

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

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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*.

Table of Contents

HERO ID	Reference	Page
Dibutyl Phthalate		
Short-term (>1-30 days)		
2219796	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.	5
1325511	BIBRA, (1986). Rat liver and lipid effects of representative phthalate esters with EPA acknowlegement letter.	13
697382	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.	19
673292	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.	28
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.	32
790212	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.	38
676594	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.	45
Chronic (>91 days)		
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.	57
Reproductive/Developmental		
1325348	Clewell, R. A., Thomas, A., Willson, G., Creasy, D. M., Andersen, M. E. (2013). A dose response study to assess effects after di- etary administration of diisononyl phthalate (DINP) in gestation and lactation on male rat sexual development. Reproductive Toxicology 35(Elsevier):70-80.	189
2510906	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.	198
9419406	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.	200
675206	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.	202

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Dibutyl Phthalate	Table of Contents	
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
676278	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.	237
674382	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.	242
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 reproduc- tive parameters of Long Evans rats and pre-pubertal development of their offspring. Toxicology 205(1-2):131-137.	347
684035	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.	355

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 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. 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 levelsMortality of dams Oral-Gavage-Duration: Short-term (>1-30 days)-1-F0 - gestation (GD 14- parturition) Rat-Albino - [rat]-Female Dibutyl Phthalate- Parent compound 2219796 					
Domain Domain 1: Domartin - O	uality	Metric	Kating	Comments		
Domain 1: Reporting Q	uality 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 condi- tions 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 ad- equately reported. Endpoints evaluated are clearly reported and quantitative data are presented. All critical information however the study failed to report important informa- tion which impacts the study evaluation.		
Domain 2: Selection and	d Darformanca					
Domain 2. Selection and	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	v / Variable Co	ntrol				
	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 Re	norting and Δt	trition				
	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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Human Health Hazard Animal Toxicology Evaluation

Dibutyl Phthalate

HERO ID: 2219796 Table: 1 of 4

		conti	nued from previ	ious page			
Study Citation:	Ahmad, R.,	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)	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,						
and Reported							
Health Effect(s):	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 of dams						
Duration and	Oral-Gavage	e-Duration: Short-term (>1-30 days)-1-F0 -	- gestation (GD 1	4- parturition)			
Exposure Route:							
Species:	Rat-Albino	- [rat]-Female					
Chemical:	Dibutyl Phtl	halate- Parent compound					
HERO ID:	2219796						
Domain		Metric	Rating	Comments			
Damain 5. Enname M	4h - J - C :4:-						
Domain 5: Exposure Me	Metric 6:	Chemical administration and	Low	The purity of the test substance is not reported and was not found on the supplier's web-			
	Wettie 0.	characterization	Low	site (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 sub- stance 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 Me	easures and Re	sults 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 expo- sure to the human population, including sensitive subgroups that are likely to be with- out 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						
	1.0						
Overall Oualit	tv Deteri	nination	Medium	l			

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					
Health Outcome(s) and Reported Health Effect(s):	development and male reproduction of rat. Environmental Science and Pollution Research 21(4):3156-3165. 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					
Duration and Exposure Route: Species: Chemical: HERO ID:	testis, serum Oral-Gavage Rat-Albino - Dibutyl Phth 2219796	testosterone levelsMortality-Mortality of d e-Duration: Short-term (>1-30 days)-1-F0 - g · [rat]-Female halate- Parent compound	ams gestation (GD 1	4- parturition)		
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality 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 condi- tions 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 ad- equately reported. Endpoints evaluated are clearly reported and quantitative data are presented. All critical information however the study failed to report important informa- tion which impacts the study evaluation.		
Domain 2: Selection an	d Performance					
Domain 2. Selection an	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	a / Variable Co	ntrol				
	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 Re	porting and At	trition				
	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 M	ethods Sensitiv	ity				
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HERO ID: 2219796 Table: 2 of 4

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Health Outcome(s) and Reported Health Effect(s): Duration and	development and male reproduction of rat. Environmental Science and Pollution Research 21(4):3156-3165. 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 levelsMortality-Mortality of dams Oral-Gavage-Duration: Short-term (>1-30 days)-1-F0 - gestation (GD 14- parturition)					
Exposure Route:						
Species: Chemical: HERO ID:	Rat-Albino Dibutyl Pht 2219796	- [rat]-Female halate- Parent compound				
Domain		Metric	Rating	Comments		
	Metric 6: Metric 7:	Chemical administration and characterization Exposure timing, frequency, and duration	Low High	The purity of the test substance is not reported and was not found on the supplier's web- site (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 sub- stance 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). 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 N	lessures and De	eulte Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Rats were treated orally with 20, 100, and 500 times of reference dose, defined as "an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily oral exposure to the human population, including sensitive subgroups that are likely to be without an appreciable risk of deleterious effects during a lifetime". Outcome assessment methodology was sensitive for the outcomes of interest and were consistently assessed across groups.		
	Metric 9:	Results presentation	Low	Statistics was performed comparing the treated groups to untreated control instead the vehicle control group, which would have been more appropriate. It is unclear how many dams were treated/group and how many pups were evaluated/group therefore independent statistics cannot be performed. Also, statistics on offspring were presented as means of individual animals rather than litter means, this has the potential to overestimate the statistical significance of experimental findings.		
Additional Comments:	None					
Overall Qual	ity Deter	mination	Medium	l		

Study Citation:	Ahmad, R., O	Gautam, A. K., Verma, Y., Sedha, S., Kumar,	S. (2014). Effe	ects of in utero di-butyl phthalate and butyl benzyl phthalate exposure on offspring		
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Duration and Exposure Route: Species: Chemical: HERO ID:	testis, serum Oral-Gavage Rat-Albino - Dibutyl Phth 2219796	testosterone levelsMortality-Mortality of d -Duration: Short-term (>1-30 days)-1-F0 - § [rat]-Female alate- Parent compound	ams gestation (GD 1	4- parturition)		
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality 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 condi- tions 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 ad- equately reported. Endpoints evaluated are clearly reported and quantitative data are presented. All critical information however the study failed to report important informa- tion which impacts the study evaluation.		
Domain 2: Selection and	d 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	y / Variable Cor	atrol				
	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.		
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Domain 5: Exposure M	ethods Sensitiv	ity				
		Contin	ued on next pa	nge		

Dibutyl Phthalate

HERO ID: 2219796 Table: 3 of 4

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Study Citation:	Ahmad, R.,	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				
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Exposure Route:	Dat Albino	[rot] Famala				
Chemical.	Dibutyl Pht	- [lat]-remaie halate- Parent compound				
HERO ID:	2219796					
Domain		Metric	Rating	Comments		
	Metric 6:	Chemical administration and characterization	Low	The purity of the test substance is not reported and was not found on the supplier's web- site (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 sub- stance 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 M	leasures and Re	esults 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					
0 110 11		•				
Overall Quali	ity Deter	mination	Medium			

Study Citation:	Ahmad, R.,	Gautam, A. K., Verma, Y., Sedha, S., Kumar,	S. (2014). Effe	ects of in utero di-butyl phthalate and butyl benzyl phthalate exposure on offspring		
Health Outcome(s) and Reported Health Effect(s):	development and male reproduction of rat. Environmental Science and Pollution Research 21(4):3156-3165. 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). 178-hydroxy steroidehydrogenase levels in					
Duration and Exposure Route: Species: Chemical: HERO ID:	testis, serum Oral-Gavage Rat-Albino - Dibutyl Phth 2219796	testosterone levelsMortality-Mortality of d e-Duration: Short-term (>1-30 days)-1-F0 - g [rat]-Female halate- Parent compound	ams gestation (GD 1	4- parturition)		
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality 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 condi- tions 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 ad- equately reported. Endpoints evaluated are clearly reported and quantitative data are presented. All critical information however the study failed to report important informa- tion which impacts the study evaluation.		
Domain 2: Selection an	d Performance					
Domain 2. Selection an	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: Confoundin	a / Variable Co	ntrol				
	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 Re	norting and At	trition				
	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 M	Domain 5: Exposure Methods Sensitivity					
	Continued on next page					

Dibutyl Phthalate

HERO ID: 2219796 Table: 4 of 4

		contin	nued from prev	ious page		
Study Citation:	Ahmad, R.,	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				
Health Outcome(s) and Reported Health Effect(s): Duration and	development and male reproduction of rat. Environmental Science and Pollution Research 21(4):3156-3165. 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 levelsMortality-Mortality of dams Oral-Gavage-Duration: Short-term (>1-30 days)-1-F0 - gestation (GD 14- parturition)					
Exposure Route:	Dat Albina	[rat] Famala				
Chemical.	Dibutyl Pht	- [lat]-remaie halate- Parent compound				
HERO ID:	2219796					
Domain		Metric	Rating	Comments		
	Metric 6:	Chemical administration and characterization	Low	The purity of the test substance is not reported and was not found on the supplier's web- site (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 sub- stance 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 M	leasures and Re	esults 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					
0 110 11		•				
Overall Quali	ity Deter	mination	Medium			

Study Citation:	BIBRA, (1986). Rat liver and lipid effects of representative phthalate esters with EPA acknowlegement letter.					
Health Outcome(s)	Renal/Kidney-Kidney weight and histology-I	Reproductive/Developmental-Testis v	weight and histology-Hepatic/Liver-Liver weight and histology. Serum			
and Reported	triglyceride and total cholesterol. Biochemi	cal analysis of liver (cyanide-insens	itive palmitoyl-CoA oxidation and protein concentration; microsomal			
Health Effect(s):	fraction rate of lauric acid 11-hydroxylase and 12-hydroxylase activity) and ultrastructure of liver assessing peroxisome proliferation (TEM)-Mortality-					
Duration and	Oral-Diet-Duration: Short-term (>1-30 days)	-7-24-21-day(s)				
Exposure Route:						
Species:	Rat-Fischer 344 - [rat]-Both					
Chemical:	Dibutyl Phthalate- Parent compound					
HERO ID:	1325511 Linked HERO ID(s): 1325511, 6749	933, 1325463, 1325547				
Domain	Metric	Rating	Comments			
Domain 1: Reporting (Quality					

		Contin	ued on next pa	nge
Domain 4: Selective Rep	porting and Att	trition		
Domain 3: Confounding	; / Variable Con Metric 4:	ntrol 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.
	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 2: Selection and	d 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 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, hu- midity, and light cycle) were reported. Animals were individually housed. Food and water were available ad libitum. The dose levels, frequency, duration, and route of expo- sure 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 ex- pected to significantly impact the study evaluation.
Domain 1. Reporting Q	uanty			

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Dibutyl Phthalate

HERO ID: 1325511 Table: 1 of 3

	continued from previous page					
Study Citation: Health Outcome(s) and Reported Health Effect(s):	BIBRA, (19 Renal/Kidne triglyceride fraction rate Mortality	BIBRA, (1986). Rat liver and lipid effects of representative phthalate esters with EPA acknowlegement letter. 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- Martelity.				
Duration and	Oral-Diet-D	Oral-Diet-Duration: Short-term (>1-30 days)-7-24-21-day(s)				
Exposure Route: Species:	Pat Fischer 344 - [rat] Both					
Chemical:	Dibutyl Phthalate- Parent compound					
HERO ID:	1325511 Lii	nked HERO ID(s): 1325511, 674933, 1325	463, 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 M	ethods Sensitiv	vity				
	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 inter- est. 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 Me	easures and Re	sults Display				
	Metric 8:	Endpoint sensitivity and specificity	High	The test animal studied was appropriate and justification for age and strain was pro- vided. The outcome methodology addressed the intended outcomes of interest and as- sessed 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 Quali	Overall Quality Determination Medium					

Study Citation: Health Outcome(s) and Reported	BIBRA, (1986). Rat liver and lipid effects of representative phthalate esters with EPA acknowlegement letter. Other (please specify below) (Clinical signs)-Clinical signs of toxicity					
Health Effect(s): Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-24-21-day(s)					
Species: Chemical: HERO ID:	Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound 1325511 Linked HERO ID(s): 1325511, 674933, 1325463, 1325547					
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality 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	d 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 Cor	strol				
	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 Re	porting and Att	rition				
	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 Mo	ethods Sensitivi	ty				
		Con	tinued on next page			

Dibutyl Phthalate

continued from previous page						
Study Citation: Health Outcome(s)	BIBRA, (198 Other (please	BIBRA, (1986). Rat liver and lipid effects of representative phthalate esters with EPA acknowlegement letter. Other (please specify below) (Clinical signs)-Clinical signs of toxicity				
and Reported Health Effect(s):						
Duration and	Oral-Diet-Duration: Short-term (>1-30 days)-7-24-21-day(s)					
Exposure Route:						
Species:	Rat-Fischer 2	344 - [rat]-Both				
Chemical:	Dibutyl Phth	alate- Parent compound				
HERO ID:	1325511 Lin	ked HERO ID(s): 1325511, 674933, 1325463	3, 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 inter- est. 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 Me	easures and Res	sults Display				
	Metric 8:	Endpoint sensitivity and specificity	High	The test animal studied was appropriate and justification for age and strain was pro- vided. The outcome methodology addressed the intended outcomes of interest and assessed consistently across the study groups. The number of animals/group was ap- propriate (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: Health Outcome(s) and Reported	BIBRA, (198 Nutritional/M	BIBRA, (1986). Rat liver and lipid effects of representative phthalate esters with EPA acknowlegement letter. Nutritional/Metabolic-Body weight and food intake					
Health Effect(s): Duration and Exposure Route:	Oral-Diet-D	Oral-Diet-Duration: Short-term (>1-30 days)-7-24-21-day(s)					
Species: Chemical: HERO ID:	Rat-Fischer Dibutyl Phth 1325511 Lin	344 - [rat]-Both nalate- Parent compound nked HERO ID(s): 1325511, 674933, 1325463	, 1325547				
Domain		Metric	Rating	Comments			
Domain 1: Reporting Q	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 an	d 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 sec- ondary histopathology review was conducted.			
Domain 3: Confoundin	a / Variable Cou	ntrol					
	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.			
Domain 4: Selective Re	eporting and Att Metric 5:	trition Selective Reporting and Attrition	High	All animals were accounted for in results. There is no indication that treated animals were excluded from analysis.			
		Con	ntinued on next page .	···			

Dibutyl Phthalate

HERO ID: 1325511 Table: 3 of 3

continued from previous page					
Study Citation: Health Outcome(s) and Reported	BIBRA, (1986). Rat liver and lipid effects of representative phthalate esters with EPA acknowlegement letter. Nutritional/Metabolic-Body weight and food intake				
Health Effect(s): Duration and Exposure Route:	Oral-Diet-Duration: Short-term (>1-30 days)-7-24-21-day(s)				
Species: Chemical: HERO ID:	Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound 1325511 Linked HERO ID(s): 1325511, 674933, 1325463, 1325547				
Domain		Metric	Rating	Comments	
Domain 5: Exposure M	fethods Sensitiv Metric 6: Metric 7:	vity Chemical administration and characterization Exposure timing, frequency, and	Low High	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.	
		duration		est. 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 M	leasures and Re Metric 8:	esults Display Endpoint sensitivity and specificity	High	The test animal studied was appropriate and justification for age and strain was pro- vided. The outcome methodology addressed the intended outcomes of interest and as- sessed 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., I	Kim, K., Kim, H., Lee, B. (2009). Comparat	tive toxicolo	gical evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for	
Health Outcome(s) and Reported Health Effect(s):	risk assessment. Journal of Toxicology and Environmental Health, Part A: Current Issues 72(21-22):1446-1454. Mortality-Mortality Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)				
Duration and Exposure Route:					
Species: Chemical:	Rat-Sprague-Dawley - [rat]-Male Dibutyl Phthalate- Parent compound				
HERO ID:	697382	-			
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	uality 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 expo- sure, 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, venti- lation, 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	d 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	g / Variable Co	ntrol			
	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					
Continued on next page					

		cont	tinued from p	revious page	
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.				
and Reported Health Effect(s):	Mortanty-Mortanty				
Duration and	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)				
Exposure Route:					
Species:	Rat-Sprague	-Dawley - [rat]-Male			
Chemical:	Dibutyl Phth	alate- Parent compound			
HERO ID:	09/382				
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 Me	ethods Sensitiv Metric 6:	ity Chemical administration and	Low	The test substance was identified definitively (name, CAS No., structure). A list of source was provided although it is unclear which substance came from which source	
		characterization		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 infor- mation 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 Me	easures and Res	sults 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 Quali	ty Detern	nination	Low		

Study Citation: Health Outcome(s) and Reported	Kwack, S., Kim, K., Kim, H., Lee, B. (2009). Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats risk assessment. Journal of Toxicology and Environmental Health, Part A: Current Issues 72(21-22):1446-1454. Nutritional/Metabolic-Body weight, food consumption					
Health Effect(s): Duration and Exposure Poute:	Effect(s): fon and Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)					
Species: Chemical: HERO ID:	Rat-Sprague-Dawley - [rat]-Male Dibutyl Phthalate- Parent compound 697382					
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality 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 expo- sure, 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, venti- lation, 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	d 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	g / Variable Co	ntrol				
	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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		cont	inued from p	revious page		
Study Citation:	Kwack, S., K risk assessm	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: Chemical: HERO ID:	Rat-Sprague Dibutyl Phth 697382	-Dawley - [rat]-Male alate- Parent compound				
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 infor- mation 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 Me	asures and Res	sults 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, al- though 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 Qualit	y Detern	nination	Low			

Study Citation:	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				
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	risk assessment. Journal of Toxicology and Environmental Health, Part A: Current Issues 72(21-22):1446-1454. Other (please specify below) (Clinical signs, endocrine)-Clinical signs, adrenal gland weight-Hepatic/Liver-Liver weight, serum chemistry (choles- terol, 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 Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s) Rat-Sprague-Dawley - [rat]-Male Dibutyl Phthalate- Parent compound 697382				
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	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 expo- sure, 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, venti- lation, 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 an	d 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	g / Variable Co	ntrol			
	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 Re	Domain 4: Selective Reporting and Attrition				
Continued on next page					

Human Health Hazard Animal Toxicology Evaluation

... continued from previous page **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)** Other (please specify below) (Clinical signs, endocrine)-Clinical signs, adrenal gland weight-Hepatic/Liver-Liver weight, serum chemistry (cholesand Reported terol, 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, Health Effect(s): 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** Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s) **Exposure Route:** Species: Rat-Sprague-Dawley - [rat]-Male Chemical: Dibutyl Phthalate- Parent compound **HERO ID:** 697382 Domain Metric Comments Rating 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 Chemical administration and Metric 6: 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. characterization 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 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 duration (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,

Results presentation Medium Data were presented quantitatively along with the appropriate statistical analysis. Urinalysis data was not reported.

Metric 9:

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.

