. Statistical significance was shown and detailed statistical methods were provided. The litter was used as the statistical unit of analysis where appropriate. Individual animal data are provided in HERO 1333020.

Additional Comments: 10.DBP Continuous breeding study in rats

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (1 week)-F0- mating-F0 - gestation (3 weeks)-F0- lactation (4 weeks (F1e litter only))-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test chemical was identified as DBP; the purity, source and lot/batch number was provided. Animal husbandry (photoperiod, temperature, cage materials, food and water availability), the test model (species, strain, source), exposure details (doses, duration, route), number of animals per group, endpoint evaluation methods, and quantitative results for all endpoints. Missing information included humidity, animal age, and parity.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	No method of animal allocation into study groups was provided.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were not subjective or were simple measures or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropriate. A positive control was not required for the study type. Animal husbandry conditions were consistent across groups. Animals were housed in polypropylene cages, and it was not reported whether authors took measures to limit exposure to other plasticizers from food, bedding, or water. No other potentially confounding factors were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative results for all endpoints (also see HERO 1333020 and 673328). All deaths or early sacrifices were clearly reported and were not expected to have an impact on the study results. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (1 week)-F0- mating-F0 - gestation (3 weeks)-F0- lactation (4 weeks (F1e litter only))-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analytically verified using GC. Preparation and storage details of the test formulations were provided. Stability was reported. Concentrations in feed were also analytically validated at several points throughout the study and were with 99 to 106% of the target. Estimated doses in mg/kg-day at different stages of the study were reported in HERO 133020.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dosing and dose spacing were based on the literature and a dose-range-finding study and were justified by the study authors. There are no concerns about the sensitivity or consistency of the outcome assessment methodologies. The test animals and sample sizes were appropriate.
	Metric 9:	Results presentation	High	Data were quantitatively reported as means ± SEM. Sample sizes were specified. Statistical significance was shown and detailed statistical methods were provided. The litter was used as the statistical unit of analysis where appropriate. Individual animal data are provided in HERO 1333020.

Additional Comments: 10.DBP Continuous breeding study in rats

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (1 week)-F0- mating-F0 - gestation (3 weeks)-F0- lactation (4 weeks (F1e litter only))-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test chemical was identified as DBP; the purity, source and lot/batch number was provided. Animal husbandry (photoperiod, temperature, cage materials, food and water availability), the test model (species, strain, source), exposure details (doses, duration, route), number of animals per group, endpoint evaluation methods, and quantitative results for all endpoints. Missing information included humidity, animal age, and parity.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	No method of animal allocation into study groups was provided.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were not subjective or were simple measures or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropriate. A positive control was not required for the study type. Animal husbandry conditions were consistent across groups. Animals were housed in polypropylene cages, and it was not reported whether authors took measures to limit exposure to other plasticizers from food, bedding, or water. No other potentially confounding factors were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative results for all endpoints (also see HERO 1333020 and 673328). All deaths or early sacrifices were clearly reported and were not expected to have an impact on the study results. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (1 week)-F0- mating-F0 - gestation (3 weeks)-F0- lactation (4 weeks (F1e litter only))-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analytically verified using GC. Preparation and storage details of the test formulations were provided. Stability was reported. Concentrations in feed were also analytically validated at several points throughout the study and were with 99 to 106% of the target. Estimated doses in mg/kg-day at different stages of the study were reported in HERO 133020.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dosing and dose spacing were based on the literature and a dose-range-finding study and were justified by the study authors. There are no concerns about the sensitivity or consistency of the outcome assessment methodologies. The test animals and sample sizes were appropriate.
	Metric 9:	Results presentation	High	Data were quantitatively reported as means ± SEM. Sample sizes were specified. Statistical significance was shown and detailed statistical methods were provided. The litter was used as the statistical unit of analysis where appropriate. Individual animal data are provided in HERO 1333020.

Additional Comments: 10.DBP Continuous breeding study in rats

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (1 week)-F0- mating-F0 - gestation (3 weeks)-F0- lactation (4 weeks (F1e litter only))-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test chemical was identified as DBP; the purity, source and lot/batch number was provided. Animal husbandry (photoperiod, temperature, cage materials, food and water availability), the test model (species, strain, source), exposure details (doses, duration, route), number of animals per group, endpoint evaluation methods, and quantitative results for all endpoints. Missing information included humidity, animal age, and parity.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	No method of animal allocation into study groups was provided.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were not subjective or were simple measures or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropriate. A positive control was not required for the study type. Animal husbandry conditions were consistent across groups. Animals were housed in polypropylene cages, and it was not reported whether authors took measures to limit exposure to other plasticizers from food, bedding, or water. No other potentially confounding factors were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative results for all endpoints (also see HERO 1333020 and 673328). All deaths or early sacrifices were clearly reported and were not expected to have an impact on the study results. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (1 week)-F0- mating-F0 - gestation (3 weeks)-F0- lactation (4 weeks (F1e litter only))-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- mating (7 days (F1e only))
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analytically verified using GC. Preparation and storage details of the test formulations were provided. Stability was reported. Concentrations in feed were also analytically validated at several points throughout the study and were with 99 to 106% of the target. Estimated doses in mg/kg-day at different stages of the study were reported in HERO 133020.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dosing and dose spacing were based on the literature and a dose-range-finding study and were justified by the study authors. There are no concerns about the sensitivity or consistency of the outcome assessment methodologies. The test animals and sample sizes were appropriate.
	Metric 9:	Results presentation	High	Data were quantitatively reported as means ± SEM. Sample sizes were specified. Statistical significance was shown and detailed statistical methods were provided. The litter was used as the statistical unit of analysis where appropriate. Individual animal data are provided in HERO 1333020.

Additional Comments: 10.DBP Continuous breeding study in rats

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test chemical was identified as DBP; the purity, source and lot/batch number was provided. Animal husbandry (photoperiod, temperature, cage materials, food and water availability), the test model (species, strain, source, age), exposure details (doses, duration, route), number of animals per group, endpoint evaluation methods, and quantitative results for all endpoints. Missing information included humidity, and parity. These are not expected to have a significant impact on the study results.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	HERO ID 061570 provided a study protocol that specifies animals were to be matched by weight and randomly assigned. However, the method used for randomization was not specified, and these details were not included in the actual study methods.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were not subjective or were simple measures or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropriate. A positive control was not required for the study type. Animal husbandry conditions were consistent across groups. Animals were housed in polypropylene cages, and it was not reported whether authors took measures to limit exposure to other plasticizers from food, bedding, or water. No other potentially confounding factors were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative or qualitative results for all endpoints (also see HERO 061570 and 061566). All deaths or early sacrifices were clearly reported and were not expected to have an impact on the study results. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analytically verified using GC. Preparation and storage details of the test formulations were provided. Stability was reported. Concentrations in feed were also analytically validated at several points throughout the study and were within 96 to 107% of the target. Animals were exposed to 0, 300, 3,000 or 10,000 ppm in feed. Doses in mg/kg-day were not provided; however, weekly body weights and daily feed consumption data are provided for different phases of the study in HERO 061570.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dosing and dose spacing were based on the literature and a dose-range-finding study in rats. There are no concerns about the sensitivity or consistency of the outcome assessment methodologies. The test animals and sample sizes were appropriate.
	Metric 9:	Results presentation	High	Data were quantitatively reported as means ± SE. Sample sizes were specified. Statistical significance was shown and detailed statistical methods were provided. The litter was used as the statistical unit of analysis where appropriate. Individual animal data are provided in HERO 061570

Additional Comments: 11.DBP Continuous breeding study in mice

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test chemical was identified as DBP; the purity, source and lot/batch number was provided. Animal husbandry (photoperiod, temperature, cage materials, food and water availability), the test model (species, strain, source, age), exposure details (doses, duration, route), number of animals per group, endpoint evaluation methods, and quantitative results for all endpoints. Missing information included humidity, and parity. These are not expected to have a significant impact on the study results.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	HERO ID 061570 provided a study protocol that specifies animals were to be matched by weight and randomly assigned. However, the method used for randomization was not specified, and these details were not included in the actual study methods.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were not subjective or were simple measures or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropriate. A positive control was not required for the study type. Animal husbandry conditions were consistent across groups. Animals were housed in polypropylene cages, and it was not reported whether authors took measures to limit exposure to other plasticizers from food, bedding, or water. No other potentially confounding factors were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative or qualitative results for all endpoints (also see HERO 061570 and 061566). All deaths or early sacrifices were clearly reported and were not expected to have an impact on the study results. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain		Metric	Rating	Comments
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analytically verified using GC. Preparation and storage details of the test formulations were provided. Stability was reported. Concentrations in feed were also analytically validated at several points throughout the study and were within 96 to 107% of the target. Animals were exposed to 0, 300, 3,000 or 10,000 ppm in feed. Doses in mg/kg-day were not provided; however, weekly body weights and daily feed consumption data are provided for different phases of the study in HERO 061570.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dosing and dose spacing were based on the literature and a dose-range-finding study in rats. There are no concerns about the sensitivity or consistency of the outcome assessment methodologies. The test animals and sample sizes were appropriate.
	Metric 9:	Results presentation	High	Data were quantitatively reported as means ± SE. Sample sizes were specified. Statistical significance was shown and detailed statistical methods were provided. The litter was used as the statistical unit of analysis where appropriate. Individual animal data are provided in HERO 061570

Additional Comments: 11.DBP Continuous breeding study in mice

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test chemical was identified as DBP; the purity, source and lot/batch number was provided. Animal husbandry (photoperiod, temperature, cage materials, food and water availability), the test model (species, strain, source, age), exposure details (doses, duration, route), number of animals per group, endpoint evaluation methods, and quantitative results for all endpoints. Missing information included humidity, and parity. These are not expected to have a significant impact on the study results.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	HERO ID 061570 provided a study protocol that specifies animals were to be matched by weight and randomly assigned. However, the method used for randomization was not specified, and these details were not included in the actual study methods.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were not subjective or were simple measures or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropriate. A positive control was not required for the study type. Animal husbandry conditions were consistent across groups. Animals were housed in polypropylene cages, and it was not reported whether authors took measures to limit exposure to other plasticizers from food, bedding, or water. No other potentially confounding factors were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative or qualitative results for all endpoints (also see HERO 061570 and 061566). All deaths or early sacrifices were clearly reported and were not expected to have an impact on the study results. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain		Metric	Rating	Comments
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analytically verified using GC. Preparation and storage details of the test formulations were provided. Stability was reported. Concentrations in feed were also analytically validated at several points throughout the study and were within 96 to 107% of the target. Animals were exposed to 0, 300, 3,000 or 10,000 ppm in feed. Doses in mg/kg-day were not provided; however, weekly body weights and daily feed consumption data are provided for different phases of the study in HERO 061570.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dosing and dose spacing were based on the literature and a dose-range-finding study in rats. There are no concerns about the sensitivity or consistency of the outcome assessment methodologies. The test animals and sample sizes were appropriate.
	Metric 9:	Results presentation	High	Data were quantitatively reported as means ± SE. Sample sizes were specified. Statistical significance was shown and detailed statistical methods were provided. The litter was used as the statistical unit of analysis where appropriate. Individual animal data are provided in HERO 061570

Additional Comments: 11.DBP Continuous breeding study in mice

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test chemical was identified as DBP; the purity, source and lot/batch number was provided. Animal husbandry (photoperiod, temperature, cage materials, food and water availability), the test model (species, strain, source, age), exposure details (doses, duration, route), number of animals per group, endpoint evaluation methods, and quantitative results for all endpoints. Missing information included humidity, and parity. These are not expected to have a significant impact on the study results.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	HERO ID 061570 provided a study protocol that specifies animals were to be matched by weight and randomly assigned. However, the method used for randomization was not specified, and these details were not included in the actual study methods.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were not subjective or were simple measures or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropriate. A positive control was not required for the study type. Animal husbandry conditions were consistent across groups. Animals were housed in polypropylene cages, and it was not reported whether authors took measures to limit exposure to other plasticizers from food, bedding, or water. No other potentially confounding factors were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative or qualitative results for all endpoints (also see HERO 061570 and 061566). All deaths or early sacrifices were clearly reported and were not expected to have an impact on the study results. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain		Metric	Rating	Comments
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analytically verified using GC. Preparation and storage details of the test formulations were provided. Stability was reported. Concentrations in feed were also analytically validated at several points throughout the study and were within 96 to 107% of the target. Animals were exposed to 0, 300, 3,000 or 10,000 ppm in feed. Doses in mg/kg-day were not provided; however, weekly body weights and daily feed consumption data are provided for different phases of the study in HERO 061570.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dosing and dose spacing were based on the literature and a dose-range-finding study in rats. There are no concerns about the sensitivity or consistency of the outcome assessment methodologies. The test animals and sample sizes were appropriate.
	Metric 9:	Results presentation	High	Data were quantitatively reported as means ± SE. Sample sizes were specified. Statistical significance was shown and detailed statistical methods were provided. The litter was used as the statistical unit of analysis where appropriate. Individual animal data are provided in HERO 061570

Additional Comments: 11.DBP Continuous breeding study in mice

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
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Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test chemical was identified as DBP; the purity, source and lot/batch number was provided. Animal husbandry (photoperiod, temperature, cage materials, food and water availability), the test model (species, strain, source, age), exposure details (doses, duration, route), number of animals per group, endpoint evaluation methods, and quantitative results for all endpoints. Missing information included humidity, and parity. These are not expected to have a significant impact on the study results.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	HERO ID 061570 provided a study protocol that specifies animals were to be matched by weight and randomly assigned. However, the method used for randomization was not specified, and these details were not included in the actual study methods.
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	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative or qualitative results for all endpoints (also see HERO 061570 and 061566). All deaths or early sacrifices were clearly reported and were not expected to have an impact on the study results. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain		Metric	Rating	Comments
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analytically verified using GC. Preparation and storage details of the test formulations were provided. Stability was reported. Concentrations in feed were also analytically validated at several points throughout the study and were within 96 to 107% of the target. Animals were exposed to 0, 300, 3,000 or 10,000 ppm in feed. Doses in mg/kg-day were not provided; however, weekly body weights and daily feed consumption data are provided for different phases of the study in HERO 061570.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dosing and dose spacing were based on the literature and a dose-range-finding study in rats. There are no concerns about the sensitivity or consistency of the outcome assessment methodologies. The test animals and sample sizes were appropriate.
	Metric 9:	Results presentation	High	Data were quantitatively reported as means ± SE. Sample sizes were specified. Statistical significance was shown and detailed statistical methods were provided. The litter was used as the statistical unit of analysis where appropriate. Individual animal data are provided in HERO 061570

Additional Comments: 11.DBP Continuous breeding study in mice

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test chemical was identified as DBP; the purity, source and lot/batch number was provided. Animal husbandry (photoperiod, temperature, cage materials, food and water availability), the test model (species, strain, source, age), exposure details (doses, duration, route), number of animals per group, endpoint evaluation methods, and quantitative results for all endpoints. Missing information included humidity, and parity. These are not expected to have a significant impact on the study results.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	HERO ID 061570 provided a study protocol that specifies animals were to be matched by weight and randomly assigned. However, the method used for randomization was not specified, and these details were not included in the actual study methods.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were not subjective or were simple measures or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropriate. A positive control was not required for the study type. Animal husbandry conditions were consistent across groups. Animals were housed in polypropylene cages, and it was not reported whether authors took measures to limit exposure to other plasticizers from food, bedding, or water. No other potentially confounding factors were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative or qualitative results for all endpoints (also see HERO 061570 and 061566). All deaths or early sacrifices were clearly reported and were not expected to have an impact on the study results. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain		Metric	Rating	Comments
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analytically verified using GC. Preparation and storage details of the test formulations were provided. Stability was reported. Concentrations in feed were also analytically validated at several points throughout the study and were within 96 to 107% of the target. Animals were exposed to 0, 300, 3,000 or 10,000 ppm in feed. Doses in mg/kg-day were not provided; however, weekly body weights and daily feed consumption data are provided for different phases of the study in HERO 061570.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dosing and dose spacing were based on the literature and a dose-range-finding study in rats. There are no concerns about the sensitivity or consistency of the outcome assessment methodologies. The test animals and sample sizes were appropriate.
	Metric 9:	Results presentation	High	Data were quantitatively reported as means ± SE. Sample sizes were specified. Statistical significance was shown and detailed statistical methods were provided. The litter was used as the statistical unit of analysis where appropriate. Individual animal data are provided in HERO 061570

Additional Comments: 11.DBP Continuous breeding study in mice

Overall Quality Determination High

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test chemical was identified as DBP; the purity, source and lot/batch number was provided. Animal husbandry (photoperiod, temperature, cage materials, food and water availability), the test model (species, strain, source, age), exposure details (doses, duration, route), number of animals per group, endpoint evaluation methods, and quantitative results for all endpoints. Missing information included humidity, and parity. These are not expected to have a significant impact on the study results.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	HERO ID 061570 provided a study protocol that specifies animals were to be matched by weight and randomly assigned. However, the method used for randomization was not specified, and these details were not included in the actual study methods.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were not subjective or were simple measures or initial histopathology.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropriate. A positive control was not required for the study type. Animal husbandry conditions were consistent across groups. Animals were housed in polypropylene cages, and it was not reported whether authors took measures to limit exposure to other plasticizers from food, bedding, or water. No other potentially confounding factors were identified.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative or qualitative results for all endpoints (also see HERO 061570 and 061566). All deaths or early sacrifices were clearly reported and were not expected to have an impact on the study results. There is no evidence of attrition or selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydrogenase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).-Nutritional/Metabolic-Terminal body weights (Studies 1, 2, 3, and 4).Body weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).-Other (please specify below) (Clinical observations)-Clinical Observations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).-Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11).-Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11).
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)
Species:	Mouse-CD-1 - [mouse]-Both
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063