Continued on next page ...

		continued from previous page				
Study Citation:	Kwack, S., Kim, K., Kim, H., Lee, B. (2009)	Kwack, S., Kim, K., Kim, H., Lee, B. (2009). Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for				
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 (choles- terol, 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					
Duration and	Oral-Gavage-Duration: Short-term (>1-30 da	ays)-1-4-week(s)				
Exposure Route:						
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						

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Health Effect(s): Duration and Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s) Exposure Route: Species: Rat-Sprague-Dawley - [rat]-Male Chemical: Dibutyl Phthalate- Parent compound HERO ID: 697382 Domain Metric Rating Comments Domain 1: Reporting Quality Medium Metric 1: Reporting Quality Metric 1: Reporting Quality Medium All of the critical information was reported, including test animal species, test substan (name, CAS. No., molecular weight, chemical structure), dose and duration of exposure, sure, orute, and results for at least one endpoint. Most of the important information wa 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 cane was not reported. The test animal was obtained from a commercial source and was reported. The test animal was obtained from a commercial source and was comme	Study Citation: Health Outcome(s) and Reported	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. Reproductive/Developmental-Testis and epididymis weights, sperm count and motility					
Species: Rat-Sprague-Dawley - [rat]-Male Chemical: Dibutyl Phthalate- Parent compound HERO ID: 697382 Domain Metric Rating Comments Domain 1: Reporting Quality Metric 1: Metric 1: Reporting Quality Metric 2: </th <th>Health Effect(s): Duration and Exposure Route:</th> <th>Oral-Gavage</th> <th colspan="5">Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)</th>	Health Effect(s): Duration and Exposure Route:	Oral-Gavage	Oral-Gavage-Duration: Short-term (>1-30 days)-1-4-week(s)				
Domain Metric Rating Comments Domain 1: Reporting Quality Metric 1: Reporting Quality All of the critical information was reported, including test animal species, test substan (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 wa also reported, along with the general husbandry conditions (temperature, humidity, ventiliation, 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 was obtained from a commer	Species: Chemical: HERO ID:	Rat-Sprague-Dawley - [rat]-Male Dibutyl Phthalate- Parent compound 697382					
Domain 1: Reporting Quality Metric 1: Reporting Quality Metric 1: Reporting Quality Metric 1: Reporting Quality Medium All of the critical information was reported, including test animal species, test substan (name, CAS. No., molecular weight, chemical structure), dose and duration of expo- sure, route, and results for at least one endpoint. Most of the important information we also reported. The test animal source, strain, age, sex, and starting body weights were reported, along with the general husbandry conditions (temperature, humidity, venti- lation, 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 we	Domain		Metric	Rating	Comments		
an appropriate animal was obtained from a commercent source and was 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 1: Reporting Qu	uality 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 expo- sure, 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, venti- lation, 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 pu- rity/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 explic- itly described. The assays used to evaluate the outcomes were adequately reported.		
Domain 2: Selection and Performance	Domain 2: Selection and	d 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 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.		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	Domain 3: Confounding	g / Variable Co	ntrol				
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 condition between the control and treatment groups.		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							

Dibutyl Phthalate

		conti	nued from previo	us page	
Study Citation:	Kwack, S., K	Kim, K., Kim, H., Lee, B. (2009). Compara	tive toxicological	evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for	
Health Outcome(s) and Reported Health Effect(s):	risk assessment. Journal of Toxicology and Environmental Health, Part A: Current Issues 72(21-22):1446-1454. Reproductive/Developmental-Testis and epididymis weights, sperm count and motility				
Duration and	Oral-Gavage	-Duration: Short-term (>1-30 days)-1-4-w	/eek(s)		
Exposure Route:					
Species:	Rat-Sprague	-Dawley - [rat]-Male			
Chemical:	697382	alate- Parent compound			
Domain	0)1302	Matric	Pating	Comments	
Domain	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.	
Damain 5. Enname Ma	4h - d- C:4::				
Domain 5: Exposure Me	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 infor- mation 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: Outaama Ma	acuras and Das	ulte Dieplay			
Domain 0. Outcome Me	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 Qualit	y Detern	nination	Medium		

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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)	Nutritional/I	Metabolic-Body weight-Hepatic/Li	iver-Liver weight-Renal/Ki	dney-Kidney weight-Other (please specify below) (Endocrine)-Adrenal weight-	
and Reported	Reproductiv	e/Developmental-The following 5	tissues were weighed: test	es, ventral prostates, combined seminal vesicles and coagulating glands, levator	
Health Effect(s):	ani/bulbocav	vernosus (LABC), and Cowper's gl	and.Serum testosterone and	d luteinizing hormone	
Duration and	Oral-Gavage	e-Duration: Short-term (>1-30 day	vs)-7-10-day(s)	C C C C C C C C C C C C C C C C C C C	
Exposure Route:	e	`` `	, , , ,		
Species:	Rat-Sprague	-Dawley - [rat]-Male			
Chemical:	Dibutyl Phth	alate- Parent compound			
HERO ID:	673292	*			
Domain		Metric	Rating	Comments	
Domain 1: Reporting Qu	uality				
	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 \geq 98% for DEHP, DBP and BBP; purity not	

	Metric 5.	Selective Reporting and Autoloi	Ingn	signs were seen)
Domain 4: Selective R	Reporting and At	trition Selective Reporting and Attrition	High	Study reported no animals died and there is no indication of health effects (no clinical
Domain 3: Confoundi	ng / Variable Co Metric 4:	ntrol Confounding / Variable Control	Medium	Husbandry conditions were reported and similar between groups. Negative and posi- tive 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 sub- stantially 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 re- sults.
	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 2: Selection a	nd 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.
				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.

PUBLIC RELEASE DRAFT May 2025

Human Health Hazard Animal Toxicology Evaluation

	continued from previous page				
Study Citation:	Lee, B. M., Issues 70(1)	Lee, B. M., Koo, H. J. (2007). Hershberger assay for antiandrogenic effects of phthalates. Journal of Toxicology and Environmental Health, Part A: Current			
Health Outcome(s)	Nutritional/	Metabolic-Body weight-Hepatic/Liver-Live	er weight-Renal/k	Kidney-Kidney weight-Other (please specify below) (Endocrine)-Adrenal weight-	
and Reported	Reproductiv	/e/Developmental-The following 5 tissues v	were weighed: tes	stes, ventral prostates, combined seminal vesicles and coagulating glands, levator	
Health Effect(s):	ani/bulboca	vernosus (LABC), and Cowper's gland.Seru	um testosterone a	nd luteinizing hormone	
Duration and	Oral-Gavag	e-Duration: Short-term (>1-30 days)-7-10-	day(s)		
Exposure Route:	-				
Species:	Rat-Sprague	e-Dawley - [rat]-Male			
Chemical:	Dibutyl Pht	halate- Parent compound			
HERO ID:	673292				
Domain		Metric	Rating	Comments	
	Metric 6:	Chemical administration and characterization	Low	Purity was reported to be \geq 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 Me	easures and Re	esults 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 Qualit	ty Deteri	mination	Medium		

Study Citation:	Lee, B. M., I	Koo, H. J. (2007). Hershberger assay for antia	ndrogenic effec	cts of phthalates. Journal of Toxicology and Environmental Health, Part A: Current	
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical signs)-Clinical signs				
Duration and	Oral-Gavage	e-Duration: Short-term (>1-30 days)-7-10-da	uy(s)		
Species: Chemical: HERO ID:	Rat-Sprague Dibutyl Phth 673292	-Dawley - [rat]-Male aalate- Parent compound			
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	uality 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 \geq 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 an	d 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	g / Variable Co	ntrol			
	Metric 4:	Confounding / Variable Control	Medium	Husbandry conditions were reported and similar between groups. Negative and posi- tive 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 sub- stantially 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 re- sults.	
Domain 4: Selective Re	porting and At Metric 5:	trition 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 M	ethods Sensitiv Metric 6:	ity Chemical administration and characterization	Low	Purity was reported to be \geq 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.	
		Contin	ued on next pa	ge	

	continued from previous page					
Study Citation:	Lee, B. M.,	Koo, H. J. (2007). Hershberger assay for an	tiandrogenic effect	s of phthalates. Journal of Toxicology and Environmental Health, Part A: Current		
	Issues 70(15	5-16):1365-1370.				
Health Outcome(s)	Other (pleas	e specify below) (Clinical signs)-Clinical s	signs			
and Reported						
Health Effect(s):						
Duration and	Oral-Gavage	e-Duration: Short-term (>1-30 days)-7-10-	-day(s)			
Exposure Route:						
Species:	Rat-Sprague	e-Dawley - [rat]-Male				
Chemical:	Dibutyl Phtl	Dibutyl Phthalate- Parent compound				
HERO ID:	673292					
Domain		Metric	Rating	Comments		
	Metric 7:	Exposure timing, frequency, and	High	Exposure duration, timing and frequency was consistent with OECD guidelines 441 for		
		duration		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 Quali	ty Deteri	nination	Medium			

Study Citation:	Marsman, D	. S. (1995). NTP technical report on the t	oxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and		
Health Outcome(s) and Reported Health Effect(s):	B6C3F1 mic Mortality-Su	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).				
Duration and	Oral-Diet-Di	uration: Short-term (>1-30 days)-7-14-day	(s)			
Exposure Route: Species:	Rat-Sprague	-Dawley - [rat]-Both				
Chemical: HERO ID:	Dibutyl Phth 680063	alate- Parent compound				
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); 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 (quantita- tive and qualitative). Missing important information included the parity of the animals and the humidity conditions.		
Domain 2: Selection and	d Performance	Allocation	Madium	The study outhous state that animals were readenized and then assigned to does around		
	Metric 2:	Anocation	Medium	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	g / Variable Co	ntrol				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received undosed feed. Control re- sponses 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 ma- terials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.		
Domain 4: Selective Re	porting and Att	rition				
	Metric 5:	Selective Reporting and Attrition	High	Quantitative or qualitative results were provided for all outcomes described in the methods.		
Domain 5: Exposure Me	ethods Sensitiv	ity				
Continued on next page						

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Dibutyl Phthalate

		con	tinued from p	previous page		
Study Citation:	Marsman, I B6C3F1 mi	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 B6C3E1 mice. Toxicity Report Series, vol. 30.30:1-G5				
Health Outcome(s) and Reported Health Effect(s):	Mortality-S	urvival (Studies 5, 6, 7, 8, 9, 10, 11, and 1	2).			
Duration and Exposure Route:	Oral-Diet-D	Ouration: Short-term (>1-30 days)-7-14-da	ay(s)			
Species: Chemical: HERO ID:	Rat-Sprague-Dawley - [rat]-Both Dibutyl Phthalate- Parent compound 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 M	looguras and De	aculta Display				
Domain 0. Outcome M	Matria 8.	Endraint consistivity and an aif aite	Madian			
	Metric 8:	Enapoint 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.		

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

Results presentation

Metric 9:

Overall Quality Determination

High

High

Study authors qualitatively stated that "during 2 weeks of treatment, no animals died."

Study Citation:	Marsman, D	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				
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 weig gain (Studies 5, 6, 7, and 12)Other (please specify below) (Clinical observations)-Clinical Observations					
Duration and	Oral-Diet-D	uration: Short-term (>1-30 days)-7-14-day(s	5)			
Exposure Route: Species: Chemical: HERO ID:	Rat-Sprague Dibutyl Phth 680063	-Dawley - [rat]-Both alate- Parent compound				
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); 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 (quantita- tive and qualitative). Missing important information included the parity of the animals and the humidity conditions.		
Domain 2: Selection and	d 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	y / Variable Co	ntrol				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received undosed feed. Control re- sponses 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 ma- terials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.		
Domain 4: Selective Re	porting and At	trition				
	Metric 5:	Selective Reporting and Attrition	High	Quantitative or qualitative results were provided for all outcomes described in the methods.		
Domain 5: Exposure Mo	ethods Sensitiv	ity				
Continued on next page						

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Human Health Hazard Animal Toxicology Evaluation

Dibutyl Phthalate

		continued from previous page			
Study Citation:	Marsman, D. S. (1995). NTP technical report	t on the toxicity studies of dibutyl phtha	alate (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)	Nutritional/Metabolic-Terminal body weights	(Studies 1, 2, 3, and 4).Body weight, fee	ed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight		
and Reported	gain (Studies 5, 6, 7, and 12)Other (please sp	becify below) (Clinical observations)-Clin	nical Observations		
Health Effect(s):					
Duration and	Oral-Diet-Duration: Short-term (>1-30 days)-7-14-day(s)				
Exposure Route:					
Species:	Rat-Sprague-Dawley - [rat]-Both				
Chemical:	Dibutyl Phthalate- Parent compound				
HERO ID:	680063				
Domain	Metric	Rating	Comments		

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.
<u>_</u>	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 Meas	sures and Res	sults Display		
1	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 an- imals 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 clini- cal 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 evalu- ation of the endpoints. The sample size (8 rats/sex/group) was appropriate for the study type. A wide range of doses were tested.
1	Metric 9:	Results presentation	Medium	Quantitative data (mean \pm SEM) was provided for body weight, body weight gain, and feed consumption. Statistical significance was provided for body weight and feed con- sumption. 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 ani- mal data were provided.

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

Overall Quality Determination	Medium
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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 D6C02E1 mine. Tensisin Parent Series and 20 20:1 C5			
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	Oral-Diet-Duration: Short-term (>1-30 days)-7-14-day(s)			
Exposure Route: Species: Chemical: HERO ID:	Rat-Sprague-Dawley - [rat]-Both Dibutyl Phthalate- Parent compound 680063			
Domain		Metric	Rating	Comments
Domain 1: Reporting Q	uality Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); 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 (quantita- tive 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 re- sponses 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 ma- terials 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				
Continued on next page				
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Human Health Hazard Animal Toxicology Evaluation

Dibutyl Phthalate

		. continued from previous page				
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)	Nutritional/Metabolic-Terminal body weights (S	tudies 1, 2, 3, and 4). Body weight,	feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight			
and Reported	gain (Studies 5, 6, 7, and 12)Other (please specify below) (Clinical observations)-Clinical Observations					
Health Effect(s):						
Duration and	Oral-Diet-Duration: Short-term (>1-30 days)-7-14-day(s)					
Exposure Route:						
Species:	Rat-Sprague-Dawley - [rat]-Both					
Chemical:	Dibutyl Phthalate- Parent compound					
HERO ID:	680063					
Domain	Metric	Rating	Comments			

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 an- imals 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 clini- cal 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 evalu- ation 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 \pm SEM) was provided for body weight, body weight gain, and feed consumption. Statistical significance was provided for body weight and feed con- sumption. 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 ani- mal data were provided.

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

Overall Quality Determination Medium
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Study Citation:	Srivastava, S	S., Singh, G. B., Srivastava, S. P., Seth, P. K.	(1990). Testicular toxi 28(1):67-70	icity of di-n-butyl phthalate in adult rats: Effect on marker enzymes of		
Health Outcome(s) and Reported Health Effect(s):	spermatogenesis. Indian Journal of Experimental Biology 28(1):67-70. 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	Oral-Gavage	-Duration: Short-term (>1-30 days)-7-15-day	v(s)			
Exposure Route	Ofur Guvuge	Duration. Short term (> 1 50 days) / 15 day	(5)			
Snecies.	Rat-Wistar -	[rat]-Male				
Chemical.	Dibutyl Phth	alate- Parent compound				
HERO ID:	790212	and I went compound				
Domain	.,,0212	Metric	Rating	Comments		
Domain 1: Reporting C	Duality		Tunng			
	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 an	d Performance					
Domain 2. Selection an	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: Confoundin	a / Variable Cor	atrol				
Domain 5. Comoulium	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 Re	eporting and Att	trition				
		Con	ntinued on next page .			

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Dibutyl Phthalate

HERO ID: 790212 Table: 1 of 3

		c	ontinued from previous	page			
Citation:	Srivastava, S	S., Singh, G. B., Srivastava, S. P., Seth, P. H	K. (1990). Testicular tox $x = 28(1) \cdot 67 - 70$	icity of di-n-butyl phthalate in adult rats: Effect on marker enzymes of			
Outcome(s) ported Effect(s):	Reproductive acid phospha	Reproductive/Developmental-Testes and epididymis weights, Sperm count, testes histopathology, Testes enzymes (SDH, LDH, G6PDH, gamma -GGT, acid phosphatase, beta-glucuronidase), testes protein content.					
on and tre Route:	Oral-Gavage	e-Duration: Short-term (>1-30 days)-7-15-da	ay(s)				
s: cal:	Rat-Wistar - Dibutyl Phth 790212	[rat]-Male aalate- Parent compound					
Domain	190212	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.			
n 5: Exposure Me	lethods Sensitiv	ity					
	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 nom- inal. 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.			
1 6: Outcome Me	easures and Res	sults 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).			
		C	ontinued on next page .	The methods did not specify the results text that no changes in 6 species/strain was not provided tion. The study used 6 animals analysis. Formalin was used to updated OECD TG 407 (2008)			

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Human Health Hazard Animal Toxicology Evaluation

HERO ID: 790212 Table: 1 of 3

		continued fr	rom previous p	age	
Study Citation:	Srivastava, S., Singh, G. B., Sr spermatogenesis. Indian Journa	vastava, S. P., Seth, P. K. (1990). ' of Experimental Biology 28(1):67-	Testicular toxic 70.	ity of di-n-butyl phthalate in adult rats: Effect on marker enzymes of	
Health Outcome(s)	Reproductive/Developmental-T	estes and epididymis weights, Speri	n count, testes	histopathology, Testes enzymes (SDH, LDH, G6PDH, gamma -GGT,	
and Reported	acid phosphatase, beta-glucuror	idase), testes protein content.	,		
Health Effect(s):		·····), ····· F······			
Duration and	Oral-Gavage-Duration: Short-te	rm (>1-30 days)-7-15-day(s)			
Exposure Route:	$\int dx dy dy dx dy dy dy dy $				
Species:	Rat-Wistar - [rat]-Male				
Chemical:	Dibutyl Phthalate- Parent compound				
HERO ID:	790212				
Domain	Metric	H	Rating	Comments	
	Metric 9: Results presenta	ion	Low	Liver enzymes were reported as means \pm 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 pre- sumably, 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

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Study Citation: Health Outcome(s)	Srivastava, S spermatoger Nutritional/I	S., Singh, G. B., Srivastava, S. P., Seth, P. K. nesis. Indian Journal of Experimental Biology Metabolic-Body weights-Mortality-Mortality	(1990). Testicular toxi 28(1):67-70.	icity of di-n-butyl phthalate in adult rats: Effect on marker enzymes of
and Reported Health Effect(s): Duration and Exposure Route:	Oral-Gavage	e-Duration: Short-term (>1-30 days)-7-15-day	7(s)	
Species:	Rat-Wistar -	[rat]-Male		
Chemical:	Dibutyl Phtł	nalate- Parent compound		
HERO ID:	790212			
Domain		Metric	Rating	Comments
Domain 1: Reporting Q	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: Salastion on	d Darformonaa			
Domain 2. Selection an	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: Confoundin	g / Variable Co Metric 4:	ntrol 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 Re	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 M	lethods Sensitiv	ity		
		Co	ntinued on next page .	••

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Human Health Hazard Animal Toxicology Evaluation

HERO ID: 790212 Table: 2 of 3

		CO	ntinued from previou	s page			
Study Citation:	Srivastava,	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/	Nutritional/Metabolic-Body weights-Mortality-Mortality					
Duration and	Oral-Gavag	e-Duration: Short-term (>1-30 days)-7-15-day	y(s)				
Exposure Koute:	Dot Wistor	[rat] Mala					
Chemical:	Dibutyl Pht	halate- Parent compound					
Domain	790212	Metric	Rating	Comments			
	Metric 6: Metric 7:	Chemical administration and characterization Exposure timing, frequency, and	Low Medium	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. This was a non-guideline study. Animals were exposed daily for 15 days. The study authors did not instify the exposure duration, but the duration seemed to be appropriate.			
		duration		for the purposes of the study.			
Domain 6: Outcome M	easures and Re	esults 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

Dibutyl Phthalate

Uninformative

PUBLIC RELEASE DRAFT May 2025 Human Health Hazard Animal Toxicology Evaluation

Study Citation: Health Outcome(s)	udy 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.ealth Outcome(s)Nutritional/Metabolic-Body weights-Mortality-Mortality				
and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	Oral-Gavage Rat-Wistar - Dibutyl Phth	-Duration: Short-term (>1-30 days)-7-15-day [rat]-Male alate- Parent compound	(s)		
HERO ID:	790212				
Domain	molity	Metric	Rating	Comments	
	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 an	d Performance				
Domain 2. Selection an	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	g / variable Co Metric 4:	ntroi 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. Salasting D-	monting and At	tuition			
Domain 4: Selective Re	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 M	ethods Sensitiv	ity			
		Con	ntinued on next page .	·· ·	

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		CO	ntinued from previous	s page
Study Citation:	Srivastava,	S., Singh, G. B., Srivastava, S. P., Seth, P. K	. (1990). Testicular to: 28(1):67-70	kicity of di-n-butyl phthalate in adult rats: Effect on marker enzymes of
Health Outcome(s) and Reported Health Effect(s):	Nutritional/	Metabolic-Body weights-Mortality-Mortality	26(1).07-70.	
Duration and	Oral-Gavage	e-Duration: Short-term (>1-30 days)-7-15-day	y(s)	
Exposure Route:				
Species:	Rat-Wistar -	- [rat]-Male		
Chemical:	Dibutyl Phtl	halate- Parent compound		
HERO ID:	790212			
Domain		Metric	Rating	Comments
	Metric 6: Metric 7:	Chemical administration and characterization Exposure timing, frequency, and	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 nom- inal. 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. This was a non-guideline study. Animals were exposed daily for 15 days. The study
		duration		authors did not justify the exposure duration, but the duration seemed to be appropriate for the purposes of the study.
Domain 6: Outcome M	easures and Re	esults 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

Dibutyl Phthalate

Uninformative

Study Citation:	Xiao-Feng, Z	Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z	. (2009). Di	i (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated		
Health Outcome(s) and Reported Health Effect(s):	pathway in rats. International Journal of Toxicology 28(5):448-456. Reproductive/Developmental-Apical: Serum testosterone, relative organ weights (testes epididymis), testes histopathology; Mechanistic: protein and g expression in the testes-Other (please specify below) (Endocrine)-Serum glucocorticoids, relative adrenal weight, adrenal histopathology					
Duration and	Oral-Gavage	e-Duration: Short-term (>1-30 days)-7-30-d	lav(s)			
Exposure Route:	8-		<u>)</u> (=)			
Species:	Rat-Sprague	-Dawley - [rat]-Male				
Chemical:	Dibutyl Phth	nalate- Parent compound				
HERO ID:	676594					
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality					
	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	d 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	g / Variable Co	ntrol				
	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 Re	porting and At	trition				
	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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Dibutyl Phthalate

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)** Reproductive/Developmental-Apical: Serum testosterone, relative organ weights (testes epididymis), testes histopathology; Mechanistic: protein and gene and Reported expression in the testes-Other (please specify below) (Endocrine)-Serum glucocorticoids, relative adrenal weight, adrenal histopathology Health Effect(s): Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s) **Duration and Exposure Route:** 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 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 characterization 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 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 duration 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

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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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Dibutyl Phthalate

		continued from p	previous page			
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	 Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-media pathway in rats. International Journal of Toxicology 28(5):448-456. Reproductive/Developmental-Apical: Serum testosterone, relative organ weights (testes epididymis), testes histopathology; Mechanistic: protein and ge expression in the testes-Other (please specify below) (Endocrine)-Serum glucocorticoids, relative adrenal weight, adrenal histopathology 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 \pm 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 \pm 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	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated					
Health Outcome(s) and Reported Health Effect(s):	pathway in ra Reproductive expression in	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	Oral-Gavage	-Duration: Short-term (>1-30 days)-7-30-c	lay(s)				
Exposure Route: Species: Chemical: HERO ID:	Rat-Sprague- Dibutyl Phth 676594	-Dawley - [rat]-Male alate- Parent compound					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Q	uality 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	d 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	y / Variable Cor	ntrol					
	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 Re	porting and Att	rition					
	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 M	ethods Sensitivi	ity					
		Contin	nued on nex	t page			

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		cont	inued from p	revious page		
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	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. 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 Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)					
Species: Chemical: HERO ID:	Rat-Sprague Dibutyl Phtl 676594	e-Dawley - [rat]-Male nalate- Parent compound				
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 Me	easures and Re	sults 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.		
		Con	tinued on nex	at page		

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Dibutyl Phthalate

Study Citation:	Xiao-Feng, Z	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated				
Health Outcome(s) and Reported Health Effect(s):	Reproductive expression in	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-	Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)				
Species: Chemical: HERO ID:	Rat-Sprague- Dibutyl Phtha 676594	Dawley - [rat]-Male alate- Parent compound				
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 \pm 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 \pm 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.		