Domain		Metric	Rating	Comments
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analytically verified using GC. Preparation and storage details of the test formulations were provided. Stability was reported. Concentrations in feed were also analytically validated at several points throughout the study and were within 96 to 107% of the target. Animals were exposed to 0, 300, 3,000 or 10,000 ppm in feed. Doses in mg/kg-day were not provided; however, weekly body weights and daily feed consumption data are provided for different phases of the study in HERO 061570.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Dosing and dose spacing were based on the literature and a dose-range-finding study in rats. There are no concerns about the sensitivity or consistency of the outcome assessment methodologies. The test animals and sample sizes were appropriate.
	Metric 9:	Results presentation	High	Data were quantitatively reported as means ± SE. Sample sizes were specified. Statistical significance was shown and detailed statistical methods were provided. The litter was used as the statistical unit of analysis where appropriate. Individual animal data are provided in HERO 061570

Additional Comments: 11.DBP Continuous breeding study in mice

Overall Quality Determination High

Study Citation:	Martino-Andrade, A. J., Morais, R. N., Botelho, G. G., Muller, G., Grande, S. W., Carpentieri, G. B., Leao, G. M., Dalsenter, P. R. (2008). Coadministration of active phthalates results in disruption of foetal testicular function in rats. International Journal of Andrology 32(6):704-12.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Testicular testosterone levels
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (GD13-GD21)
Species:	Rat-Wistar - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676281

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	All critical and most important information was reported. Reported information included information on the test substance (name, CASRN, purity and source), the test model (species, strain, sex, and source), animal husbandry details (photoperiod, temperature, food and water availability), exposure methods, experimental design, endpoint evaluations, and presentation of results.Missing information included test animal age, initial body weights, parity, humidity, and number of animals per cage.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Low	No details on the allocation of dams into study groups or on the selection of fetuses for outcome analysis were provided.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not specified but the outcome was measured using a standard laboratory kit.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Medium	A negative corn oil control group was included and gave the expected response. There were no differences in maternal body weights (fetal weights were not measured) and gavage volumes were consistent across groups. No differences in the animal husbandry parameters reported were noted. It is unclear whether the study took measures to minimize the exposure to other plasticizers (e.g., from cage, bedding, or water dispensing materials, or in food), which could influence the study results.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Medium	The number of dams used in the study was reported as a range (6-9 per group). It was not specified if any of the dams used for this endpoint died. Data were reported for the endpoint of interest and the sample sizes for the from 6-8 (litters)/group. Based on the information provided, there is no evidence of selective reporting.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Martino-Andrade, A. J., Morais, R. N., Botelho, G. G., Muller, G., Grande, S. W., Carpentieri, G. B., Leao, G. M., Dalsenter, P. R. (2008). Coadministration of active phthalates results in disruption of foetal testicular function in rats. International Journal of Andrology 32(6):704-12.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Testicular testosterone levels
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (GD13-GD21)
Species:	Rat-Wistar - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	676281

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Medium	The test material source (Sigma-Aldrich) and purity (99%) were reported. The study did not include the certificate of analysis (or catalogue number), and the test material was not verified by the performing laboratory. Certificates of analysis are generally available on the supplier's website. Animals were dosed via gavage in corn oil and the gavage volume (5mL/kg) was appropriate. No details on the preparation, storage, or stability of the test solutions were provided. Doses were reported in mg/kg-day. It is not specified whether doses were adjusted daily based on measured body weights. Doses were not analytically verified.
	Metric 7:	Exposure timing, frequency, and duration	High	Animals were exposed from GD13-21. This exposure covers the period of post-implantation embryonic development, and the critical windows of organogenesis and male sexual differentiation.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Testosterone levels were measured using an ELISA assay from presumably pooled samples from the right testes of 1-2 males (GD21) per litter, and 6-8 litters per dose. There are no major concerns about the sample size used. The study text noted that samples were measured in a single run, suggesting the lack of replicates. Two doses were tested. The lowest dose was either not expected to suppress testicular testosterone levels or only to produce small changes. The higher dose induced a response. There are no concerns about the test model used.
	Metric 9:	Results presentation	High	Results were reported in a figure (bar graph) showing means ± SEM. Statistical significance and sample size (number of litters and individual fetuses) were shown. Litters were used as the experimental unit. Individual animal data were not provided

Additional Comments: None

Overall Quality Determination Medium

Study Citation:	Moody, S., Goh, H., Bielanowicz, A., Rippon, P., Loveland, K. L., Itman, C. (2013). Prepubertal mouse testis growth and maturation and androgen production are acutely sensitive to di-n-butyl phthalate. Endocrinology 154(9):3460-3475.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Body weight, gross morphology of testis, organ weight (testis, spleen, kidney, liver, and heart), serum FSH, inhibin and testosterone levels, level of proliferation or Sertoli cells (PCNA staining), and apoptosis in testes (cleaved caspase 3 and TUNEL staining), development of Sertoli cells (PND 14; via immunohistochemistry and Western blot for SOX9 and anti-Mullerian hormone [AMH]) histopathology on testes, assessment of spermatogenesis, Immunohistochemistry in testis for connexin 43, inhibin -alpha subunit, germ cell nuclear antigen; Western blot AMH, Cx43, Sox9, alpha-tubulin, cleaved caspase 3.
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F1- post-natal (PND4-21)
Species:	Mouse-C57BL - [mouse]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1639195

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 di (n-butyl) phthalate (DBP). The source was reported (Chem Service, West Chester, PA). Purity was not reported. Test animal species, strain, sex, age and source were reported. Initial body weight of the animals was not reported. Husbandry conditions (temperature, humidity, and light cycle) were reported. A soy-free diet was provided ad libitum. Water availability was not reported. Litter size ranged from 5-10 pups housed with one dam. After weaning, the number of animals/group was not reported. 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	Medium	The study states litters were randomly assigned to treatment groups but does not report the method 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., serum levels of hormones, body weight, anogenital distance) 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 negative control group was included and appropriate. Gavage volume was appropriate (1ul/g body weight). There were no indication conditions were different between the groups. The study does not indicate if plastic or glass water bottles were used. Phthalates may leach into water from plastic, thereby potentially confounding the results (if plastic was used).
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Moody, S., Goh, H., Bielanowicz, A., Rippon, P., Loveland, K. L., Itman, C. (2013). Prepubertal mouse testis growth and maturation and androgen production are acutely sensitive to di-n-butyl phthalate. Endocrinology 154(9):3460-3475.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Body weight, gross morphology of testis, organ weight (testis, spleen, kidney, liver, and heart), serum FSH, inhibin and testosterone levels, level of proliferation or Sertoli cells (PCNA staining), and apoptosis in testes (cleaved caspase 3 and TUNEL staining), development of Sertoli cells (PND 14; via immunohistochemistry and Western blot for SOX9 and anti-Mullerian hormone [AMH]) histopathology on testes, assessment of spermatogenesis, Immunohistochemistry in testis for connexin 43, inhibin -alpha subunit, germ cell nuclear antigen; Western blot AMH, Cx43, Sox9, alpha-tubulin, cleaved caspase 3.
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F1- post-natal (PND4-21)
Species:	Mouse-C57BL - [mouse]-Male
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1639195

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	Low	It is not clear how many litters were treated/group or how many animals were treated. The study states 2 males in the 500 mg/kg/day failed to gain weight after 24 hours and were killed before completion of experiment, but it is not reported how many animals were treated so the significance of this is unclear.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	The route and gavage volume were appropriate. The purity of the test substance was not reported and could not be determined by company's website. The study did not measure concentration in corn oil or report if doses were prepared fresh.
	Metric 7:	Exposure timing, frequency, and duration	High	The exposure frequency, timing and duration were appropriate for the study's aim PND 4-21.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Endpoints evaluated were sensitive to outcomes of interest (prepubertal testis growth and maturation).
	Metric 9:	Results presentation	Low	Data were fully reported for most (but not all) outcomes. The study reports relative testis weight without corresponding data on absolute testis weight. Relative testis weight is a potentially unreliable metric for testicular toxicity because testis and body weight are not proportional. Offspring data were presented as means of individual animals, rather than as litter means, which has the potential to overestimate the statistical significance of experimental findings.

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-F0: Organ weights (uterus, ovaries), implantation sites. F1:numbers of live and dead pups, sex, pups signs of toxicity, pup weights, AGD, male nipple/areolae count, vaginal opening or preputial separation, necropsy, organ weights (ovaries, testes, seminal vesicles, epididymides, vas deferens, ventral prostate, levator ani-bulbocavernosus muscle), histopathology of male reproductive tissues
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673305

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	Test substance was reported as DBP (99.8% pure) from Aldrich chem. No CAS or structure were reported. Doses were administered via gavage and doses were reported appropriately (in mg/kg/d). Test animal species and strain and sex were reported as females mated SD-CD rats, age was 8 weeks, sourced from Charles River laboratories (mated at CR). Animal body weights were not reported, but were used for randomization: husbandry were all reported: temp, light cycle, humidity, water availability, and number of animals per cage. Number of animals per group were reported (n= 19-20 for all dose groups except the high dose group was n=11) and were consistent with OECD guideline 414. The justification for fewer animals at the high dose was that this dose is a previously identified LOAEL and less power was needed. Exposure via gavage was administered daily to dams (during gestation GD 12-21) to encompass the period of male sexual differentiation. Endpoint evaluation methods were reported and qualitative or quantitative results were reported for most endpoints.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The method of allocation to study groups was reported as "using randomization of body weights to ensure equal weight distribution among groups" for dams. F1 pups were weaned PND21 and separated by sex and treatment group through sexual maturation (80 days F and 110 days, M).
	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 vehicle (corn oil) control group that was prepared in the same manner as the dose groups but without DBP. Glass water bottles were used in lieu of plastic limiting co-exposure to plastics, but polycarbonate cages were used for housing. Negative controls responded appropriately. Two animals in the 5 mg/kg/day group died or were euthanized due to severe dehydration, however, water consumption was not reported. Food consumption and weight gain were comparable across groups.
Domain 4: Selective Reporting and Attrition				

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Study Citation:	Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-F0: Organ weights (uterus, ovaries), implantation sites. F1:numbers of live and dead pups, sex, pups signs of toxicity, pup weights, AGD, male nipple/areolae count, vaginal opening or preputial separation, necropsy, organ weights (ovaries, testes, seminal vesicles, epididymides, vas deferens, ventral prostate, levator ani-bulbocavernosus muscle), histopathology of male reproductive tissues
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673305

Domain	Metric		Rating	Comments
	Metric 5:	Selective Reporting and Attrition	High	The number of deaths was low and explained (lack of pregnancy or dehydration). The results were reported quantitatively or with a qualitative statement for each outcome and there was no evidence of selective reporting.
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	The chemical source (Aldrich chemical Co.) and purity (99.8%) were reported. No independent verification was provided by the laboratory. The test substance was prepared in a corn oil vehicle and stability was examined over a 21 day period by GC and was within 4-7% of expected values. Gavage dosing was an appropriate exposure method and gavage volume was reported (1ml/kg/d) and consistent among groups. Doses were reported as 0, 0.5, 5, 50, 100, and 500 mg/kg/d. Doses administered were verified by GCMS. The study was conducted in 2 sections with half of the animals in each dose group.
	Metric 7:	Exposure timing, frequency, and duration	High	Exposure administration was reported and timing frequency and duration were consistent with OECD414. Duration of exposure was reported as GD 12-21 and was justified to include the major period of male sexual differentiation.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	The study methodology including outcome measures were reported and appropriate for the outcome. The number of dams and litters were 20 for most groups (19 for 5 mg/kg/d due to 2 deaths). The endpoints in dams were done throughout gestation and lactation, and in offspring were evaluated on PND1, PND 14, PND 21, and at sexual maturation (PND 80 for females and PND 110 for males). Dose groups and spacing were justified by the authors and were appropriate. All treatment groups were evaluated for the outcome assessment and sampling was adequate. Test animals were obtained from a commercial source and species, strain, and sex were appropriate and consistent with OECD guideline and previous publications.
	Metric 9:	Results presentation	High	Outcomes for reproductive parameters were quantitatively reported and presented means and SE. Developmental outcomes were reported quantitatively using the litter as the experimental unit. The data were clearly reported for all dose groups and discussed in text. Statistical analysis was described in detail in the methods and appropriate for the data. Graphs (fig 1 and fig 2) were printed poorly and difficult to read, however, figure legends and discussion in text provided adequate information.

Additional Comments: None

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Study Citation:	Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-F0: Organ weights (uterus, ovaries), implantation sites. F1:numbers of live and dead pups, sex, pups signs of toxicity, pup weights, AGD, male nipple/areolae count, vaginal opening or preputial separation, necropsy, organ weights (ovaries, testes, seminal vesicles, epididymides, vas deferens, ventral prostate, levator ani-bulbocavernosus muscle), histopathology of male reproductive tissues
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673305

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

Study Citation:	Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Dam body weight, body weight gain, food consumption
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673305

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	Test substance was reported as DBP (99.8% pure) from Aldrich chem. No CAS or structure were reported. Doses were administered via gavage and doses were reported appropriately (in mg/kg/d). Test animal species and strain and sex were reported as females mated SD-CD rats, age was 8 weeks, sourced from Charles River laboratories (mated at CR). Animal body weights were not reported, but were used for randomization: husbandry were all reported: temp, light cycle, humidity, water availability, and number of animals per cage. Number of animals per group were reported (n= 19-20 for all dose groups except the high dose group was n=11) and were consistent with OECD guideline 414. The justification for fewer animals at the high dose was that this dose is a previously identified LOAEL and less power was needed. Exposure via gavage was administered daily to dams (during gestation GD 12-21) to encompass the period of male sexual differentiation. Endpoint evaluation methods were reported and qualitative or quantitative results were reported for most endpoints. Doses administered were verified by GCMS.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The method of allocation to study groups was reported as "using randomization of body weights to ensure equal weight distribution among groups" for dams. F1 pups were weaned PND21 and separated by sex and treatment group through sexual maturation (80 days F and 110 days, M).
	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 vehicle (corn oil) control group that was prepared in the same manner as the dose groups but without DBP. Glass water bottles were used in lieu of plastic limiting co-exposure to plastics, but polycarbonate cages were used for housing. Negative controls responded appropriately. Two animals in the 5 mg/kg/day group died or were euthanized due to severe dehydration, however, water consumption was not reported. Food consumption and weight gain were comparable across groups.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The number of deaths was low and explained (lack of pregnancy or dehydration). The results were reported quantitatively or with a qualitative statement for each outcome and there was no evidence of selective reporting.

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Study Citation:	Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Dam body weight, body weight gain, food consumption
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673305

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	The chemical source (Aldrich chemical Co.) and purity (99.8%) were reported. No independent verification was provided by the laboratory. The test substance was prepared in a corn oil vehicle and stability was examined over a 21 day period by GC and was within 4-7% of expected values. Gavage dosing was an appropriate exposure method and gavage volume was reported (1ml/kg/d) and consistent among groups. Doses were reported as 0, 0.5, 5, 50, 100, and 500 mg/kg/d. The study was conducted in 2 sections with half of the animals in each dose group.
	Metric 7:	Exposure timing, frequency, and duration	Medium	Exposure administration was reported and timing frequency and duration were consistent with OECD414. Duration of exposure was reported as GD 12-21 and was justified to include the major period of male sexual differentiation.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	High	The study methodology including outcome measures were reported and appropriate for the outcome. The number of dams were 20 for most groups (19 for 5 mg/kg/d due to 2 deaths). The endpoints in dams were done throughout gestation and lactation . Dose groups and spacing were justified by the authors and were appropriate. All treatment groups were evaluated for the outcome assessment and sampling was adequate. Test animals were obtained from a commercial source and species, strain, and sex were appropriate and consistent with OECD guideline and previous publications.
	Metric 9:	Results presentation	High	Outcomes for body weight, body weight gain and food consumption were reported quantitatively and presented as means and SE. The data were clearly reported for all dose groups and discussed in text. Statistical analysis was described in detail in the methods and appropriate for the data.