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 nothway in rate. International Journal of Taxicology 28(5):448-456							
Health Outcome(s) and Reported Health Effect(s):	Mortality-M	Mortality-Nutritional/Metabolic-Body weights						
Duration and	Oral-Gavage	e-Duration: Short-term (>1-30 days)-7-30-da	ay(s)					
Exposure Route: Species: Chemical: HERO ID:	Rat-Sprague Dibutyl Phth 676594	-Dawley - [rat]-Male nalate- Parent compound						
Domain		Metric	Rating	Comments				
Domain 1: Reporting Q	uality 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 an	d 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	g / Variable Co	ntrol						
	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 Re	porting and At	trition						
	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 M	ethods Sensitiv	ity						
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Dibutyl Phthalate

		contin	ued from previo	bus page			
Study Citation:	Xiao-Feng, Z	Xiao-Feng, Z., Nai-Qiang, Q., Jing, Z., Zi, L., Yang, Z. (2009). Di (n-butyl) phthalate inhibits testosterone synthesis through a glucocorticoid-mediated					
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mo	Mortality-Mortality-Nutritional/Metabolic-Body weights					
Duration and	Oral-Gavage	-Duration: Short-term (>1-30 days)-7-30-da	ay(s)				
Exposure Route:	Dat Spragua	Davilar [rot] Mala					
Chemical:	Dibutyl Phth	alate- 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 Me	asures and Res	sults Display					
	Metric 8:	Endpoint sensitivity and specificity	Medium	The dose spacing was not explicitly justified by the study authors. It was noted that be- cause "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							
Health Outcome(s) and Reported Health Effect(s):	Mortality-M	Mortality-Mortality-Nutritional/Metabolic-Body weights Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)						
Duration and Exposure Poute:	Oral-Gavage							
Species: Chemical: HERO ID:	Rat-Sprague Dibutyl Phth 676594	e-Dawley - [rat]-Male nalate- Parent compound						
Domain		Metric	Rating	Comments				
Domain 1: Reporting Q	uality 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 an	d 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	σ / Variable Co	ntrol						
	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 Re	porting and At	trition						
	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 M	ethods Sensitiv	/ity						
<u> </u>		Contin	ued on next pa	nge				

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Dibutyl Phthalate

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Study Citation: Health Outcome(s) and Reported Health Effect(s):	Xiao-Feng, pathway in Mortality-M	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. Mortality-Mortality-Nutritional/Metabolic-Body weights						
Duration and Exposure Route:	Oral-Gavag	Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)						
Species: Chemical: HERO ID:	Rat-Sprague-Dawley - [rat]-Male Dibutyl Phthalate- Parent compound 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 N	leasures and Re	esults Display						
	Metric 8:	Endpoint sensitivity and specificity	Medium	The dose spacing was not explicitly justified by the study authors. It was noted that be- cause "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.				

Additional Comments: None

Overall Quality Determination

Metric 9:

Results presentation

Medium

Medium

A qualitative description was provided for outcomes with no effects.

Study Citation:	Xiao-Feng, Z	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 Taxicology 28(5):448.456					
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	Other (please Oral-Gavage	pathway in rats. International Journal of Toxicology 28(5):448-456. Other (please specify below) (Clinical signs)-Clinical signs (a decrease in normal activity) Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)					
Species: Chemical: HERO ID:	Rat-Sprague Dibutyl Phth 676594	-Dawley - [rat]-Male alate- Parent compound					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Q	uality 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 an	d Performance	A11 - 21					
	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	a / Variable Cor	atrol					
	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 Re	porting and Att Metric 5:	rition 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 M	ethods Sensitiv	ity Conti	nued on nex	ct page			

PUBLIC RELEASE DRAFT

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Dibutyl Phthalate

HERO ID: 676594 Table: 5 of 5

		con	tinued from p	previous page				
Study Citation:	Xiao-Feng, pathway in	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): Duration and	Other (pleas Oral-Gavag	Other (please specify below) (Clinical signs)-Clinical signs (a decrease in normal activity) Oral-Gavage-Duration: Short-term (>1-30 days)-7-30-day(s)						
Exposure Route: Species:	Rat-Sprague	-Dawley - [rat]-Male						
Chemical: HERO ID:	Dibutyl Phtl 676594	halate- Parent compound						
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 Me	easures and Re	sults Display						
	Metric 8:	Endpoint sensitivity and specificity	Low	The dose spacing was not explicitly justified by the study authors. It was noted that be- cause "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; how- ever, 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 Qualit	ty Deteri	nination	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					
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 (Hymus, lymph nodes, and spleen) (Studies 8 and 9)Cuter (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)-Cuelar/Sensory-Histopathology of sys (Studies 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of king tudies 8 and 9)Castrointestinal-Histopathology of stain (Studies 8 and 9)Cher (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of sking study 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). <					
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	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 an	nd 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				
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of aboutyl phinalate (CAS No. 84-74-2) administered in feed to F344/N fats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/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 luors, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Gastrointestinal-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). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s				
Chemical:	Dibutyl Pht	halate- 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 R	enorting and Δ	ttrition			
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 M	lethods Sensitiv	vity			
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		con	tinued from p	revious page
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 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. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/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 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)Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kin (Studies 8 and 9)Gastrointestinal-Histopathology of studies 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stomes, s, 9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stomes, 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stomes, 8, 9, 10, and 11)Thyroid-Histopathology of thyroic (Study 8 and Study 9)Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroic (Study 8 and S			
Domain		Metric	Rating	Comments
Domain	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 M	feasures and Re Metric 8: Metric 9:	esults Display Endpoint sensitivity and specificity Results presentation	High Medium	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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. Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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 pro- vided.

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Study Citation:	Marsman, D. S. (1995). NTP technica B6C3F1 mice. Toxicity Report Series.	l report on the toxicity studies of dibutyl pl vol. 30 30:1-G5.	hthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Reproductive/Developmental-No. fetus of live pups/litter, number of pups/sex/l gross necropsy, offspring body weights, CoA oxidase activity of dams (Studies 1 genase, bile acids, and glucose), Histopa ify below) (Clinical observations)-Clinic spleen) (Studies 8 and 9)Cardiovascula of pancreas, pituitary, adrenal gland, an Neurological/Behavioral-Histopatholog nasal cavity, pharynx, and trachea (Studi atinine), Histopathology of kidney and Tissue-Histopathology of skin (Studies gland (Studies 8 and 9)Other (please sp Oral-Diet-Duration: Chronic (>90 days Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound 680063	ses/breeding group, Litter weight; Gestation itter, Offspring clinical observations, mortal number of implantation sites, mating index, f 1, 2, 3, and 4).Serum chemistry (ALP, ALT, t athology of liver (Studies 8 and 9). Absolute cal Observations-Immune/Hematological-He ur-Heart weight, histopathology of heart (Stud- nd parathyroids (Studies 8 and 9)-Musculos y of brain and spinal cord/sciatic nerve (Stu- ies 8 and 9)-Ocular/Sensory-Histopathology urinary bladder (Studies 8 and 9).Absolute a 8 and 9)Gastrointestinal-Histopathology specify below) (Clinical chemistry)-Creatine ecify below) (Gross necropsy)-Gross necrop s)-7-13-week(s)	a length, number of pups/litter, number of live pups/litter, percentage ity, feed consumption, histologic examinations on >30 organs/tissues, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- otal protein, albumin, total cholesterol, triglycerides, sorbitol dehydro- and relative liver weight (Studies 8, 9, 10, and 11)Other (please spec- ematology, thymus weights, histopathology (thymus, lymph nodes, and dies 8 and 9)Other (please specify below) (Endocrine)-Histopathology skeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)- idies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophagus, of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, cre- and relative kidney weights (Studies 8,9, 10, and 11)Skin/Connective of stomach, gall bladder, large intestine, small intestine, and salivary kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid osy (Study 8 and Study9).
Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		
Overall Qualit	y Determination	High	

Study Citation: Health Outcome(s) and Reported Health Effect(s):	 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. 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, fistopathology (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)Renal/Kidney-Clinical chemistry (BUN, creatinic), 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 Study 9). 					
Duration and	Oral-Diet-Du	ration: Chronic (>90 days)-7-13-week(s)				
Exposure Route:	Dat Eissbar 2	244 [r-4] D-4h				
Species:	Rat-Fischer 3	144 - [rat]-Both				
HERO ID:	680063	alate- I arent compound				
Domain		Metric	Rating	Comments		
Domain 1: Reporting O	uality	Weute	Rating	connients		
	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	l 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	g / Variable Con	trol				
Continued on next page						

Human Health Hazard Animal Toxicology Evaluation

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Study Citation: Health Outcome(s)	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. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage				
and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 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 dehydro genase, 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 of (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 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, cre atinine), Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivar gland (Studies 8 and 9)Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Stin/Connective (Study 8 and Study 9)Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid (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				
Domain		Metric	Rating	Comments	
				Commento	
	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: Solootiva P	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 Re	Metric 4: eporting and At Metric 5:	Confounding / Variable Control trition Selective Reporting and Attrition	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 Re Domain 5: Exposure M	Metric 4: eporting and At Metric 5: Iethods Sensitiv	Confounding / Variable Control trition Selective Reporting and Attrition ity	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. There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 authors was provided, but this is not expected to have a significant effect on the study authors was provided.	

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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 a B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percent of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tisst gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitt CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehyc genase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)Other (please spify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology of lungs, esophag if y below) (Studies 8 and 9)Cardiovascular-Heart weight (Studies 8 and 9)Ausculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Cular/Respiratory-Histopathology of lungs, esophag nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, 4 atinine), Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small 11)Skin/Connec Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small 11)Skin/Connec Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small 11)Skin/Connec Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small 11)Skin/Conne			
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 M	leasures and Re Metric 8: Metric 9:	esults Display Endpoint sensitivity and specificity Results presentation	High Medium	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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. Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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 pro- vided.

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Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S. (1995). NTP technica B6C3F1 mice. Toxicity Report Series.	l report on the toxicity studies of dibutyl pl vol. 30 30:1-G5.	hthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Reproductive/Developmental-No. fetus of live pups/litter, number of pups/sex/l gross necropsy, offspring body weights, CoA oxidase activity of dams (Studies 1 genase, bile acids, and glucose), Histopa ify below) (Clinical observations)-Clinic spleen) (Studies 8 and 9)Cardiovascula of pancreas, pituitary, adrenal gland, an Neurological/Behavioral-Histopatholog nasal cavity, pharynx, and trachea (Studi atinine), Histopathology of kidney and Tissue-Histopathology of skin (Studies gland (Studies 8 and 9)Other (please sp Oral-Diet-Duration: Chronic (>90 days Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound 680063	ses/breeding group, Litter weight; Gestation itter, Offspring clinical observations, mortal number of implantation sites, mating index, f 1, 2, 3, and 4).Serum chemistry (ALP, ALT, t athology of liver (Studies 8 and 9). Absolute cal Observations-Immune/Hematological-He ur-Heart weight, histopathology of heart (Stud- nd parathyroids (Studies 8 and 9)-Musculos y of brain and spinal cord/sciatic nerve (Stu- ies 8 and 9)-Ocular/Sensory-Histopathology urinary bladder (Studies 8 and 9).Absolute a 8 and 9)Gastrointestinal-Histopathology specify below) (Clinical chemistry)-Creatine ecify below) (Gross necropsy)-Gross necrop s)-7-13-week(s)	a length, number of pups/litter, number of live pups/litter, percentage ity, feed consumption, histologic examinations on >30 organs/tissues, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- otal protein, albumin, total cholesterol, triglycerides, sorbitol dehydro- and relative liver weight (Studies 8, 9, 10, and 11)Other (please spec- ematology, thymus weights, histopathology (thymus, lymph nodes, and dies 8 and 9)Other (please specify below) (Endocrine)-Histopathology skeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)- idies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophagus, of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, cre- and relative kidney weights (Studies 8,9, 10, and 11)Skin/Connective of stomach, gall bladder, large intestine, small intestine, and salivary kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid osy (Study 8 and Study9).
Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		
Overall Qualit	y Determination	High	

Study Citation: Health Outcome(s) and Reported Health Effect(s):	 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. 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, fistopathology (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)Renal/Kidney-Clinical chemistry (BUN, creatinic), 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 Study 9). 					
Duration and	Oral-Diet-Du	ration: Chronic (>90 days)-7-13-week(s)				
Exposure Route:	Dat Eissbar 2	244 [r-4] D-4h				
Species:	Rat-Fischer 3	144 - [rat]-Both				
HERO ID:	680063	alate- I arent compound				
Domain		Metric	Rating	Comments		
Domain 1: Reporting O	uality	Weute	Rating	connients		
	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	l 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	g / Variable Con	trol				
Continued on next page						

Human Health Hazard Animal Toxicology Evaluation

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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				
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1- Reproductive/Developmental-No. fetuses/breeding of live pups/litter, number of pups/sex/litter, Offspri gross necropsy, offspring body weights, number of in CoA oxidase activity of dams (Studies 1, 2, 3, and 4 genase, bile acids, and glucose), Histopathology of 1 ify below) (Clinical observations)-Clinical Observat spleen) (Studies 8 and 9)Cardiovascular-Heart weig of pancreas, pituitary, adrenal gland, and parathyro Neurological/Behavioral-Histopathology of brain at nasal cavity, pharynx, and trachea (Studies 8 and 9)-0 atinine), Histopathology of kidney and urinary blade Tissue-Histopathology of skin (Studies 8 and 9)O gland (Studies 8 and 9)Other (please specify below) (Study 8 and Study 9)Other (please specify below) Oral-Diet-Duration: Chronic (>90 days)-7-13-week Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound	GS. group, Litter w ng clinical obse nplantation sites).Serum chemis iver (Studies 8 a ions-Immune/H ght, histopatholo ids (Studies 8 a d spinal cord/s Ocular/Sensory- der (Studies 8 a Gastrointestinal- v) (Clinical che (Gross necrops (s)	weight; Gestation length, number of pups/litter, number of live pups/litter, percentage ervations, mortality, feed consumption, histologic examinations on >30 organs/tissues, s, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- try (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydro- and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)Other (please spec- tematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and bogy of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-Histopathology and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)- citatic nerve (Studies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophagus, -Histopathology of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, cre- nd 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11)Skin/Connective Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary mistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid sy)-Gross necropsy (Study 8 and Study9).		
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 1: Selective R	prorting and Attrition				
	Metric 5: Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 M	lethods Sensitivity				

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		con	tinued from p	revious page
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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 rate B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percer of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/lis gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmi CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol deh genase, bile acids, and glucose). Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)Other (please i ify below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology (Hymus, lymph nodes spleen) (Studies 8 and 9)Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-Histopatho of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9)Lenal/Kidney-Clinical chemistry (BUN atinine), Histopathology of kinney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8, 9, 10, and 11)Skin/Conne Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and sal gland (Studies 8 and 9)Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of th (Study 8 and Study 9)Other (please specify below) (Gross necropsy)-Gro			
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 M	leasures and Re Metric 8: Metric 9:	sults Display Endpoint sensitivity and specificity Results presentation	High Medium	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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. Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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 pro- vided.

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Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S. (1995). NTP technica B6C3F1 mice. Toxicity Report Series.	l report on the toxicity studies of dibutyl pl vol. 30 30:1-G5.	hthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Reproductive/Developmental-No. fetus of live pups/litter, number of pups/sex/l gross necropsy, offspring body weights, CoA oxidase activity of dams (Studies 1 genase, bile acids, and glucose), Histopa ify below) (Clinical observations)-Clinic spleen) (Studies 8 and 9)Cardiovascula of pancreas, pituitary, adrenal gland, an Neurological/Behavioral-Histopatholog nasal cavity, pharynx, and trachea (Studi atinine), Histopathology of kidney and Tissue-Histopathology of skin (Studies gland (Studies 8 and 9)Other (please sp Oral-Diet-Duration: Chronic (>90 days Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound 680063	ses/breeding group, Litter weight; Gestation itter, Offspring clinical observations, mortal number of implantation sites, mating index, f 1, 2, 3, and 4).Serum chemistry (ALP, ALT, t athology of liver (Studies 8 and 9). Absolute cal Observations-Immune/Hematological-He ur-Heart weight, histopathology of heart (Stud- nd parathyroids (Studies 8 and 9)-Musculos y of brain and spinal cord/sciatic nerve (Stu- ies 8 and 9)-Ocular/Sensory-Histopathology urinary bladder (Studies 8 and 9).Absolute a 8 and 9)Gastrointestinal-Histopathology specify below) (Clinical chemistry)-Creatine ecify below) (Gross necropsy)-Gross necrop s)-7-13-week(s)	a length, number of pups/litter, number of live pups/litter, percentage ity, feed consumption, histologic examinations on >30 organs/tissues, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- otal protein, albumin, total cholesterol, triglycerides, sorbitol dehydro- and relative liver weight (Studies 8, 9, 10, and 11)Other (please spec- ematology, thymus weights, histopathology (thymus, lymph nodes, and dies 8 and 9)Other (please specify below) (Endocrine)-Histopathology skeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)- idies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophagus, of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, cre- and relative kidney weights (Studies 8,9, 10, and 11)Skin/Connective of stomach, gall bladder, large intestine, small intestine, and salivary kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid osy (Study 8 and Study9).
Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		
Overall Qualit	y Determination	High	

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Marsman, D. B6C3F1 mice Reproductive of live pups/I gross necrops CoA oxidase genase, bile a ify below) (C spleen) (Stud of pancreas, Neurological, nasal cavity, p atinine), Hist Tissue-Histop gland (Studie (Study 8 and Oral-Diet-Du Rat-Fischer 3 Dibutyl Phtha 680063	S. (1995). NTP technical report on the t e. Toxicity Report Series, vol. 30 30:1-G5. //Developmental-No. fetuses/breeding gro itter, number of pups/sex/litter, Offspring of ey, offspring body weights, number of impla activity of dams (Studies 1, 2, 3, and 4).Se actids, and glucose), Histopathology of liver linical observations)-Clinical Observations ies 8 and 9)Cardiovascular-Heart weight, pituitary, adrenal gland, and parathyroids /Behavioral-Histopathology of brain and s oharynx, and trachea (Studies 8 and 9)Ocu opathology of kidney and urinary bladder pathology of skin (Studies 8 and 9)Gastness 8 and 9)Other (please specify below) (G study 9)Other (please specify below) (G tration: Chronic (>90 days)-7-13-week(s) 644 - [rat]-Both alate- Parent compound	oxicity stud up, Litter w clinical obse antation sites rum chemist (Studies 8 a pinal cord/so lar/Sensory- (Studies 8 a rointestinal-I Clinical cher ross necrops	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- rry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydro- nd 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)Other (please spec- ematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and gy of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-Histopathology nd 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)- ciatic nerve (Studies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophagus, Histopathology of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, cre- nd 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11)Skin/Connective Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary nistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid y)-Gross necropsy (Study 8 and Study9).
Domain	000000	Metric	Rating	Comments
Domain 1: Reporting Qu	uality			
	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	Derformance			
	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	g / Variable Con	trol		
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Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D	D. S. (1995). NTP technical report on the	e toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	B6C3F1 mic Reproductiv of live pups, gross necrop CoA oxidas genase, bile ify below) (0 spleen) (Stu- of pancreas, Neurologica nasal cavity, atinine), His Tissue-Histo gland (Studi (Study 8 and Oral-Diet-D Rat-Fischer Dibutyl Phtl 680063	ce. Toxicity Report Series, vol. 30 30:1-G e/Developmental-No. fetuses/breeding g flitter, number of pups/sex/litter, Offspring sy, offspring body weights, number of imp e activity of dams (Studies 1, 2, 3, and 4) acids, and glucose), Histopathology of liv Clinical observations)-Clinical Observatio dies 8 and 9)Cardiovascular-Heart weigh pituitary, adrenal gland, and parathyroid l/Behavioral-Histopathology of brain and pharynx, and trachea (Studies 8 and 9)-O topathology of skin (Studies 8 and 9)Ga es 8 and 9)Other (please specify below) l Study 9)Other (please specify below) (uration: Chronic (>90 days)-7-13-week(s 344 - [rat]-Both nalate- Parent compound	5. roup, Litter w g clinical obse plantation sites Serum chemiss er (Studies 8 a nns-Immune/H t, histopatholo ds (Studies 8 a l spinal cord/s cular/Sensory- er (Studies 8 a strointestinal- i (Clinical cher Gross necrops s)	reight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, s, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- try (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydro- nd 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)Other (please spec- ematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and ogy of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-Histopathology and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)- ciatic nerve (Studies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophagus, Histopathology of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, cre- nd 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11)Skin/Connective Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary mistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid y)-Gross necropsy (Study 8 and Study9).
Domain		Metric	Rating	Comments
	Metric 4.	Confounding / Variable Control	Low	The study used up doeed feed as a negative control and the negative control responses
			2011	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: Solooting P		trition		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 Re	eporting and At Metric 5:	trition Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 authors was provided, but this is not expected to have a significant effect on the study authors was provided, but this is not expected to have a significant effect on the study authors was provided, but this is not expected to have a significant effect on the study authors was provided, but this is not expected to have a significant effect on the study authors was provided, but this is not expected to have a significant effect on the study setul.
Domain 4: Selective Re Domain 5: Exposure M	eporting and At Metric 5: Iethods Sensitiv	trition Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 authors was provided, but this is not expected to have a significant effect on the study results.

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	 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. 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-Immune/Hematological-Hematology, thymus weights, histopathology of thymo, supple nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-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 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 Study 9)Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study 9). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s) Rat-Fischer 344 - [rat]-Both Dibutyl Dthedute Durate demente			
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 M	easures and Re	sults Display		
	Metric 8: Metric 9:	Endpoint sensitivity and specificity Results presentation	High Medium	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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. Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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 pro- vided.

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Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S. (1995). NTP technica B6C3F1 mice. Toxicity Report Series.	l report on the toxicity studies of dibutyl p vol. 30 30:1-G5.	hthalate (CAS No. 84-74-2) administered in feed to F344/N rats and		
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Reproductive/Developmental-No. fetus of live pups/litter, number of pups/sex/l gross necropsy, offspring body weights, CoA oxidase activity of dams (Studies 1 genase, bile acids, and glucose), Histopa ify below) (Clinical observations)-Clinic spleen) (Studies 8 and 9)Cardiovascula of pancreas, pituitary, adrenal gland, an Neurological/Behavioral-Histopatholog nasal cavity, pharynx, and trachea (Studi atinine), Histopathology of kidney and Tissue-Histopathology of skin (Studies gland (Studies 8 and 9)Other (please s (Study 8 and Study 9)Other (please sp Oral-Diet-Duration: Chronic (>90 days Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound 680063	ses/breeding group, Litter weight; Gestation itter, Offspring clinical observations, mortal number of implantation sites, mating index, 1, 2, 3, and 4).Serum chemistry (ALP, ALT, athology of liver (Studies 8 and 9). Absolute cal Observations-Immune/Hematological-H ar-Heart weight, histopathology of heart (Stu nd parathyroids (Studies 8 and 9)-Musculo ty of brain and spinal cord/sciatic nerve (Stu ies 8 and 9)-Ocular/Sensory-Histopathology urinary bladder (Studies 8 and 9).Absolute & 8 and 9)Gastrointestinal-Histopathology specify below) (Clinical chemistry)-Creating ecify below) (Gross necropsy)-Gross necrop s)-7-13-week(s)	n length, number of pups/litter, number of live pups/litter, percentage lity, feed consumption, histologic examinations on >30 organs/tissues, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- total protein, albumin, total cholesterol, triglycerides, sorbitol dehydro- e and relative liver weight (Studies 8, 9, 10, and 11)Other (please spec- ematology, thymus weights, histopathology (thymus, lymph nodes, and dies 8 and 9)Other (please specify below) (Endocrine)-Histopathology skeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)- udies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophagus, of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, cre- and relative kidney weights (Studies 8,9, 10, and 11)Skin/Connective of stomach, gall bladder, large intestine, small intestine, and salivary e kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid psy (Study 8 and Study9).		
Domain	Metric	Rating	Comments		
Additional Comments:	8.DBP 13-week feed study in rats				
Overall Quality Determination High					
Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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 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)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)-				
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Duration and Exposure Route	Oral-Diet-Du	iration: Chronic (>90 days)-7-13-week(s)			
Species:	Rat-Fischer 3	344 - [rat]-Both			
Chemical:	Dibutyl Phtha	alate- Parent compound			
HERO ID:	680063				
Domain		Metric	Rating	Comments	
Domain 1: Reporting Qu	uality				
	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	l Performance				
Domain 2. Screeton and	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	g / Variable Con	trol			
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Human Health Hazard Animal Toxicology Evaluation

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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			
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 Bidistinal, D. S. (1995). KIP technical report on the toxicity studies of ubdry philatate (CAS No. 84-74-2) administered in feed to F344/K fats an B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-65. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentag of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissue gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoy CoA oxidase activity of dams (Studies 1, 2, 3, and 4). Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydre genase, 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 (Hymus, lymph nodes, an 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, esophagu nasal cavity, pharynx, and trachea (Studies 8 and 9)Gostrointestinal-Histopathology of stander, send 10, and 11)Skin/Connectiv Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stander, send 11),-Skin/Connectiv Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stander, send 11),-Skin/Connectiv Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology			
Domain		Metric	Rating	Comments
	36.14			
	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. Solooting P	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 Re	eporting and At Metric 5:	trition Selective Reporting and Attrition	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 Ro Domain 5: Exposure M	Metric 4: eporting and At Metric 5: fethods Sensitiv	trition Selective Reporting and Attrition	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.

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Chemical: HERO ID:	Dibutyl Phth 680063	alate- Parent compound			
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 Me	asures and Res	ults Display			
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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:	Kesults presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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.	

Human Health Hazard Animal Toxicology Evaluation

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Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		
Overall Qualit	y Determination	High	

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Duration and	Oral-Diet-Du	ration: Chronic (>90 days)-7-13-week(s)			
Exposure Route:	Dat Fischer 3	44 [rot] Both			
Species: Chemical:	Dibutyl Phth	alate- Parent compound			
HERO ID:	680063				
Domain		Metric	Rating	Comments	
Domain 1: Reporting Qu	uality				
	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	1 Performance				
Bomani 2. Selection and	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	g / Variable Con	trol			
Continued on next page					

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Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 Backstall, D. S. (1995). INP technical report on the Oxferity studies of ubdry philabate (CAS No. 84-74-2) administered in feed to F344/N fats a B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percenta of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissue gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoy CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydr genase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight, histopathology (thymus, lymph nodes, as spleen) (Studies 8 and 9)Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-Histopatholog 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, esophagt nasal cavity, pharynx, and trachea (Studies 8 and 9)Gastrointestinal-Histopathology of stolides (Studies 8 and 9)Gastrointestinal-Histopathology of stolides (Studies 8 and 9)Other (please specify below) (Clinical chemistry (BUN, ci atinine), Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stoles 8, 9, 10, and 11)Skin/Connecti Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of studies 8, 9, 10, and 11)Thyroid-Histopathology of thyro (Study 8 and Study 9)Other (please specify below) (Gross necropsy)-Gross necropsy			
Domain		Metric	Rating	Comments
	Metric 4.	Confounding / Variable Control	Low	The study used up doeed feed as a negative control and the negative control responses
			2011	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: Solooting P		trition		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 Re	eporting and At Metric 5:	trition Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 authors was provided, but this is not expected to have a significant effect on the study authors was provided, but this is not expected to have a significant effect on the study authors was provided, but this is not expected to have a significant effect on the study authors was provided, but this is not expected to have a significant effect on the study authors was provided, but this is not expected to have a significant effect on the study setul.
Domain 4: Selective Re Domain 5: Exposure M	eporting and At Metric 5: Iethods Sensitiv	trition Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 authors was provided, but this is not expected to have a significant effect on the study results.

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Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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 feur 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)-Cualar/Sensory-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)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)				
Duration and Exposure Route:	Oral-Diet-D	Duration: Chronic (>90 days)-7-13-week(s	5)		
Species: Chemical: HERO ID:	Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound 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 Great Animals were dosed via the diet for 13-weeks. This is consistent types (OECD 408).		Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).		
Domain 6: Outcome M	easures and Re	esults Display			
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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 \pm 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.	

Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S. (1995). NTP technica B6C3F1 mice. Toxicity Report Series.	l report on the toxicity studies of dibutyl pl vol. 30 30:1-G5.	hthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Reproductive/Developmental-No. fetus of live pups/litter, number of pups/sex/l gross necropsy, offspring body weights, CoA oxidase activity of dams (Studies 1 genase, bile acids, and glucose), Histopa ify below) (Clinical observations)-Clinic spleen) (Studies 8 and 9)Cardiovascula of pancreas, pituitary, adrenal gland, an Neurological/Behavioral-Histopatholog nasal cavity, pharynx, and trachea (Studi atinine), Histopathology of kidney and Tissue-Histopathology of skin (Studies gland (Studies 8 and 9)Other (please sp Oral-Diet-Duration: Chronic (>90 days Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound 680063	ses/breeding group, Litter weight; Gestation itter, Offspring clinical observations, mortal number of implantation sites, mating index, f 1, 2, 3, and 4).Serum chemistry (ALP, ALT, t athology of liver (Studies 8 and 9). Absolute cal Observations-Immune/Hematological-He ur-Heart weight, histopathology of heart (Stud- nd parathyroids (Studies 8 and 9)-Musculos y of brain and spinal cord/sciatic nerve (Stu- ies 8 and 9)-Ocular/Sensory-Histopathology urinary bladder (Studies 8 and 9).Absolute a 8 and 9)Gastrointestinal-Histopathology specify below) (Clinical chemistry)-Creatine ecify below) (Gross necropsy)-Gross necrop s)-7-13-week(s)	a length, number of pups/litter, number of live pups/litter, percentage ity, feed consumption, histologic examinations on >30 organs/tissues, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- otal protein, albumin, total cholesterol, triglycerides, sorbitol dehydro- and relative liver weight (Studies 8, 9, 10, and 11)Other (please spec- ematology, thymus weights, histopathology (thymus, lymph nodes, and dies 8 and 9)Other (please specify below) (Endocrine)-Histopathology skeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)- idies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophagus, of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, cre- and relative kidney weights (Studies 8,9, 10, and 11)Skin/Connective of stomach, gall bladder, large intestine, small intestine, and salivary kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid osy (Study 8 and Study9).
Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		
Overall Qualit	y Determination	High	

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	 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. 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 fungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s) Rat-Fischer 344 - [rat]-Both Dibutyl Bhcheta Demonted 				
HERO ID:	680063				
Domain Domain 1: Reporting Or	ality	Metric	Rating	Comments	
	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: Salastion and	Darformanaa				
Domain 2: Selection and	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 Con	trol			
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Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D.	S. (1995). NTP technical report on th	e toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and		
Health Outcome(s) and Reported Health Effect(s): Duration and	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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-Immue/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, creatinne), 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 (S					
Exposure Route:						
Species:	Rat-Fischer 34	44 - [rat]-Both				
Chemical:	Dibutyl Phtha	late- 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.		
D 1 4 0 1 1 5		111011				
Domain 4: Selective Re	eporting and Attr	Metric 5: Selective Reporting and Attrition High There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 4: Selective Re	porting and Attr Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 4: Selective Re Domain 5: Exposure M	Porting and Attr Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 4: Selective Re Domain 5: Exposure M	Porting and Attr Metric 5: Iethods Sensitivit	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 di B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.Health Outcome(s) and Reported Health Effect(s):Marsman, D. S. (1995). NTP technical report on the toxicity studies of di B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; C of live pups/litter, number of pups/sex/litter, Offspring clinical observations gross necropsy, offspring body weights, number of implantation sites, mating CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALF genase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). A ify below) (Clinical observations)-Clinical Observations-Immune/Hematolo spleen) (Studies 8 and 9)Cardiovascular-Heart weight, histopathology of he of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-N Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic ne nasal cavity, pharynx, and trachea (Studies 8 and 9)-Coular/Sensory-Histopat atinine), Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopat gland (Studies 8 and 9)Other (please specify below) (Clinical chemistry)-C (Study 8 and Study 9)Other (please specify below) (Gross necropsy)-Gros Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)Duration and Exposure Route: Species:Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound		ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- try (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydro- nd 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)Other (please spec- ematological-Hematology, thymus weights, histopathology (thymus, lymph nodes, and gy of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-Histopathology nd 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)- ciatic nerve (Studies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophagus, Histopathology of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, cre- nd 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11)Skin/Connective Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary nistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid y)-Gross necropsy (Study 8 and Study9).		
Domain	000000	Metric	Rating	Comments
2 Jinan	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 M	Measures and Re Metric 8: Metric 9:	sults Display Endpoint sensitivity and specificity Results presentation	High Medium	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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. Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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 pro- vided.

Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S. (1995). NTP technica B6C3F1 mice. Toxicity Report Series.	l report on the toxicity studies of dibutyl pl vol. 30 30:1-G5.	hthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Reproductive/Developmental-No. fetus of live pups/litter, number of pups/sex/l gross necropsy, offspring body weights, CoA oxidase activity of dams (Studies 1 genase, bile acids, and glucose), Histopa ify below) (Clinical observations)-Clinic spleen) (Studies 8 and 9)Cardiovascula of pancreas, pituitary, adrenal gland, an Neurological/Behavioral-Histopatholog nasal cavity, pharynx, and trachea (Studi atinine), Histopathology of kidney and Tissue-Histopathology of skin (Studies gland (Studies 8 and 9)Other (please sp Oral-Diet-Duration: Chronic (>90 days Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound 680063	ses/breeding group, Litter weight; Gestation itter, Offspring clinical observations, mortal number of implantation sites, mating index, f 1, 2, 3, and 4).Serum chemistry (ALP, ALT, t athology of liver (Studies 8 and 9). Absolute cal Observations-Immune/Hematological-He ur-Heart weight, histopathology of heart (Stud- nd parathyroids (Studies 8 and 9)-Musculos y of brain and spinal cord/sciatic nerve (Stu- ies 8 and 9)-Ocular/Sensory-Histopathology urinary bladder (Studies 8 and 9).Absolute a 8 and 9)Gastrointestinal-Histopathology specify below) (Clinical chemistry)-Creatine ecify below) (Gross necropsy)-Gross necrop s)-7-13-week(s)	a length, number of pups/litter, number of live pups/litter, percentage ity, feed consumption, histologic examinations on >30 organs/tissues, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- otal protein, albumin, total cholesterol, triglycerides, sorbitol dehydro- and relative liver weight (Studies 8, 9, 10, and 11)Other (please spec- ematology, thymus weights, histopathology (thymus, lymph nodes, and dies 8 and 9)Other (please specify below) (Endocrine)-Histopathology skeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)- idies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophagus, of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, cre- and relative kidney weights (Studies 8,9, 10, and 11)Skin/Connective of stomach, gall bladder, large intestine, small intestine, and salivary kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid osy (Study 8 and Study9).
Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		
Overall Qualit	y Determination	High	

Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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, sorbiol 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)Renal/Kidney-Clinical chemistry (BUN, creatinne), 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 (Studies 8 and 9)Ga				
Duration and	Oral-Diet-Du	ration: Chronic (>90 days)-7-13-week(s)			
Exposure Route:	Dat Fischer 3	44 [rot] Both			
Species: Chemical:	Dibutyl Phth	alate- Parent compound			
HERO ID:	680063				
Domain		Metric	Rating	Comments	
Domain 1: Reporting Qu	uality				
	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	1 Performance				
Bomani 2. Selection and	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	g / Variable Con	trol			
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Study Citation:	Marsman, D	D. S. (1995). NTP technical report on the	e toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Marsman, D. S. (1995). N1P 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. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of ive pups/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 (fupmus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, histopathology of feart (Studies 8 and 9)Charology 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)Gastrointestinal-Histopathology of sees (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)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and s			
Domain		Metric	Rating	Comments
	Metric 4.	Confounding / Variable Control	Low	The study used up doeed feed as a negative control and the negative control responses
			2011	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: Solooting P		trition		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 Re	eporting and At Metric 5:	trition Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 authors was provided, but this is not expected to have a significant effect on the study authors was provided, but this is not expected to have a significant effect on the study authors was provided, but this is not expected to have a significant effect on the study authors was provided, but this is not expected to have a significant effect on the study authors was provided, but this is not expected to have a significant effect on the study setul.
Domain 4: Selective Re Domain 5: Exposure M	eporting and At Metric 5: Iethods Sensitiv	trition Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 authors was provided, but this is not expected to have a significant effect on the study results.

Human Health Hazard Animal Toxicology Evaluation

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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 weight 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 fearur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9)Cher (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)Renal/Kidney-Clinical chemistry (BUN, creatinne), Histopathology of kin (Studies 8 and 9)-Ocular/Sensory-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)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology			
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 Me	asures and Res Metric 8: Metric 9:	ults Display Endpoint sensitivity and specificity Results presentation	High Medium	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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. Endpoint summary tables quantitatively reported data for most endpoints as means \pm SEM or incidences. Histopathology reports did not include severity scores. Statistical
				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.

Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S. (1995). NTP technica B6C3F1 mice. Toxicity Report Series.	l report on the toxicity studies of dibutyl pl vol. 30 30:1-G5.	hthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Reproductive/Developmental-No. fetus of live pups/litter, number of pups/sex/l gross necropsy, offspring body weights, CoA oxidase activity of dams (Studies 1 genase, bile acids, and glucose), Histopa ify below) (Clinical observations)-Clinic spleen) (Studies 8 and 9)Cardiovascula of pancreas, pituitary, adrenal gland, an Neurological/Behavioral-Histopatholog nasal cavity, pharynx, and trachea (Studi atinine), Histopathology of kidney and Tissue-Histopathology of skin (Studies gland (Studies 8 and 9)Other (please sp Oral-Diet-Duration: Chronic (>90 days Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound 680063	ses/breeding group, Litter weight; Gestation itter, Offspring clinical observations, mortal number of implantation sites, mating index, f 1, 2, 3, and 4).Serum chemistry (ALP, ALT, t athology of liver (Studies 8 and 9). Absolute cal Observations-Immune/Hematological-He ur-Heart weight, histopathology of heart (Stud- nd parathyroids (Studies 8 and 9)-Musculos y of brain and spinal cord/sciatic nerve (Stu- ies 8 and 9)-Ocular/Sensory-Histopathology urinary bladder (Studies 8 and 9).Absolute a 8 and 9)Gastrointestinal-Histopathology specify below) (Clinical chemistry)-Creatine ecify below) (Gross necropsy)-Gross necrop s)-7-13-week(s)	a length, number of pups/litter, number of live pups/litter, percentage ity, feed consumption, histologic examinations on >30 organs/tissues, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- otal protein, albumin, total cholesterol, triglycerides, sorbitol dehydro- and relative liver weight (Studies 8, 9, 10, and 11)Other (please spec- ematology, thymus weights, histopathology (thymus, lymph nodes, and dies 8 and 9)Other (please specify below) (Endocrine)-Histopathology skeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)- idies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophagus, of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, cre- and relative kidney weights (Studies 8,9, 10, and 11)Skin/Connective of stomach, gall bladder, large intestine, small intestine, and salivary kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid osy (Study 8 and Study9).
Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		
Overall Qualit	y Determination	High	

Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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, fistopathology (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 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 skin (Studies 8 and 9)Oater (please 8 and 9)Other (please 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				
Duration and	Oral-Diet-Du	ration: Chronic (>90 days)-7-13-week(s)			
Exposure Route:	Dat Eissbar 2	244 [r-4] D-4h			
Species:	Rat-Fischer 3	144 - [rat]-Both			
HERO ID:	680063	alate- I arent compound			
Domain		Metric	Rating	Comments	
Domain 1: Reporting O	uality	Weute	Rating	connients	
	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	l 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	g / Variable Con	trol			
Continued on next page					

Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, I	D. S. (1995). NTP technical report on th	e toxicity stud	lies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species:	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. 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, histopathology (thymus, lymph nodes, and spleen) (Studies 8 and 9)Clardiovascular-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 fumur 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 lung, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)Guatr/Sensory-Histopathology of eyes (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). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)			
Chemical:	Dibutyl Pht	halate- 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 R	enorting and Δ	ttrition		
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 M	lethods Sensitiv	vity		
		Cor	ntinued on ne	xt page

Human Health Hazard Animal Toxicology Evaluation

		contir	nued from p	revious page
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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 weight 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 fearur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9)Cher (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)Renal/Kidney-Clinical chemistry (BUN, creatinne), Histopathology of kin (Studies 8 and 9)-Ocular/Sensory-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)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology			
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 Me	asures and Res Metric 8: Metric 9:	ults Display Endpoint sensitivity and specificity Results presentation	High Medium	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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. Endpoint summary tables quantitatively reported data for most endpoints as means \pm SEM or incidences. Histopathology reports did not include severity scores. Statistical
				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.

Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S. (1995). NTP technica B6C3F1 mice. Toxicity Report Series.	l report on the toxicity studies of dibutyl pl vol. 30 30:1-G5.	hthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Reproductive/Developmental-No. fetus of live pups/litter, number of pups/sex/l gross necropsy, offspring body weights, CoA oxidase activity of dams (Studies 1 genase, bile acids, and glucose), Histopa ify below) (Clinical observations)-Clinic spleen) (Studies 8 and 9)Cardiovascula of pancreas, pituitary, adrenal gland, an Neurological/Behavioral-Histopatholog nasal cavity, pharynx, and trachea (Studi atinine), Histopathology of kidney and Tissue-Histopathology of skin (Studies gland (Studies 8 and 9)Other (please sp Oral-Diet-Duration: Chronic (>90 days Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound 680063	ses/breeding group, Litter weight; Gestation itter, Offspring clinical observations, mortal number of implantation sites, mating index, f 1, 2, 3, and 4).Serum chemistry (ALP, ALT, t athology of liver (Studies 8 and 9). Absolute cal Observations-Immune/Hematological-He ur-Heart weight, histopathology of heart (Stud- nd parathyroids (Studies 8 and 9)-Musculos y of brain and spinal cord/sciatic nerve (Stu- ies 8 and 9)-Ocular/Sensory-Histopathology urinary bladder (Studies 8 and 9).Absolute a 8 and 9)Gastrointestinal-Histopathology specify below) (Clinical chemistry)-Creatine ecify below) (Gross necropsy)-Gross necrop s)-7-13-week(s)	a length, number of pups/litter, number of live pups/litter, percentage ity, feed consumption, histologic examinations on >30 organs/tissues, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- otal protein, albumin, total cholesterol, triglycerides, sorbitol dehydro- and relative liver weight (Studies 8, 9, 10, and 11)Other (please spec- ematology, thymus weights, histopathology (thymus, lymph nodes, and dies 8 and 9)Other (please specify below) (Endocrine)-Histopathology skeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)- idies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophagus, of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, cre- and relative kidney weights (Studies 8,9, 10, and 11)Skin/Connective of stomach, gall bladder, large intestine, small intestine, and salivary kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid osy (Study 8 and Study9).
Domain	Metric	Rating	Comments
Additional Comments:	8.DBP 13-week feed study in rats		
Overall Qualit	y Determination	High	

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	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 30:1-65. 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 (Itymus, 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)Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and 9)-Ocular/Sensory-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)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)-Cardiovascular-Heart weight)-Creatine kinase (Studies: 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)-Cast				
Domain	680063	Metric	Rating	Comments	
Domain 1: Reporting Qu	uality	Wette	Rating	comments	
	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	Darformance				
	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	Domain 3: Confounding / Variable Control				
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Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, I	D. S. (1995). NTP technical report on th	e toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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)Catariovascular-Heart weight, 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)Ostology of eyes (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)Sthyroid-Histopathology of thyroid (Study 8 and Study 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) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify below) (Clinical chemistry)-C				
HERO ID:	680063		D.C.		
Domain	Matria 4	Metric Confounding / Veriable Control	Rating	Comments	
	Metric 4.	Contouring / variable Control	Low	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: Salaativa Da	norting and A	trition			
Domain 4. Selective Re	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 M	lethods Sensitiv	vity			

Human Health Hazard Animal Toxicology Evaluation

		cont	tinued from p	revious page
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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 a B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-65. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percenta of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissu gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmito CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbiol dehyd genase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight, histopathology (Ithruns, lymph nodes, a spleen) (Studies 8 and 9)Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-Histopatholog of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Coular/Sensory-Histopathology of eyes (Studies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophag nasal cavity, pharynx, and trachea (Studies 8 and 9)-Coular/Sensory-Histopathology of eyes (Studies 8, 9, 10, and 11)Skin/Connect Tissue-Histopathology of skin (Studies 8 and 9)-Gastrointestinal-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of studies 8, 9, 10, and 11)Skin/Connect Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of studies 8, 9, 10, and 11)Skin/Connect Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of Studies 8, 9, 10, and 11)Thyroid-Histopathology of thyr (Study 8 and Study 9)Other (please specify below) (Clinical chemistry)-Creatine kinase (Studi			
HERO ID:	680063			
Domain	Metric 6:	Metric 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 N	leasures and Re	esults Display		
	 Measures and Results Display Metric 8: Endpoint sensitivity and specificity High Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), ticular guideline was followed; however, the study was conducted in a manner of OECD 408 and rationale was provided for the selected doses. A toxicity value determined even if the high-dose is excluded due to potential palatability issues ods of outcome assessment were clearly described including frequencies of obs and were generally consistent with OECD 408 guidelines. The test model and were appropriate. 			
	Metric 9:	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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.

Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S. (1995). NTP technical re B6C3F1 mice. Toxicity Report Series, vol.	port on the toxicity studies of dibutyl 30 30:1-G5.	phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and					
Health Outcome(s)	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage							
and Reported	of live pups/litter, number of pups/sex/litte	r, Offspring clinical observations, mor	tality, feed consumption, histologic examinations on >30 organs/tissues,					
Health Effect(s):	gross necropsy, offspring body weights, nur	nber of implantation sites, mating index	x, 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	Γ, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydro-					
	genase, bile acids, and glucose), Histopatho	ology of liver (Studies 8 and 9). Absolu	te and relative liver weight (Studies 8, 9, 10, and 11)Other (please spec-					
	ify below) (Clinical observations)-Clinical	Observations-Immune/Hematological-	Hematology, thymus weights, histopathology (thymus, lymph nodes, and					
	spleen) (Studies 8 and 9)Cardiovascular-H	leart weight, histopathology of heart (S	tudies 8 and 9)Other (please specify below) (Endocrine)-Histopathology					
	of pancreas, pituitary, adrenal gland, and p	parathyroids (Studies 8 and 9)-Muscu	loskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-					
	Neurological/Behavioral-Histopathology o	f brain and spinal cord/sciatic nerve (S	Studies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophagus,					
	nasal cavity, pharynx, and trachea (Studies	8 and 9)-Ocular/Sensory-Histopatholog	gy of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, cre-					
	atinine), 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							
Duration and	(Study 8 and Study 9)Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)							
Exposure Route:								
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 Qualit	y Determination	High						

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	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. 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 (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)Other (please specify below) (Endocrine)-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 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 Study 9).					
Species:	Rat-Fischer 3	344 - [rat]-Both				
Chemical:	Dibutyl Phth	alate- Parent compound				
HERO ID:	680063					
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality					
	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.		
Demain 2. Calenting and	1 Df.					
Domain 2: Selection and	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						
Continued on next page						

Human Health Hazard Animal Toxicology Evaluation

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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				
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 dehydro-genase, 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)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)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 (Studies 8				
Demain	080005	Dating	Commente		
	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 R	eporting and Attrition Metric 5: Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 M	Iethods Sensitivity				

Human Health Hazard Animal Toxicology Evaluation

		con	tinued from p	revious page	
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and	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. 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, alburnin, 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 (Hymus, 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)-Cualr/Sensory-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)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).				
Exposure Route:			·)		
Species: Chemical: HERO ID:	Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound 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 M	fancuras and Da	sulte Display			
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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 \pm 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.	

Human Health Hazard Animal Toxicology Evaluation

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Health Outcome(s) and Reported Health Effect(s): Duration and	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 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 Study 9).						
Exposure Route:	Pat Fischer 244 [rat] Path						
Chemical:	Dibutyl Phthalate- Parent compound						
HERO ID:	680063						
Domain	Metric	Rating	Comments				
Additional Comments:	8.DBP 13-week feed study in rats						
Overall Qualit	y Determination	High					

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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 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 beart (Studies 8 and 9)Cuter (please specify below) (Endocrine)-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 kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8, 9, 10, and 11)Skin/Connective Tissue-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 kidney and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of kidney and urinary bladder (Studies 8 and 9).Absol				
Domain	000005	Metric	Rating	Comments	
Domain 1: Reporting Q	uality				
	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.	
	10 0				
Domain 2: Selection and	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					
Continued on next page					

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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)Gastrointestinal-Histopathology of skin (Studies 8 and 9)Other (please specify below) (Clinical chemistry)-Creatine kinase (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) (Gross necropsy)-Gross necropsy (Stu					
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 Re	porting 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 Me	thods Sensitivity					
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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and	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. 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)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)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				
Exposure Route:	Olai-Dict-D	viration. Enrome (>>0 days)-7-15-week(s)		
Species: Chemical: HERO ID:	Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound 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 M	leasures and Re	esults Display			
	Metric 8: Endpoint sensitivity and specificity Metric 8: Aside from USFDA Good Laboratory Practices regulations (21 CFR, Particular guideline was followed; however, the study was conducted in a ma OECD 408 and rationale was provided for the selected doses. A toxicity determined even if the high-dose is excluded due to potential palatability ods of outcome assessment were clearly described including frequencies and were generally consistent with OECD 408 guidelines. The test mode were appropriate.		Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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 \pm 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.	

Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S. (1995). NTP technica B6C3F1 mice. Toxicity Report Series.	l report on the toxicity studies of dibutyl p vol. 30 30:1-G5.	phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and				
Health Outcome(s) and Reported Health Effect(s): Duration and	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 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 Study 9).						
Exposure Route:	Pat Fischer 244 [rat] Path						
Chemical:	Dibutyl Phthalate- Parent compound						
HERO ID:	680063						
Domain	Metric	Rating	Comments				
Additional Comments:	8.DBP 13-week feed study in rats						
Overall Qualit	y Determination	High					

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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				
Health Outcome(s) and Reported Health Effect(s): Duration and	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 (Hymus, 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 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)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 Stu				
Exposure Route:		() () () () () () () () () () () () () (
Species:	Rat-Fischer 3	344 - [rat]-Both			
Chemical:	Dibutyl Phtha	alate- Parent compound			
HERO ID:	680063				
Domain		Metric	Rating	Comments	
Domain 1: Reporting Qu	uality				
	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	Derformance				
Domain 2: Selection and	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					
Continued on next page					

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Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, I	D. S. (1995). NTP technical report on th	e toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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, 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 lung, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)Calari/Stopathology of stain and spinal cord/sciatic nerve (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, creatinne), 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)Sthyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Sthyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study 9). Oral-Diet-Duration: Ch				
Domain	080003	Metric	Dating	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 1: Selective P	porting and At	trition			
Joniani 4. Selective K	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 M	Iethods Sensitiv	vity			

Human Health Hazard Animal Toxicology Evaluation

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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 an B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentag of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissue: gross necropsy, offspring body weights, number of implantation sites, maring index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyi CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydro: genase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weights, histopathology (thymus, lymph nodes, an spleen) (Studies 8 and 9)Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-Histopatholog 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, esophagu nasal cavity, pharynx, and trachea (Studies 8 and 9)-Gastrointestinal-Histopathology of seys (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, erc atinine), Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stander, gen durinary bladder (Studies 8 and 9)Asolute and relative kidney weights (Studies 8, 9, 10, and 11)Thyroid-Histopathology of thyroi (Studies 8 and 9)Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroi (Study 8 and Study 9)Other (please specify below) (Clinical chemistry)-Creatine kinase			
HERO ID:	680063			
Domain	Metric 6:	Metric 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 N	leasures and Re	esults Display		
	Metric 8: Endpoint sensitivity and specificity Metric 8: Aside from USFDA Good Laboratory Pract ticular guideline was followed; however, the OECD 408 and rationale was provided for t determined even if the high-dose is exclude ods of outcome assessment were clearly des and were generally consistent with OECD 4 were appropriate.		Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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 \pm 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.

Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S. (1995). NTP technica B6C3F1 mice. Toxicity Report Series.	l report on the toxicity studies of dibutyl p vol. 30 30:1-G5.	phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and				
Health Outcome(s) and Reported Health Effect(s): Duration and	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 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 Study 9).						
Exposure Route:	Pat Fischer 244 [rat] Path						
Chemical:	Dibutyl Phthalate- Parent compound						
HERO ID:	680063						
Domain	Metric	Rating	Comments				
Additional Comments:	8.DBP 13-week feed study in rats						
Overall Qualit	y Determination	High					

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Exposure Route: Species: Rat-Fischer 344 - [rat]-Both Chemical: Dibutyl Phthalate- Parent compound
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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Human Health Hazard Animal Toxicology Evaluation

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 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. 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 fungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9)Lenal/Kidney-Clinical chemistry (DN, creatinnie), 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)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of skin (10, creatine), Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopath					
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 Rer	porting and Attrition					
	Metric 5: Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 Me	thods Sensitivity					
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Human Health Hazard Animal Toxicology Evaluation

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species:	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 ra B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, perco of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/ti gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, paln CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol del genase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)Other (please if y below) (Clinical observations)-Clinical Observations-Immune/Hematological-Hematology, thymus weights, histopathology of liveng). (Studies 8 and 9)Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-Histopath of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)Cardiovascular-Heart weight (Studies 8 and 9)Lang/Respiratory-Histopathology of lungs, esop nasal cavity, pharynx, and trachea (Studies 8 and 9)Cuelar/Sensory-Histopathology of sys (Studies 8, 9, 10, and 11)Skin/Conr Tissue-Histopathology of king and urinary bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8, 9, 10, and 11)Skin/Conr Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and sz gland (Studies 8 and 9)Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of t (Studies 8				
Species:	Rat-Fischer	344 - [rat]-Both			
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 N	feasures and Re	esults Display			
	6: Outcome Measures and Results Display Metric 8: Endpoint sensitivity and specificity High Aside from USFDA ticular guideline wa OECD 408 and ratio determined even if t ods of outcome asse and were generally o were appropriate.		Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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 \pm 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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Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S. (1995). NTP technica B6C3F1 mice. Toxicity Report Series.	l report on the toxicity studies of dibutyl p vol. 30 30:1-G5.	phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and			
Health Outcome(s) and Reported Health Effect(s): Duration and	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 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, creatinne), Histopathology of skine (Studies 8 and 9)Absolute and relative kidney weights (Studies 8, 10, and 11)Stry (BUN, creatinne), Histopathology of skine (Studies 8 and 9)Castrointestinal-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) (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 Study 9).					
Exposure Route:	Pat Fischer 244 [rat] Path					
Chemical:	Dibutyl Phthalate- Parent compound					
HERO ID:	680063					
Domain	Metric	Rating	Comments			
Additional Comments:	8.DBP 13-week feed study in rats					
Overall Qualit	y Determination	High				

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and	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. 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 (Hymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9)Cher (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 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)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)					
Exposure Route:						
Species:	Rat-Fischer 3	344 - [rat]-Both				
Chemical:	Dibutyl Phth	alate- Parent compound				
HERO ID:	680063					
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality 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	d 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	g / Variable Con	trol				
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Human Health Hazard Animal Toxicology Evaluation

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					
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 Marsman, D. S. (1995). NIP 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. 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-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)-Gcular/Sensory-Histopathology of stain (Studies 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)-Ocular/Sensory-Histopathology of stain (Studies 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)-Gcular/Sensory-Histopathology of stain (Studies 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)-Gastrointestinal-Hi					
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 Ret	porting and Attrition		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 Rep	porting and Attrition Metric 5: Selective Reporting and Attrition	High	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 Rep Domain 5: Exposure Me	porting and Attrition Metric 5: Selective Reporting and Attrition thods Sensitivity	High	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.			

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Human Health Hazard Animal Toxicology Evaluation

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F3 B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 c gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dat CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sort genase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight, histopathology (Hymus, lym spleen) (Studies 8 and 9)Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-H of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)Cardiovascular-Heart weight (Studies 8 and 9)Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)Cardiovascular-Heart Veigent (Studies 8 and 9)Lung/Respiratory-Histopathology of lung nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of seys (Studies 8, 9, 10, and 11)Sk Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of skin (Studies 8 and 9)Absolute and relative kiney weights (Studies 8, 9, 10, and 11)Sk Tissue-Histopathology of skin (Studies 8 and 9)Greatin kinase (Studies 8, 9, 10, and 11)Thyroid-Histopathology of seys (Studies 8 and 9)Cher (please specify below) (Clinical chemistry)-Creatine kinase (Studies 8, 9, 10, and 11)Thyroid-Histopatholog (Study 8 and Study 9)Other (please specify below) (Clinical chem				
HERO ID:	680063				
Domain	Metric 6:	Metric 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 High duration		High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).	
Domain 6: Outcome N	leasures and Re	esults Display			
	Measures and Results Display Metric 8: Endpoint sensitivity and specificity High		High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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 \pm 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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Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S. (1995). NTP technica B6C3F1 mice. Toxicity Report Series.	l report on the toxicity studies of dibutyl p vol. 30 30:1-G5.	phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and			
Health Outcome(s) and Reported Health Effect(s): Duration and	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 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, creatinne), Histopathology of skine (Studies 8 and 9)Absolute and relative kidney weights (Studies 8, 10, and 11)Stry (BUN, creatinne), Histopathology of skine (Studies 8 and 9)Castrointestinal-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) (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 Study 9).					
Exposure Route:	Pat Fischer 244 [rat] Path					
Chemical:	Dibutyl Phthalate- Parent compound					
HERO ID:	680063					
Domain	Metric	Rating	Comments			
Additional Comments:	8.DBP 13-week feed study in rats					
Overall Qualit	y Determination	High				

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	 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. 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 of three (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)-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)Skin/Connective Tissue-Histopathology of kidney and urinary bladder (Studies 8 and 9)Cardiovas 8, 9, 10, and 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please spe					
Domain	080005	Metric	Rating	Comments		
Domain 1: Reporting Q	uality		Tuning			
	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	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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Human Health Hazard Animal Toxicology Evaluation

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 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. 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 of hymus, 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 lemur 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)Gastrointestinal-Histopathology of eyes (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)Skin/Connective Tissue-Histopa					
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 Rer	orting and Attrition					
	Metric 5: Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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 Me	thods Sensitivity					
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Human Health Hazard Animal Toxicology Evaluation

		cont	tinued from p	revious page	
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F3 B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 c gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dat CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sort genase, bile acids, and glucose), Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight, histopathology (Hymus, lym spleen) (Studies 8 and 9)Cardiovascular-Heart weight, histopathology of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-H of pancreas, pituitary, adrenal gland, and parathyroids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)Cardiovascular-Heart weight (Studies 8 and 9)Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)Cardiovascular-Heart Veigent (Studies 8 and 9)Lung/Respiratory-Histopathology of lung nasal cavity, pharynx, and trachea (Studies 8 and 9)-Ocular/Sensory-Histopathology of seys (Studies 8, 9, 10, and 11)Sk Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of skin (Studies 8 and 9)Absolute and relative kiney weights (Studies 8, 9, 10, and 11)Sk Tissue-Histopathology of skin (Studies 8 and 9)Greatin kinase (Studies 8, 9, 10, and 11)Thyroid-Histopathology of seys (Studies 8 and 9)Cher (please specify below) (Clinical chemistry)-Creatine kinase (Studies 8, 9, 10, and 11)Thyroid-Histopatholog (Study 8 and Study 9)Other (please specify below) (Clinical chem				
HERO ID:	680063				
Domain	Metric 6:	Metric 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 High duration		High	Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).	
Domain 6: Outcome N	leasures and Re	esults Display			
	Measures and Results Display Metric 8: Endpoint sensitivity and specificity High		High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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 \pm 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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Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S. (1995). NTP technica B6C3F1 mice. Toxicity Report Series.	l report on the toxicity studies of dibutyl p vol. 30 30:1-G5.	phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and			
Health Outcome(s) and Reported Health Effect(s): Duration and	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 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, creatinne), Histopathology of skine (Studies 8 and 9)Absolute and relative kidney weights (Studies 8, 10, and 11)Stry (BUN, creatinne), Histopathology of skine (Studies 8 and 9)Castrointestinal-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) (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 Study 9).					
Exposure Route:	Pat Fischer 244 [rat] Path					
Chemical:	Dibutyl Phthalate- Parent compound					
HERO ID:	680063					
Domain	Metric	Rating	Comments			
Additional Comments:	8.DBP 13-week feed study in rats					
Overall Qualit	y Determination	High				

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Study Citation: Health Outcome(s) and Reported	Marsman, D B6C3F1 mic Mortality-Su	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 36C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).						
Health Effect(s): Duration and Exposure Route:	Oral-Diet-D	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)						
Species: Chemical: HERO ID:	Rat-Fischer Dibutyl Phth 680063	344 - [rat]-Both lalate- Parent compound						
Domain		Metric	Rating	Comments				
Domain 1: Reporting Q	uality 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	d 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	g / Variable Co	ntrol						
	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 Re	porting and Att	trition						
	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.				
		Contin	nued on ne	xt page				

PUBLIC RELEASE DRAFT May 2025 Human Health Hazard Animal Toxicology Evaluation

		conti	inued from p	orevious page		
Study Citation:	Marsman, I B6C3F1 mi	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	Mortality-S	urvival (Studies 5, 6, 7, 8, 9, 10, 11, and 12	2).			
Duration and Exposure Route:	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)					
Species: Chemical: HERO ID:	Rat-Fischer Dibutyl Phtl 680063	344 - [rat]-Both halate- Parent compound				
Domain		Metric	Rating	Comments		
Domain 5: Exposure M	ethods Sensitiv	vity Chamical administration and	Uiah	In this study to starting have been also DDD does differed. The second have been		
	Metric 0:	characterization	Figli	In this study, test animals were exposed to DBP-dosed feed. The source, to 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 Me	easures and Re	esults Display				
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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-w	veek feed study in rats				
Overall Quali	ty Deteri	mination	High			