Additional Comments: None

Overall Quality Determination — High

Study Citation:	Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151.
Health Outcome(s) and Reported Health Effect(s):	Hepatic/Liver-Liver weight-Renal/Kidney-Kidney weight-Other (please specify below) (endocrine)-adrenal gland weight
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673305

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	Test substance was reported as DBP (99.8% pure) from Aldrich chem. No CAS or structure were reported. Doses were administered via gavage and doses were reported appropriately (in mg/kg/d). Test animal species and strain and sex were reported as females mated SD-CD rats, age was 8 weeks, sourced from Charles River laboratories (mated at CR). Animal body weights were not reported, but were used for randomization: husbandry were all reported: temp, light cycle, humidity, water availability, and number of animals per cage. Number of animals per group were reported (n= 19-20 for all dose groups except the high dose group was n=11) and were consistent with OECD guideline 414. The justification for fewer animals at the high dose was that this dose is a previously identified LOAEL and less power was needed. Exposure via gavage was administered daily to dams (during gestation GD 12-21) to encompass the period of male sexual differentiation. Endpoint evaluation methods were reported and qualitative or quantitative results were reported for most endpoints. Doses administered were verified by GCMS.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The method of allocation to study groups was reported as ”using randomization of body weights to ensure equal weight distribution among groups” for dams. F1 pups were weaned PND21 and separated by sex and treatment group through sexual maturation (80 days F and 110 days, M).
	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 vehicle (corn oil) control group that was prepared in the same manner as the dose groups but without DBP. Gavage volumes were the same across all groups. Glass water bottles were used in lieu of plastic limiting co-exposure to plastics, but polycarbonate cages were used for housing. Negative controls responded appropriately. Two animals in the 5 mg/kg/day group died or were euthanized due to severe dehydration, however, water consumption was not reported. Food consumption and weight gain were comparable across groups.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The number of deaths was low and explained (lack of pregnancy or dehydration). The results were reported quantitatively or with a qualitative statement for each outcome and there was no evidence of selective reporting.

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Study Citation:	Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151.
Health Outcome(s) and Reported Health Effect(s):	Hepatic/Liver-Liver weight-Renal/Kidney-Kidney weight-Other (please specify below) (endocrine)-adrenal gland weight
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673305

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	The chemical source (Aldrich chemical Co.) and purity (99.8%) were reported. No independent verification was provided by the laboratory. The test substance was prepared in a corn oil vehicle and stability was examined over a 21 day period by GC and was within 4-7% of expected values. Gavage dosing was an appropriate exposure method and gavage volume was reported (1ml/kg/d) and consistent among groups. Doses were reported as 0, 0.5, 5, 50, 100, and 500 mg/kg/d. The study was conducted in 2 sections with half of the animals in each dose group.
	Metric 7:	Exposure timing, frequency, and duration	Low	Exposure administration was reported and timing frequency and duration were consistent with OECD414. Duration of exposure was reported as GD 12-21 and was justified to include the major period of male sexual differentiation, but was insufficient for effects on organ weights.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Low	The study methodology for organ weights was described but was limited to organ weights and did not include clinical chemistry or histopathology. The number of dams were 20 for most groups (19 for 5 mg/kg/d due to 2 deaths). The endpoints in dams were done after weaning, PND 21. Dose groups and spacing were focused on male reproductive development and did not encompass effects on the organs (liver kidney or adrenal gland). All treatment groups were evaluated for the outcome assessment and sampling was adequate. Test animals were obtained from a commercial source and species, strain, and sex were appropriate and consistent with OECD guideline and previous publications.
	Metric 9:	Results presentation	Medium	Outcomes for organ weights (kidney liver and adrenal gland) did not have exposure related effects and were reported qualitatively in the text for all dose groups. Statistical analysis was described in detail in the methods and appropriate for the data.

Additional Comments: None

Overall Quality Determination Medium

Study Citation:	Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151.
Health Outcome(s) and Reported Health Effect(s):	Hepatic/Liver-Liver weight-Renal/Kidney-Kidney weight-Other (please specify below) (endocrine)-adrenal gland weight
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673305

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	Test substance was reported as DBP (99.8% pure) from Aldrich chem. No CAS or structure were reported. Doses were administered via gavage and doses were reported appropriately (in mg/kg/d). Test animal species and strain and sex were reported as females mated SD-CD rats, age was 8 weeks, sourced from Charles River laboratories (mated at CR). Animal body weights were not reported, but were used for randomization: husbandry were all reported: temp, light cycle, humidity, water availability, and number of animals per cage. Number of animals per group were reported (n= 19-20 for all dose groups except the high dose group was n=11) and were consistent with OECD guideline 414. The justification for fewer animals at the high dose was that this dose is a previously identified LOAEL and less power was needed. Exposure via gavage was administered daily to dams (during gestation GD 12-21) to encompass the period of male sexual differentiation. Endpoint evaluation methods were reported and qualitative or quantitative results were reported for most endpoints. Doses administered were verified by GCMS.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The method of allocation to study groups was reported as ”using randomization of body weights to ensure equal weight distribution among groups” for dams. F1 pups were weaned PND21 and separated by sex and treatment group through sexual maturation (80 days F and 110 days, M).
	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 vehicle (corn oil) control group that was prepared in the same manner as the dose groups but without DBP. Gavage volumes were the same across all groups. Glass water bottles were used in lieu of plastic limiting co-exposure to plastics, but polycarbonate cages were used for housing. Negative controls responded appropriately. Two animals in the 5 mg/kg/day group died or were euthanized due to severe dehydration, however, water consumption was not reported. Food consumption and weight gain were comparable across groups.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The number of deaths was low and explained (lack of pregnancy or dehydration). The results were reported quantitatively or with a qualitative statement for each outcome and there was no evidence of selective reporting.

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Study Citation:	Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151.
Health Outcome(s) and Reported Health Effect(s):	Hepatic/Liver-Liver weight-Renal/Kidney-Kidney weight-Other (please specify below) (endocrine)-adrenal gland weight
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673305

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	The chemical source (Aldrich chemical Co.) and purity (99.8%) were reported. No independent verification was provided by the laboratory. The test substance was prepared in a corn oil vehicle and stability was examined over a 21 day period by GC and was within 4-7% of expected values. Gavage dosing was an appropriate exposure method and gavage volume was reported (1ml/kg/d) and consistent among groups. Doses were reported as 0, 0.5, 5, 50, 100, and 500 mg/kg/d. The study was conducted in 2 sections with half of the animals in each dose group.
	Metric 7:	Exposure timing, frequency, and duration	Low	Exposure administration was reported and timing frequency and duration were consistent with OECD414. Duration of exposure was reported as GD 12-21 and was justified to include the major period of male sexual differentiation, but was insufficient for effects on organ weights.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Low	The study methodology for organ weights was described but was limited to organ weights and did not include clinical chemistry or histopathology. The number of dams were 20 for most groups (19 for 5 mg/kg/d due to 2 deaths). The endpoints in dams were done after weaning, PND 21. Dose groups and spacing were focused on male reproductive development and did not encompass effects on the organs (liver kidney or adrenal gland). All treatment groups were evaluated for the outcome assessment and sampling was adequate. Test animals were obtained from a commercial source and species, strain, and sex were appropriate and consistent with OECD guideline and previous publications.
	Metric 9:	Results presentation	Medium	Outcomes for organ weights (kidney liver and adrenal gland) did not have exposure related effects and were reported qualitatively in the text for all dose groups. Statistical analysis was described in detail in the methods and appropriate for the data.

Additional Comments: None

Overall Quality Determination Medium

Study Citation:	Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151.
Health Outcome(s) and Reported Health Effect(s):	Hepatic/Liver-Liver weight-Renal/Kidney-Kidney weight-Other (please specify below) (endocrine)-adrenal gland weight
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673305

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	High	Test substance was reported as DBP (99.8% pure) from Aldrich chem. No CAS or structure were reported. Doses were administered via gavage and doses were reported appropriately (in mg/kg/d). Test animal species and strain and sex were reported as females mated SD-CD rats, age was 8 weeks, sourced from Charles River laboratories (mated at CR). Animal body weights were not reported, but were used for randomization: husbandry were all reported: temp, light cycle, humidity, water availability, and number of animals per cage. Number of animals per group were reported (n= 19-20 for all dose groups except the high dose group was n=11) and were consistent with OECD guideline 414. The justification for fewer animals at the high dose was that this dose is a previously identified LOAEL and less power was needed. Exposure via gavage was administered daily to dams (during gestation GD 12-21) to encompass the period of male sexual differentiation. Endpoint evaluation methods were reported and qualitative or quantitative results were reported for most endpoints. Doses administered were verified by GCMS.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	Medium	The method of allocation to study groups was reported as "using randomization of body weights to ensure equal weight distribution among groups" for dams. F1 pups were weaned PND21 and separated by sex and treatment group through sexual maturation (80 days F and 110 days, M).
	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 vehicle (corn oil) control group that was prepared in the same manner as the dose groups but without DBP. Gavage volumes were the same across all groups. Glass water bottles were used in lieu of plastic limiting co-exposure to plastics, but polycarbonate cages were used for housing. Negative controls responded appropriately. Two animals in the 5 mg/kg/day group died or were euthanized due to severe dehydration, however, water consumption was not reported. Food consumption and weight gain were comparable across groups.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	The number of deaths was low and explained (lack of pregnancy or dehydration). The results were reported quantitatively or with a qualitative statement for each outcome and there was no evidence of selective reporting.