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and	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. 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). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)				
Exposure Route: Species: Chemical: HERO ID:	Rat-Fischer Dibutyl Phtł 680063	344 - [rat]-Both nalate- Parent compound			
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	uality 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	d Performance				
	Metric 2:	Allocation	High	The study authors state that animals were weighed and randomized into groups using a	
	Metric 3:	Observational Bias / Blinding Changes	Medium	computer program. 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.	
Demain 2: Conferration	- / Wasiahla Ca				
Domain 3: Confounding	g / Variable Co Metric 4:	ntrol 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 Re	porting and At	trition			
	Metric 5:	Selective Reporting and Attrition	High	There is no evidence of animal attrition or selective reporting. Qualitative or quantita- tive 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.	
Continued on next page					

Human Health Hazard Animal Toxicology Evaluation

HERO ID: 680063 Table: 18 of 35

		cont	tinued from p	revious page			
Study Citation:	Marsman, I B6C3F1 mi	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 B6C3E1 mice. Toxicity Report Series, vol. 30 30:1-05					
Health Outcome(s) and Reported Health Effect(s):	Nutritional/ gain (Studie	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-D	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)					
Species: Chemical: HERO ID:	Rat-Fischer Dibutyl Pht 680063	Rat-Fischer 344 - [rat]-Both Dibutyl Phthalate- Parent compound 680063					
Domain		Metric	Rating	Comments			
Domain 5: Exposure M	ethods Sensitiv	vity					
	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 Me	easures and Re	esults Display					
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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. Meth- ods 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 vari- ance. Individual animal data were not provided.			
Additional Comments:	8.DBP 13-w	veek feed study in rats					
Overall Quali	ty Deteri	mination	High				

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Snecies:	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. 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 impuls/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 stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify below) (Clinical chemistry (BUN, creatinne), 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			
Species: Chamical:	Mouse-B6C3	alate. Parent compound		
HERO ID:	680063	alate- i arent compound		
Domain		Metric	Rating	Comments
Domain 1: Reporting Qu	uality 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	d Performance		II: -h	
	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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Dibutyl Phthalate

Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D	. S. (1995). NTP technical report on th	e toxicity studi	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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 feart (Studies 8 and 9)Cuter (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 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)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study9). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)			
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. Salastive D.	norting and Att	rition		
Domain 4: Selective Ke	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 Mo	ethods Sensitiv	ity		
Continued on next page				

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Human Health Hazard Animal Toxicology Evaluation

		co	ntinued from p	previous page				
Study Citation:	Marsman, I	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 mi	ce. Toxicity Report Series, vol. 30 30:1-	-G5.					
Health Outcome(s)	Reproductiv	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage						
and Reported	of live pups	s/litter, number of pups/sex/litter, Offspri	ing clinical obse	ervations, mortality, feed consumption, histologic examinations on >30 organs/tissues,				
Health Effect(s):	gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, pa CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, dehydrogenase, bile acids, and glucose). Histopathology of liver (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10 ac							
	Immune/He	matological-Hematology thymus weigh	te histonatholo	av (thymus lymph nodes and spleen) (Studies 8 and 0). Cardiovascular Heart weight				
	histopatholo	ogy of heart (Studies 8 and 9)Other (p	blease specify b	elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy- end thick muscle (Studies 2 and 0) Neurolasias/Babaiage/Histopathology of brain				
	Totas (Stua		biogy of ternur	and thigh muscle (Studies 8 and 9)-Neurological/Benavioral-Histopathology of brain				
	and spinal of	cord/sciatic nerve (Studies 8 and 9)Lun	ng/Respiratory-I	Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and				
	9)-Ocular/S	9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary						
	bladder (Sti	udies 8 and 9). Absolute and relative kidi	ney weights (St	udies 8,9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and				
	9)Gastroir	9)Gastrointestinal-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify						
	below) (Cli	nical chemistry)-Creatine kinase (Studie	es: 8, 9, 10, and	11)Invroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify				
Derestion and	below) (Gro	oss necropsy)-Gross necropsy (Study 8 au	nd Study9).					
Duration and	Oral-Diet-L	Juration: Chronic (>90 days)-7-13-week	(S)					
Exposure Koute:								
Species:	Mouse-B6C	_3F1 - [mouse]-Both						
Chemical:	Dibutyl Pht	halate- Parent compound						
HERO ID:	680063							
Domain		Metric	Rating	Comments				
	Metric 6:	Chemical administration and	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lot number,				
		characterization		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 re-				
				ported. 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 suited to the test substance. Doses in mg/kg_day were provided. However, the au_a				
				thors 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				

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High

High

types (OECD 408).

model and source were appropriate.

conduct an independent calculation excluding any outliers.

Animals were dosed via the diet for 13-weeks. This is consistent with similar study

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

Dibutyl Phthalate

Metric 7:

Metric 8:

Domain 6: Outcome Measures and Results Display

Exposure timing, frequency, and

Endpoint sensitivity and specificity

duration

Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S B6C3F1 mice	. (1995). NTP technical report Toxicity Report Series, vol. 30	rt on the toxicity studi	es of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
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 seys (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, creatinine), 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) (Clinical chemistry)-Creatine kinase (Studies 8, 9, 10, and 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies 8, 9, 10, and 11)Thyroid-Histopa				
Duration and Exposure Route:	Oral-Diet-Dura	tion: Chronic (>90 days)-7-13	3-week(s)		
Species:	Mouse-B6C3F1	l - [mouse]-Both			
Chemical: HERO ID:	Dibutyl Phthala 680063	te- Parent compound			
Domain		Metric	Rating	Comments	
	Metric 9: 1	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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	c feed study in mice			
Overall Qualit	ty Determi	nation	High		

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	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. 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 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)Cuarl/Sensory-Histopathology of seyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, creatinine), 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) (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 Study 9).			
Species:	Mouse-B6C3	BF1 - [mouse]-Both		
Chemical:	Dibutyl Phtha	alate- Parent compound		
HERO ID:	680063			
Domain		Metric	Rating	Comments
Domain 1: Reporting Qu	ıality			
	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.
Dennein 2. Celestien en	1 D			
Domain 2: Selection and	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				
Continued on next page				

Human Health Hazard Animal Toxicology Evaluation

		cont	tinued from p	revious page	
Study Citation:	Marsman, D	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 P6C2E1 mice. Toxicity Paraet Series and 20 201 C5			
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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 seys (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)Stin/Connective Tissue-Histopathology of skin (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). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s) Mouse-B6C3F1 - [mouse]-Both Dibutyl Phthalate- Parent compound 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 Re	porting and Att	rition			
	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 M	ethods Sensitiv	ity			
		Con	tinued on nex	ct page	

May 2025

Human Health Hazard Animal Toxicology Evaluation

		0	ontinued from p	revious page					
Study Citation:	Marsman, l B6C3F1 mi	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)	Reproductiv	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage							
and Reported	of live pups	of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues,							
Health Effect(s): Duration and Exposure Route:	gross necro CoA oxida dehydrogen Immune/He histopathole roids (Stud and spinal o 9)-Ocular/S bladder (Stu 9)Gastroin below) (Cli below) (Gro Oral-Diet-E	psy, offspring body weights, number of i se activity of dams (Studies 1, 2, 3, a nase, bile acids, and glucose), Histopa ematological-Hematology, thymus weigi ogy of heart (Studies 8 and 9)Other (ies 8 and 9)-Musculoskeletal-Histopath cord/sciatic nerve (Studies 8 and 9)Lu Sensory-Histopathology of eyes (Studies udies 8 and 9).Absolute and relative kio ntestinal-Histopathology of stomach, ga inical chemistry)-Creatine kinase (Studi oss necropsy)-Gross necropsy (Study 8 a Duration: Chronic (>90 days)-7-13-wee	mplantation sites and 4).Serum ch thology of liver hts, histopatholog please specify be ology of femur a ing/Respiratory-F s 8 and 9)Renal dney weights (Stu all bladder, large es: 8, 9, 10, and and Study9). k(s)	a, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- memistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11) gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy- and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and I/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary udies 8,9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify					
Exposure Koute:	Mouse B60	73E1 [mouse] Both							
Species: Chomical	Dibutyl Dbt	thelate Derent compound							
HERO ID:	680063	marate- Farent compound							
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 re- ported. 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 au- thors 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 par- ticular 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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Human Health Hazard Animal Toxicology Evaluation

	co	ntinued from p	revious page	
Study Citation: Health Outcome(s) and Reported Health Effect(s):	Marsman, D. S. (1995). NTP technical report on the B6C3F1 mice. Toxicity Report Series, vol. 30 30:14 Reproductive/Developmental-No. fetuses/breeding of live pups/litter, number of pups/sex/litter, Offspring gross necropsy, offspring body weights, number of in CoA oxidase activity of dams (Studies 1, 2, 3, a dehydrogenase, bile acids, and glucose), Histopatt Immune/Hematological-Hematology, thymus weight histopathology of heart (Studies 8 and 9)Other (proids (Studies 8 and 9)-Musculoskeletal-Histopathand spinal cord/sciatic nerve (Studies 8 and 9)Luu 9)-Ocular/Sensory-Histopathology of eyes (Studies 8)	ntinued from p he toxicity stud G5. group, Litter w ing clinical obse nplantation sites nd 4).Serum ch hology of liver nts, histopatholog blease specify b blogy of femur ng/Respiratory-F 8 and 9)Rena	revious page ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11) gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy- and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and //Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary	
Duration and Exposure Route: Species: Chemical: HERO ID:	 9)-Octuar/Sensory-Fristopathology of eyes (Studies 8 and 9)Renal/Ridney-Clinical chemistry (BUN, creatinne), Histopathology of Ridney and urmary 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). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s) Mouse-B6C3F1 - [mouse]-Both Dibutyl Phthalate- Parent compound 680063 			
Domain	Metric	Rating	Comments	
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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 Qualit	y 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				
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	 B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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)-Cular/Sensory-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) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of study 8 and Study 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)				
HERO ID:	680063				
HERO ID: Domain	680063	Metric	Rating	Comments	
HERO ID: Domain Domain 1: Reporting Q	uality	Metric	Rating	Comments	
HERO ID: Domain Domain 1: Reporting Q	uality Metric 1:	Metric Reporting Quality	Rating High	Comments 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 Domain 1: Reporting Q	uality Metric 1:	Metric Reporting Quality	Rating High	Comments 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 Domain 1: Reporting Q Domain 2: Selection and	d Performance	Metric Reporting Quality	Rating High	Comments 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 Domain 1: Reporting Q Domain 2: Selection an	d Performance Metric 2:	Metric Reporting Quality Allocation	Rating High High	Comments 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. The study authors state that animals were weighed and randomized into groups using a computer program.	
HERO ID: Domain Domain 1: Reporting Q Domain 2: Selection and	d Performance Metric 2: Metric 3:	Metric Reporting Quality Allocation Observational Bias / Blinding Changes	Rating High High Medium	Comments 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. The study authors state that animals were weighed and randomized into groups using a computer program. 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 Domain 1: Reporting Q Domain 2: Selection and Domain 3: Confounding	d Performance Metric 1: d Performance Metric 2: Metric 3:	Metric Metric Reporting Quality Allocation Observational Bias / Blinding Changes attrol	Rating High High Medium	Comments 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. The study authors state that animals were weighed and randomized into groups using a computer program. 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.	

Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D	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			
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	BecSF1 mice. Toxicity Report Series, vol. 30 30:1-G5. Reproductive/Developmental-No. fetuese/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 parathy- roids (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 seys (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of studies: 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of 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). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s) Mouse-B6C3F1 - [mouse]-Both Dibutyl Phthalate- Parent compound 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 Re	norting and Att	rition			
	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 Ma	ethods Sensitivi	ity			
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Human Health Hazard Animal Toxicology Evaluation

		0	continued from p	revious page	
Study Citation:	Marsman, I B6C3F1 mi	D. S. (1995). NTP technical report on ice. Toxicity Report Series, vol. 30,30	the toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
Health Outcome(s)	Reproductiv	ve/Developmental-No_fetuses/breedin	g group Litter w	eight. Gestation length number of pups/litter number of live pups/litter percentage	
and Reported	of live pups	volution number of pups/sex/litter Offsn	ring clinical obse	rvations mortality feed consumption histologic examinations on >30 organs/tissues	
Health Effect(s):	of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissue gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoy CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbit 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 weigh histopathology of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy roids (Studies 8 and 9)-Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of bra and spinal cord/sciatic nerve (Studies 8 and 9)Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 ard 9)-Ocular/Sensory-Histopathology of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinan bladder (Studies 8 and 9).Absolute and relative kidney weights (Studies 8,9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 ard 9) -Gastrointestinal-Histopathology of stomach, gall bladder large intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify				
	below) (Cli	nical chemistry)-Creatine kinase (Stud	ies: 8, 9, 10, and	11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify	
	below) (Gro	oss necropsy)-Gross necropsy (Study 8	and Study9).);) (() (+ (+)	
Duration and	Oral-Diet-D	Duration: Chronic (>90 days)-7-13-wee	ek(s)		
Exposure Route:					
Species:	Mouse-B60	C3F1 - [mouse]-Both			
Chemical:	Dibutyl Pht	halate- 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	

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Metric 8: Endpoint sensitivity and specificity Metric 8: Endpoint sensitivity and specificity High Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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.						
Domain 6: Outcome Measure	Domain 6: Outcome Measures and Results Display					
Me	etric 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).		
				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.		

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Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D. S. (1995). NTP tech B6C3F1 mice. Toxicity Report Seri	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)	Reproductive/Developmental-No. f	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage					
and Reported	of live pups/litter, number of pups/s	ex/litter, Offspring clinical obser	vations, mortality, feed consumption, histologic examinations on >30 organs/tissues,				
Health Effect(s):	gross necropsy, offspring body weig	hts, number of implantation sites	mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-				
	CoA oxidase activity of dams (Str	idies 1, 2, 3, and 4).Serum ch	emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol				
	dehydrogenase, bile acids, and glu	cose), Histopathology of liver	(Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)				
	Immune/Hematological-Hematolog	y, thymus weights, histopatholog	y (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight,				
	roids (Studies 8 and 9)-Musculosk	and 9)Other (please specify be	nd thigh muscle (Studies 8 and 9) Neurological/Behavioral Histopathology of brain				
	and spinal cord/sciatic nerve (Studi	es 8 and 9) -Lung/Respiratory-H	fistonathology of lungs esonhagus nasal cavity pharyny and trachea (Studies 8 and				
	9)-Ocular/Sensory-Histopathology	of eves (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 (Stu	idies 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)-Creatin	e kinase (Studies: 8, 9, 10, and	11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify				
Demotion and	below) (Gross necropsy)-Gross necr	copsy (Study 8 and Study9).					
Duration and Exposure Douter	Orai-Diet-Duration: Chronic (>90 a	lays)-7-15-week(s)					
Species	Mouse-B6C3F1 - [mouse]-Both						
Chemical:	Dibutyl Phthalate- Parent compound	1					
HERO ID:	680063						
Domain	Metric	Rating	Comments				
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means \pm				
			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 pro-				
			vided.				
Additional Comments:	9.DBP 13-week feed study in mice						
Overall Qualit	y Determination	High					

Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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 (Hymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, histopathology of lenur 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 stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify below) (Clinical chemistry (BUN, creatinine), 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 thyro			
	below) (Gros	as necropsy)-Gross necropsy (Study 8 and S	(), 10, and (), tudy	11). Thyrona Thistopathology of myrona (Stady o and Stady 7). Onlor (please speeny
Duration and	Oral-Diet-Du	iration: Chronic (>90 days)-7-13-week(s)	(uugy).	
Exposure Route:				
Species:	Mouse-B6C3	BF1 - [mouse]-Both		
Chemical:	Dibutyl Phtha	alate- Parent compound		
HERO ID:	680063			
Domain		Metric	Rating	Comments
Domain 1: Reporting Qu	uality			
	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	d 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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Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D	. S. (1995). NTP technical report on the	he toxicity studi	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
	B6C3F1 mic	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.			
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	 B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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)-Cular/Sensory-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify below) (Clinical chemistry (BLN, creatinnie), 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) (Clinical chemistry)-Creatine kinase (Studies 8, 9, 10, and 11).				
	080003	N# / *	D (
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 Rej	porting and Att	inition	TT' 1		
	Metric 5:	Selective Reporting and Attrition	Hıgh	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 Ma	ethods Sensitiv	ity			
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Human Health Hazard Animal Toxicology Evaluation

		C	ontinued from p	previous page			
Study Citation:	Marsman, I B6C3F1 mi	D. S. (1995). NTP technical report on ce. Toxicity Report Series, vol. 30 30:1	the toxicity stud -G5.	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and			
Health Outcome(s)	Reproductiv	ve/Developmental-No. fetuses/breeding	g group, Litter w	reight; Gestation length, number of pups/litter, number of live pups/litter, percentage			
and Reported	of live pups	of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues					
Health Effect(s): Duration and	of five 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, sorbito 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 parathy roids (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 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 Study 9). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)						
Exposure Route:							
Species:	Mouse-B6C	C3F1 - [mouse]-Both					
Chemical: HERO ID:	Dibutyl Pht 680063	halate- Parent compound					
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" if does not annear 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. Exposure timing, frequency, and Metric 7: High Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408). duration 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. Continued on next page ...

Human Health Hazard Animal Toxicology Evaluation

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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 36C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.						
Health Outcome(s)	Reproductive/Developmental-No. fetuses	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage					
and Reported	of live pups/litter, number of pups/sex/litt	er, Offspring clinical obser	rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues,				
Health Effect(s):	gross necropsy, offspring body weights, nu	mber 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 ch	emistry (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)				
	histopathology of heart (Studies 8 and 9)	Other (please specify be	(low) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy-				
	roids (Studies 8 and 9)-Musculoskeletal-	Histopathology of femur a	and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain				
	and spinal cord/sciatic nerve (Studies 8 a	nd 9)Lung/Respiratory-H	listopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and				
	9)-Ocular/Sensory-Histopathology of eye	s (Studies 8 and 9)Renal	/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary				
	bladder (Studies 8 and 9). Absolute and re	elative kidney weights (Stu	idies 8,9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and integring, small integring, and calify gland (Studies 8 and 0). Other (places specify				
	below) (Clinical chemistry)-Creatine kina	use (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	Oral-Diet-Duration: Chronic (>90 days)-	7-13-week(s)					
Exposure Route:							
Species:	Mouse-B6C3F1 - [mouse]-Both						
HERO ID:	680063						
Domain	Metric	Rating	Comments				
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means \pm				
			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 pro-				
			vided.				
Additional Comments:	9.DBP 13-week feed study in mice						
Overall Qualit	ty Determination	High					
-	-	<u> </u>					

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species:	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. 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 of 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 stomach, gall bladder, large intestine, small in1)Skin/Connective Tissue-Histopathology of skin (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) (Clinical chemistry)-Creatine kinase (Studies 8, 9, 10, and 11)Thyroid-Histopathology of stomach, gall bladder, large intestine, small intestine, and saliva				
Chemical: HERO ID:	Dibutyl Phth 680063	alate- Parent compound			
Domain		Metric	Rating	Comments	
Domain 1: Reporting Qu	uality 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	d Performance Metric 2: Metric 3:	Allocation Observational Bias / Blinding Changes	High Medium	The study authors state that animals were weighed and randomized into groups using a computer program. Blinding was not reported: however, most endpoints were objective or simple in nature	
	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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Dibutyl Phthalate

Human Health Hazard Animal Toxicology Evaluation

		con	tinued from p	revious page	
Study Citation:	Marsman, D B6C3F1 mic	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 R6C3E1 mise. Toxicity Perpert Series, vol. 20, 20:1-C5			
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 parathy- roids (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 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 Study 9). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s) Mouse-B6C3F1 - [mouse]-Both Dibutyl Phthalate- Parent compound 650063				
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 Re	porting and Att	trition			
	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 M	ethods Sensitiv	ity			
	Continued on next page				

Human Health Hazard Animal Toxicology Evaluation

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Dibutyl	Phthalate	

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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 femur and thigh muscle (Studies 8 and 9)Curadiovascular-Heart weight, 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)Cutar/Sensory-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) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-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						
Domain		Metric	Rating	Comments			
	Metric 6: Metric 7:	Chemical administration and characterization Exposure timing, frequency, and duration	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 re- ported. 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 au- thors 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. Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).			
Domain 6: Outcome M	leasures and Re	esults Display					
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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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Human Health Hazard Animal Toxicology Evaluation