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Study Citation:	Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151.
Health Outcome(s) and Reported Health Effect(s):	Hepatic/Liver-Liver weight-Renal/Kidney-Kidney weight-Other (please specify below) (endocrine)-adrenal gland weight
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673305

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Medium	The chemical source (Aldrich chemical Co.) and purity (99.8%) were reported. No independent verification was provided by the laboratory. The test substance was prepared in a corn oil vehicle and stability was examined over a 21 day period by GC and was within 4-7% of expected values. Gavage dosing was an appropriate exposure method and gavage volume was reported (1ml/kg/d) and consistent among groups. Doses were reported as 0, 0.5, 5, 50, 100, and 500 mg/kg/d. The study was conducted in 2 sections with half of the animals in each dose group.
	Metric 7:	Exposure timing, frequency, and duration	Low	Exposure administration was reported and timing frequency and duration were consistent with OECD414. Duration of exposure was reported as GD 12-21 and was justified to include the major period of male sexual differentiation, but was insufficient for effects on organ weights.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Low	The study methodology for organ weights was described but was limited to organ weights and did not include clinical chemistry or histopathology. The number of dams were 20 for most groups (19 for 5 mg/kg/d due to 2 deaths). The endpoints in dams were done after weaning, PND 21. Dose groups and spacing were focused on male reproductive development and did not encompass effects on the organs (liver kidney or adrenal gland). All treatment groups were evaluated for the outcome assessment and sampling was adequate. Test animals were obtained from a commercial source and species, strain, and sex were appropriate and consistent with OECD guideline and previous publications.
	Metric 9:	Results presentation	Medium	Outcomes for organ weights (kidney liver and adrenal gland) did not have exposure related effects and were reported qualitatively in the text for all dose groups. Statistical analysis was described in detail in the methods and appropriate for the data.

Additional Comments: None

Overall Quality Determination — Medium

Study Citation:	Salazar, V., Castillo, C., Ariznavarreta, C., Campón, R., Tresguerres, F., J.A. (2004). Effect of oral intake of dibutyl phthalate on reproductive parameters of Long Evans rats and pre-pubertal development of their offspring. Toxicology 205(1-2):131-137.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Percentage of pregnant rats; Litter size (PND0, 2, and 6); Pup survival; Female:male ratio of pups (PND2, PND6); Body weights of pups (PND2, PND6); Days to eyes' opening (assessed PND6 onwards); Male pup body weight (PND14); Testis relative weight of male pups (PND14); Thymus relative weight of male pups (PND14); Plasma of male pups (PND14); Days to vaginal opening and first estrous in female pups; Days to pre-putial separation in male pups-Nutritional/Metabolic-Dam body weights; Total dam body weight gain (g/3 months)
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (unclear 2-2.5 months)-F0- mating (NR)-F0 - gestation (NR)-F0- lactation (NR)-F1- premating (PND 22 - up to PND 41)
Species:	Rat-Long-Evans - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673308

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Low	All critical and most important information was reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Sigma-Aldrich); test animal characteristics (strain, age, and sex); general animal husbandry conditions (temperature, light/dark cycle, diet and water availability); exposure methods (test substance source, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). The study lacked the source and starting body weights of the test animals. They were also missing some details on animal husbandry conditions and procedures, including humidity and the number of animals per cage at the start of the study. In addition, the purity of the test substance was not reported. The duration of exposure to the test substance is somewhat unclear. In the abstract, the authors state that rats were exposed to DBP-dosed chow for 2 months prior to being mated. In the materials and methods section, the authors state that rats were exposed to DBP-dosed chow for 2.5 months prior to being mated. However, it is not stated how long the mating period was and whether the females received control chow during the mating period. After mating, the females were housed individually and fed their respective control or DBP-dosed chows. However, it is not stated whether these females were maintained on this chow during lactation and prior to pup weaning. This is crucial information to know with regard to the duration of exposure. All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation. However, uncertainties about the duration of exposure, a critical piece of information, is expected to significantly reduce the ability to evaluate this study.
Domain 2: Selection and Performance			

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Study Citation:	Salazar, V., Castillo, C., Ariznavarreta, C., Campón, R., Tresguerres, F., J.A. (2004). Effect of oral intake of dibutyl phthalate on reproductive parameters of Long Evans rats and pre-pubertal development of their offspring. Toxicology 205(1-2):131-137.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Percentage of pregnant rats; Litter size (PND0, 2, and 6); Pup survival; Female:male ratio of pups (PND2, PND6); Body weights of pups (PND2, PND6); Days to eyes' opening (assessed PND6 onwards); Male pup body weight (PND14); Testis relative weight of male pups (PND14); Thymus relative weight of male pups (PND14); Plasma of male pups (PND14); Days to vaginal opening and first estrous in female pups; Days to pre-putial separation in male pups-Nutritional/Metabolic-Dam body weights; Total dam body weight gain (g/3 months)
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (unclear 2-2.5 months)-F0- mating (NR)-F0 - gestation (NR)-F0- lactation (NR)-F1- premating (PND 22 - up to PND 41)
Species:	Rat-Long-Evans - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673308

Domain	Metric		Rating	Comments
	Metric 2:	Allocation	Low	No information on the methods of allocation of animals into test groups or selection of animals for the interim sacrifice of male pups was provided. No other methods to control for modifying factors across groups were noted by the study authors. For this experiment, breeding groups were formed with multiple females being mated with a single male rat (as only 10 male rats total were mated in this experiment). For prenatal developmental toxicity studies (OECD guideline 414) it is recommended that females inseminated by the same male be evenly distributed across the study groups. It is not clear whether this was the case for this study. This could potentially substantially impact the interpretation of the results. The study authors also did not provide the starting body weights of the exposed females in this study. Therefore, it could not be determined whether body weights were evenly spread out across all three study groups. This could potentially substantially impact the interpretation of the results.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	The study included a negative control group, which received undosed feed. A positive control group was not included and is not required. There was very little information provided on animal husbandry conditions and it is not fully known whether these conditions were consistent across study groups; or if they were appropriate to prevent co-exposures to plasticizers. The study authors did not measure food consumption among the dams in the study. It is possible that, rather than being a true effect of the test substance exposure, reduced total body weight gain (over 3 months) among the dams and reduced pup body weights may be attributable to decreased food consumption by the dams (due to reduced palatability of the chow). This factor could potentially confound the exposure-response relationship.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods. Data for dam body weight, the number of pups on PND2, and the plasma collected from male pups on PND14 were not provided. This missing data for dam body weight is expected to impact the interpretation of the results. There is no indication of animal attrition; however, mortality data were not recorded and some data tables do not include (n) sample sizes.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Salazar, V., Castillo, C., Ariznavarreta, C., Campón, R., Tresguerres, F., J.A. (2004). Effect of oral intake of dibutyl phthalate on reproductive parameters of Long Evans rats and pre-pubertal development of their offspring. Toxicology 205(1-2):131-137.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Percentage of pregnant rats; Litter size (PND0, 2, and 6); Pup survival; Female:male ratio of pups (PND2, PND6); Body weights of pups (PND2, PND6); Days to eyes' opening (assessed PND6 onwards); Male pup body weight (PND14); Testis relative weight of male pups (PND14); Thymus relative weight of male pups (PND14); Plasma of male pups (PND14); Days to vaginal opening and first estrous in female pups; Days to pre-putial separation in male pups-Nutritional/Metabolic-Dam body weights; Total dam body weight gain (g/3 months)
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (unclear 2-2.5 months)-F0- mating (NR)-F0 - gestation (NR)-F0- lactation (NR)-F1- premating (PND 22 - up to PND 41)
Species:	Rat-Long-Evans - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673308

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Uninformative	In this study, test animals were exposed to DBP in feed. The purity, storage conditions, and preparation (e.g., frequency, homogeneity) of the test substance were not reported. The study authors did not perform Independent analytical verification of the test substance purity and composition. In addition, the concentrations of DBP in feed and the stability of the DBP feed mixtures were not verified. The route and method of exposure were suited to the test substance and the authors justify exposing the test animals via diet. The authors report the calculated doses/animal/day of 12 and 50 mg/kg-day. However, it cannot be adequately independently verified as test animal weights and food intake were not provided. Although body weights weren't reported, reductions in body weight gains (26%) were observed and it is unclear if this is due to reductions in food consumption. Additionally, the mg/kg/day values reported by the authors vary significantly from calculations of 61.2 and 250.8 mg/kg-day made for this review using default animal body weight and food intake values (U.S. EPA, 1988). The uncertainty in dosing precludes the ability to identify accurate study toxicity values and makes this study uninformative.
	Metric 7:	Exposure timing, frequency, and duration	Low	For this study, the route (diet) and frequency (continuous) were appropriate. Discrepancies and missing information in the study text make the duration of exposure unclear. The study abstract states that females were treated for 2 months and were mated during this time; however, the methods state that females were dosed for 2.5 months prior to mating. Table 1 in the study alludes to a total exposure duration of 3 months. It is also unclear whether females were exposed during lactation, and this could have a significant impact on the offspring results.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Low	This was a non-guideline reproductive/developmental toxicity study. Although females appear to have been dosed for some time prior to mating, the study did not evaluate any systemic endpoints in dams and also did not include other typical reproductive endpoints such as mating index, gestation length, and uterine weight. Birth weights and anogenital distance were also not recorded. Other methodological details were lacking (e.g., % pup survival was reported but it was not indicated whether this was survival at birth or survival at weaning etc.,). The test animals (rats) and sex (females) were appropriate for the evaluation of the endpoints. The number of exposure groups (0, 0.61, and 2.5 g/kg DBP in chow) was small for the type of study. The sample size (15 females/group) was small, especially since ≤81.8% of females became pregnant.

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Study Citation:	Salazar, V., Castillo, C., Ariznavarreta, C., Campón, R., Tresguerres, F., J.A. (2004). Effect of oral intake of dibutyl phthalate on reproductive parameters of Long Evans rats and pre-pubertal development of their offspring. Toxicology 205(1-2):131-137.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Percentage of pregnant rats; Litter size (PND0, 2, and 6); Pup survival; Female:male ratio of pups (PND2, PND6); Body weights of pups (PND2, PND6); Days to eyes' opening (assessed PND6 onwards); Male pup body weight (PND14); Testis relative weight of male pups (PND14); Thymus relative weight of male pups (PND14); Plasma of male pups (PND14); Days to vaginal opening and first estrous in female pups; Days to pre-putial separation in male pups-Nutritional/Metabolic-Dam body weights; Total dam body weight gain (g/3 months)
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (unclear 2-2.5 months)-F0- mating (NR)-F0 - gestation (NR)-F0- lactation (NR)-F1- premating (PND 22 - up to PND 41)
Species:	Rat-Long-Evans - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673308

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Low	Quantitative data (mean ± SEM) were provided for most of the endpoints where results were reported. Pup weight gain was reported without a measure of variance. Sample sizes (n) were not included in any of the data tables or figures. The total number of litters per study group was not provided by the study authors. Instead, the mean litter size (number of animals per litter) was presented. Details of statistical methods were limited and it was not specified whether the litter was used as the experimental unity for any analyses. For offspring findings, the data appears to be presented as means of individual animals, rather than as litter means, and the sample sizes (that the means were derived from) and individual data were not provided, precluding the ability to conduct an independent analysis. This has the potential to overestimate the statistical significance of experimental findings and is expected to substantially impact the interpretation of the results. Male offspring relative testis weights were reported in the absence of absolute weights. Statistical significance was not indicated in all data tables but was mentioned in the study text. The study authors did not provide any results on dam body weight for the plasma collected from male pups on PND14 at different points throughout the study, such as prior to mating and during pregnancy, or for the plasma collected from male pups on PND14. No individual animal data were provided.

Additional Comments: None

Overall Quality Determination Uninformative

Study Citation:	Salazar, V., Castillo, C., Ariznavarreta, C., Campón, R., Tresguerres, F., J.A. (2004). Effect of oral intake of dibutyl phthalate on reproductive parameters of Long Evans rats and pre-pubertal development of their offspring. Toxicology 205(1-2):131-137.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Percentage of pregnant rats; Litter size (PND0, 2, and 6); Pup survival; Female:male ratio of pups (PND2, PND6); Body weights of pups (PND2, PND6); Days to eyes' opening (assessed PND6 onwards); Male pup body weight (PND14); Testis relative weight of male pups (PND14); Thymus relative weight of male pups (PND14); Plasma of male pups (PND14); Days to vaginal opening and first estrous in female pups; Days to pre-putial separation in male pups-Nutritional/Metabolic-Dam body weights; Total dam body weight gain (g/3 months)
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (unclear 2-2.5 months)-F0- mating (NR)-F0 - gestation (NR)-F0- lactation (NR)-F1- premating (PND 22 - up to PND 41)
Species:	Rat-Long-Evans - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673308

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Low	All critical and most important information was reported in this study. The study included identification of the test substance (Dibutyl phthalate), and source (Sigma-Aldrich); test animal characteristics (strain, age, and sex); general animal husbandry conditions (temperature, light/dark cycle, diet and water availability); exposure methods (test substance source, method of administration); experimental design (frequency of exposure, number of animals per study group, animal age during exposure); and endpoint evaluation methods (quantitative and qualitative). The study lacked the source and starting body weights of the test animals. They were also missing some details on animal husbandry conditions and procedures, including humidity and the number of animals per cage at the start of the study. In addition, the purity of the test substance was not reported. The duration of exposure to the test substance is somewhat unclear. In the abstract, the authors state that rats were exposed to DBP-dosed chow for 2 months prior to being mated. In the materials and methods section, the authors state that rats were exposed to DBP-dosed chow for 2.5 months prior to being mated. However, it is not stated how long the mating period was and whether the females received control chow during the mating period. After mating, the females were housed individually and fed their respective control or DBP-dosed chows. However, it is not stated whether these females were maintained on this chow during lactation and prior to pup weaning. This is crucial information to know with regard to the duration of exposure. All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation. However, uncertainties about the duration of exposure, a critical piece of information, is expected to significantly reduce the ability to evaluate this study.
Domain 2: Selection and Performance			

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Study Citation:	Salazar, V., Castillo, C., Ariznavarreta, C., Campón, R., Tresguerres, F., J.A. (2004). Effect of oral intake of dibutyl phthalate on reproductive parameters of Long Evans rats and pre-pubertal development of their offspring. Toxicology 205(1-2):131-137.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Percentage of pregnant rats; Litter size (PND0, 2, and 6); Pup survival; Female:male ratio of pups (PND2, PND6); Body weights of pups (PND2, PND6); Days to eyes' opening (assessed PND6 onwards); Male pup body weight (PND14); Testis relative weight of male pups (PND14); Thymus relative weight of male pups (PND14); Plasma of male pups (PND14); Days to vaginal opening and first estrous in female pups; Days to pre-putial separation in male pups-Nutritional/Metabolic-Dam body weights; Total dam body weight gain (g/3 months)
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (unclear 2-2.5 months)-F0- mating (NR)-F0 - gestation (NR)-F0- lactation (NR)-F1- premating (PND 22 - up to PND 41)
Species:	Rat-Long-Evans - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673308

Domain	Metric		Rating	Comments
	Metric 2:	Allocation	Low	No information on the methods of allocation of animals into test groups or selection of animals for the interim sacrifice of male pups was provided. No other methods to control for modifying factors across groups were noted by the study authors. For this experiment, breeding groups were formed with multiple females being mated with a single male rat (as only 10 male rats total were mated in this experiment). For prenatal developmental toxicity studies (OECD guideline 414) it is recommended that females inseminated by the same male be evenly distributed across the study groups. It is not clear whether this was the case for this study. This could potentially substantially impact the interpretation of the results. The study authors also did not provide the starting body weights of the exposed females in this study. Therefore, it could not be determined whether body weights were evenly spread out across all three study groups. This could potentially substantially impact the interpretation of the results.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	The study included a negative control group, which received undosed feed. A positive control group was not included and is not required. There was very little information provided on animal husbandry conditions and it is not fully known whether these conditions were consistent across study groups; or if they were appropriate to prevent co-exposures to plasticizers. The study authors did not measure food consumption among the dams in the study. It is possible that, rather than being a true effect of the test substance exposure, reduced total body weight gain (over 3 months) among the dams and reduced pup body weights may be attributable to decreased food consumption by the dams (due to reduced palatability of the chow). This factor could potentially confound the exposure-response relationship.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes described in the methods. Data for dam body weight, the number of pups on PND2, and the plasma collected from male pups on PND14 were not provided. This missing data for dam body weight is expected to impact the interpretation of the results. There is no indication of animal attrition; however, mortality data were not recorded and some data tables do not include (n) sample sizes.
Domain 5: Exposure Methods Sensitivity				

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Study Citation:	Salazar, V., Castillo, C., Ariznavarreta, C., Campón, R., Tresguerres, F., J.A. (2004). Effect of oral intake of dibutyl phthalate on reproductive parameters of Long Evans rats and pre-pubertal development of their offspring. Toxicology 205(1-2):131-137.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Percentage of pregnant rats; Litter size (PND0, 2, and 6); Pup survival; Female:male ratio of pups (PND2, PND6); Body weights of pups (PND2, PND6); Days to eyes' opening (assessed PND6 onwards); Male pup body weight (PND14); Testis relative weight of male pups (PND14); Thymus relative weight of male pups (PND14); Plasma of male pups (PND14); Days to vaginal opening and first estrous in female pups; Days to pre-putial separation in male pups-Nutritional/Metabolic-Dam body weights; Total dam body weight gain (g/3 months)
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (unclear 2-2.5 months)-F0- mating (NR)-F0 - gestation (NR)-F0- lactation (NR)-F1- premating (PND 22 - up to PND 41)
Species:	Rat-Long-Evans - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673308