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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 B6C3E1 mice. Toxicity Report Series, vol. 30 30:1-G5						
Health Outcome(s)	Reproductive/Devel	Reproductive/Developmental-No. fetuses/breeding group. Litter weight: Gestation length, number of pups/litter, number of live pups/litter, percentage					
and Reported	of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues,						
Health Effect(s):	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/Hematolog	gical-Hematology, thymus wei	ghts, histopatholog	y (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 parathy-						
	rolus (Studies 8 and 9)-infusculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-ineurological/Behavioral-Histopathology of brain and spinal cord/sciptic perve (Studies 8 and 0). Lung/Persistery Histopathology of lungs, esophagus, pasal cavity, pherway, and traches (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						
Downstian and	below) (Gross necropsy)-Gross necropsy (Study 8 and Study9).						
Duration and Exposure Doute:	Oral-Diet-Duration	: Chronic (>90 days)-7-15-we	eek(s)				
Species:	Mouse-B6C3F1 - [mouse]-Both						
Chemical:	Dibutyl Phthalate- Parent compound						
HERO ID:	680063	I I I I I I I I I I I I I I I I I I I					
Domain		Metric	Rating	Comments			
	Metric 9: Resi	ults presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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 pro-			
				viucu.			
Additional Comments:	9.DBP 13-week fee	ed study in mice					
Overall Quality Determination High							
			2				
Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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 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 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 blow) (Endocrine) functional chemistry (BUN, creatinine), 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 blow) (Concetive Tissue-Histopathology of skin (Studies 8 and 9)Other (please specify blow) (Studies 8, 9, 10, and 11)Sk						
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	below) (Gros	as necropsy)-Gross necropsy (Study 8 and S	(), 10, and ().	11). Thyrona Thistopathology of myrona (Stady o and Stady 7). Onlor (please speeny			
Duration and	Oral-Diet-Du	iration: Chronic (>90 days)-7-13-week(s)	(uugy).				
Exposure Route:							
Species:	Mouse-B6C3	BF1 - [mouse]-Both					
Chemical:	Dibutyl Phtha	alate- Parent compound					
HERO ID:	680063						
Domain		Metric	Rating	Comments			
Domain 1: Reporting Qu	uality						
	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	d 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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Human Health Hazard Animal Toxicology Evaluation

HERO ID: 680063 Table: 24 of 35

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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 D(C2E) miss. Tanicity Parent Series and 20 20 1 C5				
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 parathy- roids (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)-Ccular/Sensory-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). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s) Mouse-B6C3F1 - [mouse]-Both Dibutyl Phthalate- Parent compound				
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 Re	porting and Att	rition			
	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 M	ethods Sensitiv	ity			
Continued on next page					

Human Health Hazard Animal Toxicology Evaluation

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Dibutyl Phthalate	

Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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					
	9)-Ocular/Se	ensory-Histopathology of eyes (Studies 8	and 9)Renal	/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary		
	bladder (Stu	dies 8 and 9). Absolute and relative kidne	ey weights (Stu bladder, large	udies 8,9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and intesting, small intesting, and salivary gland (Studies 8 and 0). Other (places specify		
	below) (Clir	ical chemistry)-Creatine kinase (Studies:	8, 9, 10, and	11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify		
Duration and Exposure Route: Species: Chemical: HERO ID:	below) (Gro Oral-Diet-D Mouse-B6C Dibutyl Phth 680063	ss necropsy)-Gross necropsy (Study 8 and uration: Chronic (>90 days)-7-13-week(s 3F1 - [mouse]-Both halate- Parent compound	l Study9).			
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 M	ansuras and Da	sulte Dieploy				
Domain 0. Outcome Me	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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.		
		Con	tinued on nex	ct page		

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	continued from previous page								
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 B6C3E1 mice. Toxicity Report Series vol. 30 30:1-C5								
Health Outcome(s)	Reproductive/Developmental-No. fetus	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage							
and Reported	of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues,								
Health Effect(s):	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 (Studie	s 1, 2, 3, and 4).Serum che	emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol						
	dehydrogenase, bile acids, and glucos	e), Histopathology of liver	(Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)						
	Immune/Hematological-Hematology, th	ymus weights, histopatholog	gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight,						
	histopathology of heart (Studies 8 and raida (Studies 8 and 0) Museuloskalate	9)Other (please specify be	clow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy-						
	and spinal cord/sciptic perve (Studies 8	and (0) Lung/Respiratory H	ind inigh muscle (Studies 8 and 9)-Neurological/Benavioral-Histopathology of brain						
	9)-Ocular/Sensory-Histonathology of e	ves (Studies 8 and 9) -Renal	/Kidney-Clinical chemistry (BUN creatinine) Historiathology of kidney and urinary						
	bladder (Studies 8 and 9). Absolute and	relative kidney weights (Stu	idies 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 ki	nase (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	Oral-Diet-Duration: Chronic (>90 days	s)-7-13-week(s)							
Exposure Route:	Maura DCC2E1 [maural Dath								
Species: 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 \pm						
			SEM or incidences. Histopathology reports did not include severity scores. Statistical						
			significance is shown and statistical methods were described and appropriate. Sample						
			mortality, clinical signs, gross necropsy findings). Individual animal data were not pro-						
			vided.						
Additional Comments:	9.DBP 13-week feed study in mice								
Overall Qualit	y Determination	High							
<u> </u>	v	8							

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	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. 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 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)Gustrointestinal-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) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of stand (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) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thy				
Species:	Mouse-B6C3	BF1 - [mouse]-Both			
Chemical:	Dibutyl Phtha	alate- Parent compound			
HERO ID:	680063				
Domain		Metric	Rating	Comments	
Domain 1: Reporting Qu	ıality				
	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.	
Dennein 2. Celestien en	1 D				
Domain 2: Selection and	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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Dibutyl Phthalate

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Study Citation:	Marsman, D	. S. (1995). NTP technical report on the	e toxicity studi	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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/scx/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)Caular/Sensory-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) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-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				
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 1: Selective Re	porting and Att	rition			
Domain 4. Selective Re	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 Me	Domain 5: Exposure Methods Sensitivity				
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Human Health Hazard Animal Toxicology Evaluation

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Dibutyl Phthalate	

Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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					
	9)-Ocular/Se	ensory-Histopathology of eyes (Studies 8	and 9)Renal	/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary		
	bladder (Stu	dies 8 and 9). Absolute and relative kidne	ey weights (Stu bladder, large	udies 8,9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and intesting, small intesting, and salivary gland (Studies 8 and 0). Other (places specify		
	below) (Clir	ical chemistry)-Creatine kinase (Studies:	8, 9, 10, and	11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify		
Duration and Exposure Route: Species: Chemical: HERO ID:	below) (Gro Oral-Diet-D Mouse-B6C Dibutyl Phth 680063	ss necropsy)-Gross necropsy (Study 8 and uration: Chronic (>90 days)-7-13-week(s 3F1 - [mouse]-Both halate- Parent compound	l Study9).			
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 M	assures and Da	sulte Dieploy				
Domain 0. Outcome Me	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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.		
		Con	tinued on nex	ct page		

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	continued from previous page						
Study Citation: Health Outcome(s)	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. Reproductive/Developmental-No. fetuses/breeding group. Litter weight: Gestation length, number of pups/litter, number of live pups/litter, percentage						
and Reported Health Effect(s):	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 stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify below) (Clinical chemistry (BUN, creatinine), 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) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid (Study 8 and Study 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 spe						
Duration and	Oral-Diet-Duration: Chronic (>90 day	s)-7-13-week(s)					
Exposure Route:	Mausa D6C2E1 [mausa] Dath						
Chemical: HERO ID:	Dibutyl Phthalate- Parent compound 680063						
Domain	Metric	Rating	Comments				
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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 Qualit	ty Determination	High					

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	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. 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 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)Gustrointestinal-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) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of stand (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) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thy				
Species:	Mouse-B6C3	BF1 - [mouse]-Both			
Chemical:	Dibutyl Phtha	alate- Parent compound			
HERO ID:	680063				
Domain		Metric	Rating	Comments	
Domain 1: Reporting Qu	ıality				
	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.	
Dennein 2. Celestien en	1 D				
Domain 2: Selection and	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 B6C3F1 mic	S. (1995). NTP technical report on the e. Toxicity Report Series, vol. 30 30:1-G	e toxicity stud 35.	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	Bocorr inter-toxicity Report Series, vol. 30 30:1-03. 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 parathy- roids (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 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). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s) Mouse-B6C3F1 - [mouse]-Both Dibuted Dthelater Dernet commended				
Domain	080005	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 con- sumption 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 hus- bandry conditions across groups were identified.	
Domain 4: Selective Re	porting and At	trition			
	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 M	ethods Sensitiv	ity			
	Continued on next page				

Human Health Hazard Animal Toxicology Evaluation

		0	ontinued from p	revious page			
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 B6C3E1 mine. Toxicity Report Series, vol. 30 30:1-C5						
Health Outcome(s)	Reproductiv	Reproductive/Developmental-No. fetuses/breeding group. Litter weight: Gestation length, number of number of live number of liv					
and Reported	of live pups	s/litter. number of pups/sex/litter. Offspi	ing clinical obse	rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues.			
Health Effect(s):	of the pups/niter, number of pups/sex/niter, Onspring chinear observations, mortality, feed consumption, instologic examinations on >50 organs/itssues, 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 stomes 0, and 9)Renal/Kidney-Clinical chemistry (BUN, creatinine), 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 Study 9)Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study 9)Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study 9)Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study 9)Other (please specify below) (Gross necropsy)-Gross necropsy (Study 8 and Study 9).						
Exposure Route:							
Species:	Mouse-B6C	C3F1 - [mouse]-Both					
Chemical:	Dibutyl Pht	halate- 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 edge and ensure that the animals upper			

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. Exposure timing, frequency, and Metric 7: High Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408). duration 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. Continued on next page ...

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Study Citation: Health Outcome(s)	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.						
and Reported Health Effect(s):	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 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 (Studies 8 and 9)Other (please specify below) (Clinical chemistry (BUN, creatinine), 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 (Studies 8 and 9)Other (please specify belo						
Duration and	Oral-Diet-Duration: Chronic (>90 days)-7-13-v	week(s)					
Exposure Route:							
Species:	Mouse-B6C3F1 - [mouse]-Both						
HERO ID:	680063						
Domain	Metric	Rating	Comments				
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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 Qualit	ty Determination	High					

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 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 at B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissue gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoy CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbit 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 (Indymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weigh histopathology of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parath noids (Studies 8 and 9)Musculoskeletal-Histopathology of femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of bas and solicel certaine (Studies 8 and 9)Cuarl/Sensory-Histopathology of eyes (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, creatinine), 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 speci below) (Clinical chemistry)-Creatine kinase (Studies 8, 9, 10, and 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please speci below) (Clinical chemistry)-Creatine kinase (Studies 8, 9, 10, and 11)Thyroid-Histopathology of skin (Studies 8 and 9)Other (please speci below) (Clinical chemistry)-Creatine k				
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	uality 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	d Performance	A11	TT' 1		
	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					
Continued on next page					

May 2025

Human Health Hazard Animal Toxicology Evaluation

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Study Citation:	Marsman, D	. S. (1995). NTP technical report on th	ne toxicity studi	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	B6C3F1 mic Reproductive of live pups/ gross necrop CoA oxidase dehydrogena Immune/Her histopatholo roids (Studie and spinal cc 9)-Ocular/Se bladder (Stu 9)Gastroint below) (Clin below) (Gros Oral-Diet-Du Mouse-B6C Dibutyl Phth 680063	e. Toxicity Report Series, vol. 30 30:1-0 e/Developmental-No. fetuses/breeding g litter, number of pups/sex/litter, Offsprin sy, offspring body weights, number of im e activity of dams (Studies 1, 2, 3, an use, bile acids, and glucose), Histopath natological-Hematology, thymus weight gy of heart (Studies 8 and 9)Other (pl es 8 and 9)-Musculoskeletal-Histopathol ord/sciatic nerve (Studies 8 and 9)Lung ensory-Histopathology of eyes (Studies 8 dies 8 and 9).Absolute and relative kidn estinal-Histopathology of stomach, gall ical chemistry)-Creatine kinase (Studies ss necropsy)-Gross necropsy (Study 8 an uration: Chronic (>90 days)-7-13-week(BF1 - [mouse]-Both alate- Parent compound	35. group, Litter w ng clinical obse uplantation sites ad 4).Serum ch ology of liver s, histopatholog lease specify be logy of femur a g/Respiratory-H 8 and 9)Renal uey weights (Stu bladder, large s: 8, 9, 10, and ad Study9). (s)	eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11) gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy- and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and /Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify	
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 Re	porting and Att	rition			
	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 Mo	Domain 5: Exposure Methods Sensitivity				
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Human Health Hazard Animal Toxicology Evaluation

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Dibutyl Phthalate	

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Marsman, E B6C3F1 mid Reproductiv of live pups/ gross necrop CoA oxidas dehydrogena Immune/Het histopatholo roids (Studie and spinal c 9)-Ocular/Se bladder (Stu 9)Gastroin below) (Clir below) (Gro Oral-Diet-D Mouse-B6C Dibutyl Phth 680063	D. S. (1995). NTP technical report on the ce. Toxicity Report Series, vol. 30 30:1-G e/Developmental-No. fetuses/breeding g/litter, number of pups/sex/litter, Offspring body weights, number of impe activity of dams (Studies 1, 2, 3, and ase, bile acids, and glucose), Histopathoc matological-Hematology, thymus weights gy of heart (Studies 8 and 9)Other (ple es 8 and 9)-Musculoskeletal-Histopatholo ord/sciatic nerve (Studies 8 and 9)Lung ensory-Histopathology of eyes (Studies 8 dies 8 and 9).Absolute and relative kidnet testinal-Histopathology of stomach, gall hical chemistry)-Creatine kinase (Studies: ss necropsy)-Gross necropsy (Study 8 and uration: Chronic (>90 days)-7-13-week(s 3F1 - [mouse]-Both nalate- Parent compound	e toxicity stud 5. roup, Litter w g clinical obse blantation sites 1 4).Serum ch blogy of liver , histopatholog ease specify be ogy of femur a /Respiratory-F and 9)Renal ey weights (Str bladder, large 8, 9, 10, and 1 Study9).	tes of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11) gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy- and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain listopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and /Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and /Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify	
Domain		Metric	Rating	Comments	
	Metric 6: Metric 7:	Chemical administration and characterization Exposure timing, frequency, and	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 re- ported. 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 au- thors 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. Animals were dosed via the diet for 13-weeks. This is consistent with similar study	
		duration	C	types (OECD 408).	
Domain 6: Outcome M	easures and Re	sults Display			
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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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			continued from p	revious page				
Study Citation:	Marsman, D. S B6C3F1 mice.	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 B6C3E1 mice. Toxicity Report Series vol. 30.30:1-G5						
Health Outcome(s)	Reproductive/D	Reproductive/Developmental-No. fetuses/breeding group, Litter weight: Gestation length, number of pups/litter, number of live pups/litter, percentage						
and Reported	of live pups/litte	er, number of pups/sex/litter, O	ffspring clinical obser	vations, mortality, feed consumption, histologic examinations on >30 organs/tissues,				
Health Effect(s):	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 parathy- roids (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 Study 9).							
Exposure Route:		····· ································						
Species:	Mouse-B6C3F1	l - [mouse]-Both						
Chemical:	Dibutyl Phthala	te- Parent compound						
HERO ID:	680063							
Domain		Metric	Rating	Comments				
	Metric 9: 1	Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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	t feed study in mice						
Overall Quali	ty Determi	nation	High					

Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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 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)Guari/Sensory-Histopathology of stomach, gall bladder, large intestine, and salivary gland (Studies 8 and 9)Other (please specify below) (Endocrine)-Kin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Guari/Sensory-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify below) (Clinical chemistry (BUN, creatinne), Histopathology of skin (Studies 8 and 9)Guari/Sensory-Histopathology of stomach, gall bladder, large intestine, small intestine, and salivary gland (Studie 8 and 9)Other (please specify below) (Clinical chemistine, and salivary gland (Studie 8 and 9)Other (please				
	below) (Gros	as necropsy)-Gross necropsy (Study 8 and S	(), 10, and (), tudy	11). Thyrona Thistopathology of myrona (Stady o and Stady 7). Onlor (please speeny	
Duration and	Oral-Diet-Du	iration: Chronic (>90 days)-7-13-week(s)	(uugy).		
Exposure Route:					
Species:	Mouse-B6C3	BF1 - [mouse]-Both			
Chemical:	Dibutyl Phtha	alate- Parent compound			
HERO ID:	680063				
Domain		Metric	Rating	Comments	
Domain 1: Reporting Qu	uality				
	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	d 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					
Continued on next page					

Human Health Hazard Animal Toxicology Evaluation

		continued from p	revious page			
Study Citation:	Marsman, D. S. (1995). NTP techn B6C3E1 mice. Toxicity Report Series	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and				
Health Outcome(s)	Reproductive/Developmental-Nof	etuses/breeding group Litter w	eight: Gestation length number of nuns/litter number of live nuns/litter percentage			
and Reported	of live pups/litter, number of pups/s	ex/litter. Offspring clinical obse	rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues			
Health Effect(s):	gross necropsy, offspring body weig	its. number of implantation sites	mating index. fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl			
	CoA oxidase activity of dams (Stu	idies 1, 2, 3, and 4).Serum ch	emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbito			
	dehydrogenase, bile acids, and glu	cose), Histopathology of liver	(Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11).			
	Immune/Hematological-Hematology	y, thymus weights, histopatholo	gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight			
	histopathology of heart (Studies 8 a	and 9)Other (please specify b	elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy-			
	roids (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					
Duration and	below) (Gross necropsy)-Gross necr Oral-Diet-Duration: Chronic (>90 c	opsy (Study 8 and Study9). lays)-7-13-week(s)				
Exposure Route:						
Species:	Mouse-B6C3F1 - [mouse]-Both					
Chemical:	Dibutyl Phthalate- Parent compound	l				
HERO ID:	680063					
Domain	Metric	Rating	Comments			
	Metric 4: Confounding / Varial	ole 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 annuals were excluded as outliers, and therefore, average feed con-			

Selective Reporting and Attrition

Domain 5: Exposure Methods Sensitivity

Domain 4: Selective Reporting and Attrition

Metric 5:

Continued on next page ...

High

sumption 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 hus-

There is no evidence of animal attrition or selective reporting. Qualitative or quantitative

results were provided for all specified endpoints. No animals died.

bandry conditions across groups were identified.

Human Health Hazard Animal Toxicology Evaluation

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Dibutyl Phthalate	

Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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					
	9)-Ocular/Se	ensory-Histopathology of eyes (Studies 8	and 9)Renal	/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary		
	bladder (Stu	dies 8 and 9). Absolute and relative kidne	ey weights (Stubledder Jarge	udies 8,9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and intesting, small intesting, and salivary gland (Studies 8 and 0). Other (places specify		
	below) (Clir	ical chemistry)-Creatine kinase (Studies:	8, 9, 10, and	11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify		
Duration and Exposure Route: Species: Chemical: HERO ID:	below) (Gro Oral-Diet-D Mouse-B6C Dibutyl Phth 680063	ss necropsy)-Gross necropsy (Study 8 and uration: Chronic (>90 days)-7-13-week(s 3F1 - [mouse]-Both halate- Parent compound	l Study9).			
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 M	assures and Da	sulte Dieploy				
Domain 0. Outcome Me	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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.		
		Con	tinued on nex	ct page		

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	•	continued from p	revious page			
Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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)					
Duration and Exposure Route: Species: Chemical: HERO ID:	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). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s) Mouse-B6C3F1 - [mouse]-Both Dibutyl Phthalate- Parent compound					
Domain	Metric	Rating	Comments			
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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 Qualit	y Determination	High				

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	Marsman, D. B6C3F1 mice Reproductive of live pups/I gross necrops CoA oxidase dehydrogena: Immune/Hen histopatholog roids (Studie and spinal co 9)-Ocular/Set bladder (Stud 9)Gastrointe below) (Clini below) (Gross Oral-Diet-Du	S. (1995). NTP technical report on the t e. Toxicity Report Series, vol. 30 30:1-G5. c/Developmental-No. fetuses/breeding gro litter, number of pups/sex/litter, Offspring of sy, offspring body weights, number of impla- e activity of dams (Studies 1, 2, 3, and se, bile acids, and glucose), Histopatholo natological-Hematology, thymus weights, H gy of heart (Studies 8 and 9)Other (pleas s 8 and 9)-Musculoskeletal-Histopatholog ord/sciatic nerve (Studies 8 and 9)Lung/R nsory-Histopathology of eyes (Studies 8 a dies 8 and 9).Absolute and relative kidney estinal-Histopathology of stomach, gall bl ical chemistry)-Creatine kinase (Studies 8 aration: Chronic (>90 days)-7-13-week(s)	up, Litter w clinical obse untation sites 4).Serum ch ogy of liver nistopatholog se specify be y of femur a cespiratory-H nd 9)Renal weights (Stu adder, large 8, 9, 10, and Study9).	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11) gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy- and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and /Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify
Species:	Mouse-B6C3	BF1 - [mouse]-Both		
Chemical:	Dibutyl Phtha	alate- Parent compound		
HERO ID:	680063			
Domain		Metric	Rating	Comments
Domain 1: Reporting Qu	ıality			
	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.
Dennein 2. Celestien en	1 D			
Domain 2: Selection and	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 Con	ıtrol		
		Conti	nued on nex	t page