Domain	Metric		Rating	Comments
	Metric 6:	Chemical administration and characterization	Uninformative	In this study, test animals were exposed to DBP in feed. The purity, storage conditions, and preparation (e.g., frequency, homogeneity) of the test substance were not reported. The study authors did not perform Independent analytical verification of the test substance purity and composition. In addition, the concentrations of DBP in feed and the stability of the DBP feed mixtures were not verified. The route and method of exposure were suited to the test substance and the authors justify exposing the test animals via diet. The authors report the calculated doses/animal/day of 12 and 50 mg/kg-day. However, it cannot be adequately independently verified as test animal weights and food intake were not provided. Although body weights weren't reported, reductions in body weight gains (26%) were observed and it is unclear if this is due to reductions in food consumption. Additionally, the mg/kg/day values reported by the authors vary significantly from calculations of 61.2 and 250.8 mg/kg-day made for this review using default animal body weight and food intake values (U.S. EPA, 1988). The uncertainty in dosing precludes the ability to identify accurate study toxicity values and makes this study uninformative.
	Metric 7:	Exposure timing, frequency, and duration	Low	For this study, the route (diet) and frequency (continuous) were appropriate. Discrepancies and missing information in the study text make the duration of exposure unclear. The study abstract states that females were treated for 2 months and were mated during this time; however, the methods state that females were dosed for 2.5 months prior to mating. Table 1 in the study alludes to a total exposure duration of 3 months. It is also unclear whether females were exposed during lactation, and this could have a significant impact on the offspring results.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Low	This was a non-guideline reproductive/developmental toxicity study. Although females appear to have been dosed for some time prior to mating, the study did not evaluate any systemic endpoints in dams and also did not include other typical reproductive endpoints such as mating index, gestation length, and uterine weight. Birth weights and anogenital distance were also not recorded. Other methodological details were lacking (e.g., % pup survival was reported but it was not indicated whether this was survival at birth or survival at weaning etc.,). The test animals (rats) and sex (females) were appropriate for the evaluation of the endpoints. The number of exposure groups (0, 0.61, and 2.5 g/kg DBP in chow) was small for the type of study. The sample size (15 females/group) was small, especially since ≤81.8% of females became pregnant.

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Study Citation:	Salazar, V., Castillo, C., Ariznavarreta, C., Campón, R., Tresguerres, F., J.A. (2004). Effect of oral intake of dibutyl phthalate on reproductive parameters of Long Evans rats and pre-pubertal development of their offspring. Toxicology 205(1-2):131-137.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Percentage of pregnant rats; Litter size (PND0, 2, and 6); Pup survival; Female:male ratio of pups (PND2, PND6); Body weights of pups (PND2, PND6); Days to eyes' opening (assessed PND6 onwards); Male pup body weight (PND14); Testis relative weight of male pups (PND14); Thymus relative weight of male pups (PND14); Plasma of male pups (PND14); Days to vaginal opening and first estrous in female pups; Days to pre-putial separation in male pups-Nutritional/Metabolic-Dam body weights; Total dam body weight gain (g/3 months)
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (unclear 2-2.5 months)-F0- mating (NR)-F0 - gestation (NR)-F0- lactation (NR)-F1- premating (PND 22 - up to PND 41)
Species:	Rat-Long-Evans - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	673308

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Low	Quantitative data (mean ± SEM) were provided for most of the endpoints where results were reported. Pup weight gain was reported without a measure of variance. Sample sizes (n) were not included in any of the data tables or figures. The total number of litters per study group was not provided by the study authors. Instead, the mean litter size (number of animals per litter) was presented. Details of statistical methods were limited and it was not specified whether the litter was used as the experimental unity for any analyses. For offspring findings, the data appears to be presented as means of individual animals, rather than as litter means, and the sample sizes (that the means were derived from) and individual data were not provided, precluding the ability to conduct an independent analysis. This has the potential to overestimate the statistical significance of experimental findings and is expected to substantially impact the interpretation of the results. Male offspring relative testis weights were reported in the absence of absolute weights. Statistical significance was not indicated in all data tables but was mentioned in the study text. The study authors did not provide any results on dam body weight for the plasma collected from male pups on PND14 at different points throughout the study, such as prior to mating and during pregnancy, or for the plasma collected from male pups on PND14. No individual animal data were provided.

Additional Comments: None

Overall Quality Determination Uninformative

Study Citation:	Struve, M. F., Gaido, K. W., Hensley, J. B., Lehmann, K. P., Ross, S. M., Sochaski, M. A., Willson, G. A., Dorman, D. C. (2009). Reproductive toxicity and pharmacokinetics of di-n-butyl phthalate (DBP) following dietary exposure of pregnant rats. Birth Defects Research, Part B: Developmental and Reproductive Toxicology 86(4):345-354.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Fetal testosterone
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12- GD 19)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	684035

Domain	Metric		Rating	Comments
Domain 1: Reporting Quality				
	Metric 1:	Reporting Quality	Medium	The test substance was identified as dibutyl phthalate (DBP). Neither the source nor purity of the test substance were reported. Timed-pregnant Sprague-Dawley rats (obtained from Charles River Laboratories, Raleigh N.C.) were shipped on gestation day 0. Age and initial body weights were not reported. Husbandry conditions were (temperature, humidity, light/dark cycle) were reported. Animals were housed one/cage. Food and water were available ad libitum. The frequency, duration, and route of exposure were reported. Nominal and analytical doses were reported. Endpoint evaluation methods were reported along with quantitative data. All critical information was reported; although important information was not reported, it is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance				
	Metric 2:	Allocation	High	Animals were randomly assigned to treatment groups by body weight using Provantis (Instem LSS, Stone, UK) in order to ensure equal weight distribution.
	Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoint evaluated was not subjective in nature (measured testosterone levels).
Domain 3: Confounding / Variable Control				
	Metric 4:	Confounding / Variable Control	Low	Body weight gain and terminal body weights were not different from control (data for terminal body weights shown). Food consumption was measured daily; however, the study does not report these data or comment if any significant differences were seen. Therefore, potential palatability issues cannot be assessed. The study authors do calculate the actual intake of DBP consumed as mean mg DBP/kg/day for each group with SEMs. A negative control group was included, and response was appropriate. Husbandry conditions were fully reported, and no differences were identified. Exposure to DBP did not affect the litter size, sex ratio, fetal survival or fetal weights. One male was randomly selected from each litter for testicular testosterone measurements.
Domain 4: Selective Reporting and Attrition				
	Metric 5:	Selective Reporting and Attrition	High	All animals were accounted for in the results. There is no indication of selective reporting or attrition.

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Study Citation:	Struve, M. F., Gaido, K. W., Hensley, J. B., Lehmann, K. P., Ross, S. M., Sochaski, M. A., Willson, G. A., Dorman, D. C. (2009). Reproductive toxicity and pharmacokinetics of di-n-butyl phthalate (DBP) following dietary exposure of pregnant rats. Birth Defects Research, Part B: Developmental and Reproductive Toxicology 86(4):345-354.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Fetal testosterone
Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12- GD 19)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	684035

Domain	Metric		Rating	Comments
Domain 5: Exposure Methods Sensitivity				
	Metric 6:	Chemical administration and characterization	Low	The purity and source of the test substance were not reported. "Concentration and homogeneity of all DBP-containing diets were verified using an Agilent 6890 gas chromatograph with 5973 mass spectrometer". These data were not reported. Study authors measured body weight and food consumption and calculated mean daily dose as mg/kg/day. The study did not provide any details on the preparation, stability, or storage of test substance or the diets.
	Metric 7:	Exposure timing, frequency, and duration	High	The timing, duration and frequency of exposure (GD 12- GD 19) were appropriate for the study's aim.
Domain 6: Outcome Measures and Results Display				
	Metric 8:	Endpoint sensitivity and specificity	Medium	The test animal species was appropriate. The number of animals/group/time point was acceptable (n=7-9). Justification was provided for the dose levels chosen; the study wanted to compare responses to those from previously obtained when DBP was administered via gavage. The number and dose spacing of exposure groups was not sufficient to obtain both a NOAEL and LOAEL. Outcome methodologies were described and sensitive to outcome of interest. Timing of outcome assessments were clearly reported.
	Metric 9:	Results presentation	High	Data were reported graphically as means +/-SEM. Statistical analysis was described and is appropriate. The litter was the experimental unit.

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

Overall Quality Determination Medium