Human Health Hazard Animal Toxicology Evaluation

		r i i i i i i i i i i i i i i i i i i i	
Study Citation:	Marsman, D. S. (1995). NTP technical report on	the toxicity studi	es of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1 Reproductive/Developmental-No. fetuses/breeding of live pups/litter, number of pups/sex/litter, Offsp gross necropsy, offspring body weights, number of CoA oxidase activity of dams (Studies 1, 2, 3, dehydrogenase, bile acids, and glucose), Histopa Immune/Hematological-Hematology, thymus weig histopathology of heart (Studies 8 and 9)Other of roids (Studies 8 and 9)-Musculoskeletal-Histopath and spinal cord/sciatic nerve (Studies 8 and 9)Lu 9)-Ocular/Sensory-Histopathology of eyes (Studie bladder (Studies 8 and 9).Absolute and relative ki 9)Gastrointestinal-Histopathology of stomach, gr below) (Clinical chemistry)-Creatine kinase (Studi below) (Gross necropsy)-Gross necropsy (Study 8 Oral-Diet-Duration: Chronic (>90 days)-7-13-wee Mouse-B6C3F1 - [mouse]-Both Dibutyl Phthalate- Parent compound 680063	I-G5. g group, Litter w ring clinical obse- implantation sites and 4).Serum ch thology of liver shts, histopatholog (please specify be nology of femur a nng/Respiratory-F is 8 and 9)Renal dney weights (Stu all bladder, large ies: 8, 9, 10, and and Study9). ek(s)	eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11) gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy- and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain listopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and /Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify
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 con- sumption 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 hus- bandry conditions across groups were identified.
Domain 4: Selective Re	porting 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 M	ethods Sensitivity		
	(Continued on nex	t page

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Dibutyl Phthalate	

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Study Citation:	Marsman, D	. S. (1995). NTP technical report on the	toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	B6C3F1 mic Reproductive of live pups/ gross necrop CoA oxidase dehydrogena Immune/Her histopatholo roids (Studie and spinal co 9)-Ocular/Se bladder (Stu 9)Gastroint below) (Clin below) (Gros Oral-Diet-Do	e. Toxicity Report Series, vol. 30 30:1-GS e/Developmental-No. fetuses/breeding gro litter, number of pups/sex/litter, Offspring sy, offspring body weights, number of impli- e activity of dams (Studies 1, 2, 3, and use, bile acids, and glucose), Histopatholog natological-Hematology, thymus weights, gy of heart (Studies 8 and 9)Other (plea es 8 and 9)-Musculoskeletal-Histopatholog ord/sciatic nerve (Studies 8 and 9)Lung/R ensory-Histopathology of eyes (Studies 8 a dies 8 and 9).Absolute and relative kidney estinal-Histopathology of stomach, gall bl ical chemistry)-Creatine kinase (Studies: 3 ss necropsy)-Gross necropsy (Study 8 and uration: Chronic (>90 days)-7-13-week(s) BF1 - [mouse]-Both alate. Parent compound	bup, Litter w clinical obse antation sites 4).Serum ch ogy of liver histopatholog se specify be gy of femur a Respiratory-F and 9)Renal weights (Str ladder, large 3, 9, 10, and Study9).	eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11) gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy- and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain listopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and /Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify
HERO ID:	680063	arate- i arent compound		
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 M	easures and Res	sults Display		
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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.

		continued from p	revious page
Study Citation:	Marsman, D. S. (1995). NTP technical report B6C3E1 mice Toxicity Report Series vol 30	t on the toxicity studi	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s)	Reproductive/Developmental-No. fetuses/bree	eding group. Litter w	eight: Gestation length, number of pups/litter, number of live pups/litter, percentage
and Reported	of live pups/litter, number of pups/sex/litter, O	ffspring clinical obser	rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues,
Health Effect(s):	gross necropsy, offspring body weights, number	r 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 ch	emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol
	dehydrogenase, bile acids, and glucose), His	topathology of liver	(Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)
	Immune/Hematological-Hematology, thymus	weights, histopatholog	gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight,
	histopathology of heart (Studies 8 and 9)Oth	her (please specify be	elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy-
	and spinal cord/sciatic nerve (Studies 8 and 9)	Jung/Respiratory-H	ling ingri muscle (Studies 8 and 9)-Neurological/Benavioral-Histopathology of brain
	9)-Ocular/Sensory-Histopathology of eyes (Stu	udies 8 and 9)Renal	/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of kidney and urinary
	bladder (Studies 8 and 9). Absolute and relativ	e kidney weights (Stu	idies 8,9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and
	9)Gastrointestinal-Histopathology of stomac	h, gall bladder, large	intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify
	below) (Clinical chemistry)-Creatine kinase (S	Studies: 8, 9, 10, and	11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify
Duration and	below) (Gross necropsy)-Gross necropsy (Stud Oral Diet Duration: Chronic (>90 days) 7.13	ly 8 and Study9).	
Exposure Route:	Grai-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 \pm 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 pro-
			viucu.
Additional Comments:	9.DBP 13-week feed study in mice		
Overall Qualit	y Determination	High	
<u> </u>	v	0	

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	Marsman, D. B6C3F1 mice Reproductive of live pups/I gross necrops CoA oxidase dehydrogena: Immune/Hen histopatholog roids (Studie and spinal co 9)-Ocular/Set bladder (Stud 9)Gastrointe below) (Clini below) (Gross Oral-Diet-Du	S. (1995). NTP technical report on the t e. Toxicity Report Series, vol. 30 30:1-G5. c/Developmental-No. fetuses/breeding gro litter, number of pups/sex/litter, Offspring of sy, offspring body weights, number of impla- e activity of dams (Studies 1, 2, 3, and se, bile acids, and glucose), Histopatholo natological-Hematology, thymus weights, H gy of heart (Studies 8 and 9)Other (pleas s 8 and 9)-Musculoskeletal-Histopatholog ord/sciatic nerve (Studies 8 and 9)Lung/R nsory-Histopathology of eyes (Studies 8 a dies 8 and 9).Absolute and relative kidney estinal-Histopathology of stomach, gall bl ical chemistry)-Creatine kinase (Studies 8 aration: Chronic (>90 days)-7-13-week(s)	up, Litter w clinical obse untation sites 4).Serum ch ogy of liver nistopatholog se specify be y of femur a cespiratory-H nd 9)Renal weights (Stu adder, large 8, 9, 10, and Study9).	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11) gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy- and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and /Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify
Species:	Mouse-B6C3	BF1 - [mouse]-Both		
Chemical:	Dibutyl Phtha	alate- Parent compound		
HERO ID:	680063			
Domain		Metric	Rating	Comments
Domain 1: Reporting Qu	ıality			
	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.
Dennein 2. Celestien en	1 D			
Domain 2: Selection and	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 Con	ıtrol		
		Conti	nued on nex	t page

Human Health Hazard Animal Toxicology Evaluation

		con	tinued from p	revious page
Study Citation:	Marsman, D	. S. (1995). NTP technical report on the	e toxicity studi	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	BoC3F1 hite Reproductive of live pups/l gross necrops CoA oxidase dehydrogena Immune/Hen histopatholog roids (Studie and spinal co 9)-Ocular/Se bladder (Stud 9)Gastroint below) (Clin below) (Gros Oral-Diet-Du Mouse-B6C3 Dibutyl Phth 680063	e. Toxicity Report Series, vol. 50 50:1-C c/Developmental-No. fetuses/breeding g litter, number of pups/sex/litter, Offsprin sy, offspring body weights, number of imp e activity of dams (Studies 1, 2, 3, an- se, bile acids, and glucose), Histopathon natological-Hematology, thymus weights gy of heart (Studies 8 and 9)Other (pla- is 8 and 9)-Musculoskeletal-Histopatholor ord/sciatic nerve (Studies 8 and 9)Lung nsory-Histopathology of eyes (Studies 8 dies 8 and 9).Absolute and relative kidne estinal-Histopathology of stomach, gall ical chemistry)-Creatine kinase (Studies as necropsy)-Gross necropsy (Study 8 an- rration: Chronic (>90 days)-7-13-week(BF1 - [mouse]-Both alate- Parent compound	group, Litter w group, Litter w g clinical obse plantation sites d 4).Serum ch ology of liver s, histopatholog ease specify be ogy of femur a g/Respiratory-H 3 and 9)Renal ey weights (Stu bladder, large : 8, 9, 10, and d Study9). s)	eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11) gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy- and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and //Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify
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. Salaating De	nonting and Att	mition		
Domain 4: Selective Re	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 M	ethods Sensitivi	ity		
		Cor	ntinued on nex	t page

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Human Health Hazard Animal Toxicology Evaluation

... continued from previous page

HERO ID: 680063 Table: 30 of 35

Dibutyl Phthalate

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Marsman, D B6C3F1 mic Reproductive of live pups// gross necropy CoA oxidase dehydrogena Immune/Her histopatholog roids (Studie and spinal cc 9)-Ocular/Se bladder (Stud 9)Gastroint below) (Clin below) (Gros Oral-Diet-Du Mouse-B6C2 Dibutyl Phth 680063	S. (1995). NTP technical report on t e. Toxicity Report Series, vol. 30 30:1- e/Developmental-No. fetuses/breeding litter, number of pups/sex/litter, Offspri sy, offspring body weights, number of in e activity of dams (Studies 1, 2, 3, a se, bile acids, and glucose), Histopat natological-Hematology, thymus weigh gy of heart (Studies 8 and 9)Other (p is 8 and 9)-Musculoskeletal-Histopath ord/sciatic nerve (Studies 8 and 9)Lun nsory-Histopathology of eyes (Studies dies 8 and 9).Absolute and relative kid estinal-Histopathology of stomach, ga ical chemistry)-Creatine kinase (Studie s necropsy)-Gross necropsy (Study 8 a tration: Chronic (>90 days)-7-13-weel BF1 - [mouse]-Both alate- Parent compound	the toxicity studi -G5. group, Litter we ing clinical obser mplantation sites. and 4).Serum ch- hology of liver tts, histopatholog blease specify be ology of femur a ng/Respiratory-H 8 and 9)Renal ney weights (Stu ll bladder, large es: 8, 9, 10, and nd (Study9). c(s)	es of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11) gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy- ind thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain listopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and /Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify
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 re- ported. 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 au- thors 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 High Animals were dosed via the diet for 13-weeks. This is consistent with similar study duration 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. Continued on next page ...

	•	continued from p	revious page
Study Citation:	Marsman, D. S. (1995). NTP technical report B6C3E1 mice Toxicity Report Series vol. 30.3	on the toxicity studi	es of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-No. fetuses/breed of live pups/litter, number of pups/sex/litter, Of gross necropsy, offspring body weights, number CoA oxidase activity of dams (Studies 1, 2, dehydrogenase, bile acids, and glucose), Hist Immune/Hematological-Hematology, thymus w histopathology of heart (Studies 8 and 9)Oth roids (Studies 8 and 9)-Musculoskeletal-Histop and spinal cord/sciatic nerve (Studies 8 and 9). 9)-Ocular/Sensory-Histopathology of eyes (Stu bladder (Studies 8 and 9).Absolute and relative	ding group, Litter we fspring clinical observed of implantation sites 3, and 4).Serum ch opathology of liver veights, histopatholog er (please specify be pathology of femur a -Lung/Respiratory-H dies 8 and 9)Renal	eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoylemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11) gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, clow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy- nd thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain listopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and /Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and 1)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 1)Skin/Connective Tissue-
	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 (St	tudies: 8, 9, 10, and	11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify
Duration and	below) (Gross necropsy)-Gross necropsy (Study Oral-Diet-Duration: Chronic (>90 days)-7-13-	y 8 and Study9).	
Exposure Route:	oral Diet Duration. Chrome (> >0 days) + 15	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 \pm 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 Qualit	ty Determination	High	

Study Citation:	Marsman, D	. S. (1995). NTP technical report on the t	oxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	B6C3F1 mic Reproductive of live pups// gross necrops CoA oxidase dehydrogena Immune/Her histopatholog roids (Studie and spinal cc 9)-Ocular/Se bladder (Stud 9)Gastroint below) (Clin below) (Gros Oral-Diet-Du Mouse-B6C3 Dibutyl Phth	e. Toxicity Report Series, vol. 30 30:1-G5. Provide the series of the s	up, Litter w clinical obse intation sites 4).Serum ch ogy of liver histopatholog se specify bo y of femur a espiratory-H nd 9)Renal weights (Str adder, large 5, 9, 10, and Study9).	eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11) gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy- and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and /Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify
HERO ID:	680063			
HERO ID: Domain	680063	Metric	Rating	Comments
HERO ID: Domain Domain 1: Reporting Q	uality	Metric	Rating	Comments
HERO ID: Domain Domain 1: Reporting Q	uality Metric 1:	Metric Reporting Quality	Rating High	Comments 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 Domain 1: Reporting Q	uality Metric 1:	Metric Reporting Quality	Rating High	Comments 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 Domain 1: Reporting Q Domain 2: Selection and	d Performance	Metric Reporting Quality	Rating High	Comments 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 Domain 1: Reporting Q Domain 2: Selection an	d Performance Metric 2:	Metric Reporting Quality Allocation	Rating High High	Comments 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. The study authors state that animals were weighed and randomized into groups using a computer program.
HERO ID: Domain Domain 1: Reporting Q Domain 2: Selection and	d Performance Metric 2: Metric 3:	Metric Reporting Quality Allocation Observational Bias / Blinding Changes	Rating High High Medium	Comments 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. The study authors state that animals were weighed and randomized into groups using a computer program. 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 Domain 1: Reporting Q Domain 2: Selection and Domain 3: Confounding	d Performance Metric 1: d Performance Metric 2: Metric 3:	Metric Metric Reporting Quality Allocation Observational Bias / Blinding Changes attrol	Rating High High Medium	Comments 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. The study authors state that animals were weighed and randomized into groups using a computer program. 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.

Human Health Hazard Animal Toxicology Evaluation

HERO ID: 680063 Table: 31 of 35

		con	tinued from p	revious page
Study Citation:	Marsman, D	. S. (1995). NTP technical report on the	e toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 BocsPT lince. Tokicty Report Series, vol. 50:50:1-CD. 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 femur and thigh muscle (Studies 8 and 9)Cardiovascular-Heart weight, roids (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)-Gular/Sensory-Histopathology of studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of studies (Studies 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Guter (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). Oral-Diet-Dur			
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 Re	porting and Att	rition		
	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				
Continued on next page				

Human Health Hazard Animal Toxicology Evaluation

Dibutyl Phthalate	

continued from p	orevious page
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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	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. 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 of (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy-roids (Studies 8 and 9)-Other (please specify below) (Endocrine)-Histopathology of pancreas, pituitary, and trachea (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)Lung/Respiratory-Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and 9)-Gastrointestinal-Histopathology of stim (Studies 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of studies: 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology			
HERO ID:	680063			
Domain	Metric 6:	Metric Chemical administration and	Rating	Comments
	Metric 6:	characterization	Medium	In this study, test animals were exposed to DBP-dosed feed. The source, lof 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 re- ported. 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 au- thors 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 M	leasures and Re	sults Display		
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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.
		Cont	inued on nex	ct page

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 30:1-65. Health Outcome(s) and Reported Health Outcome(s) and Reported Health Effect(s): fibre pup/litter, number of pup/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, 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/Hematology, thymus weights, histopathology of thymus, lymph nodes, and spleen) (Studies 8 and 9). Ang/Respiratory-Histopathology of pancreas, pituitary, adrend gland, and parathyroid (Studies 8 and 9). Active (Studies 8 and 9). Active (Studies 8, 9). O, and 11). Skint/Consecture These effects (Studies 8 and 9). Occular/Sensory-Histopathology of eyes (Studies 8, 9). O, and 11). Skint/Connective Tissue-Histopathology of king wait writery effect (Studies 8 and 9). Occular/Sensory-Histopathology of eyes (Studies 8, 9). (D, and 11). Skint/Connective Tissue-Histopathology of skin (Studies 8 and 9). Contentive Tissue-Histopathology of skin (Studies 8 and 9). Occular/Sensory-Histopathology of stomach, gall bladder, large intestine, and salivary gland (Studies 8 and 9). Ocher (please specify below) (Clinical tehmistry)-Creatine kinase (Studies: 8, 9). (D, and 11). Skint/Connective Tissue-Histopathology of skin (Studies 8 and 9). Ocher (please specify below) (Clinical tehmistry)-Creatine kinase (Studies: 8,			0	ontinued from p	revious page				
Health Outcome(s) and Reported Health Effect(s): Reproductive/Developmental-No. fetuses/byreeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, number of pups/sex/litter, Offspring gloup weights, number of implantations, mortality, feed consumption, histologic examinations on >30 organs/lissues, for live pups/litter, number of pups/sex/litter, Offspring gloup, weights, number of implantations, kerfiltily index-Hepatic/Liver-Absolute liver weights of dams, palmitop- CoA oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, abbumin, 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/Henatology of heart (Studies 8 and 9)Other (please specify below) (Endocrine)-Histopathology of panceas, pituitary, adrenal gland, and parathy- roids (Studies 8 and 9)Musculoskeletal-Histopathology of lurge, scophagus, nasal cavity, pharynx, and trached (Studies 8 and 9)-Ocular/Sensory-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)Tinyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify below) (Clinical chemistry)-Creatine kinase (Studies 8, 9, 10, and 11)Tinyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify below) (Gross necropsy)-Gross necropsy)-Gross necropsy (Study 8 and Study 9). Duration and Exposure Route: Species: Mouse-B6C3F1 - [mouse]-Both Chemical: Domain Metric Rating Comments Metric 9: Results presentation Medium Endpoint summary tables quantitatively reported data for m	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 B6C3E1 mice. Toxicity Penort Series, vol. 30, 30, 1, C5							
and Reported 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, palmit09-106-04 oxidase activity of dams (Studies 1, 2, 3, and 4).Serum chemistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbiol 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 of flower (Bidose 8 and 9)Cardiovascular-Heart weight, histopathology of feart (Studies 8 and 9)Cutar/Sensory-Histopathology of ferent and thigh muscle (Studies 8 and 9)Cardiovascular-Heart weight, histopathology of fewer (Studies 8 and 9)Cutar/Sensory-Histopathology of ferent and thigh muscle (Studies 8 and a)-Neurological/Behavioral-Histopathology of brain and spinal correlycicatine erve (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, creatinne), Histopathology of skine y and urinary bladder (Studies 8 and 9)Absolute index, here yielts (Studies 8, 9, 10, and 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify below) (Clicat 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 Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s) Exposure Route: Species: Motric Rating Comments Species: Motric Rating Comments Domain Metric <th>Health Outcome(s)</th> <th colspan="7">Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage</th>	Health Outcome(s)	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage							
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Overall Quality Determination High	Additional Comments:	9.DBP 13-week feed s	tudy in mice						
	Overall Quali	Overall Quality Determination High							

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and	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. 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/liter, 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 femur and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain and spinal cord/sciatic nerve (Studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and 9)Ocular/Sensory-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) (Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and 9)Gestrointestinal-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					
Exposure Koute: Species:	Mausa B6C2E1 [mausa] Dath					
Chemical:	Dibutyl Phth	alate- Parent compound				
HERO ID:	680063					
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality					
	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	a Performance	Allocation	Uich	The study options state that animals ware weighed and readomized into an even with a		
	Metric 2:	Anocation	High	I ne 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	g / Variable Cor	ıtrol				
		Conti	nued on nex	t page		

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Dibutyl Phthalate

Human Health Hazard Animal Toxicology Evaluation

HERO ID: 680063 Table: 32 of 35

		con	tinued from p	revious page
Study Citation:	Marsman, D	. S. (1995). NTP technical report on the	e toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 BocsPT lince. Tokicty Report Series, vol. 50:50:1-CD. 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 femur and thigh muscle (Studies 8 and 9)Cardiovascular-Heart weight, roids (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)-Gular/Sensory-Histopathology of studies 8 and 9)Renal/Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and 9)Gastrointestinal-Histopathology of studies (Studies 8, 9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and 9)Guter (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). Oral-Diet-Dur			
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 Re	porting and Att	rition		
	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				
Continued on next page				

Human Health Hazard Animal Toxicology Evaluation

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Dibutyl Phthalate	

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				
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	Marshal, D. S. (1995). NTP technical report on the toxicity studies of unduly pintalate (CAS No. 84-74-2) administered in feed to F344/X fats and B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 feart (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)-Coular/Sensory-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)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 (Studie				
Demain	080003	Matria	Dating	Comments	
Domain	Metric 6: Metric 7:	Metric Chemical administration and characterization Exposure timing, frequency, and duration	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 re- ported. 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 au- thors 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. Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).	
Domain 6: Outcome M	easures and Re Metric 8:	sults Display Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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.	
		Cont	tinued on nex	t page	

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Human Health Hazard Animal Toxicology Evaluation

		continued from p	revious page				
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)	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage						
and Reported	of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues,						
Health Effect(s):	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 gluce	ose), Histopathology of liver	(Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)				
	Immune/Hematological-Hematology,	thymus weights, histopatholog	y (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight,				
	nistopathology of heart (Studies 8 and 0) Museuloskal	id 9)Other (please specify be	low) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy-				
	and spinal cord/sciatic nerve (Studies	(8 and 9) -L ung/Respiratory-H	istonathology of lungs, esophagus, pasal cavity, pharyny, and trachea (Studies 8 and				
	9)-Ocular/Sensory-Histopathology of	eves (Studies 8 and 9)Renal	Kidnev-Clinical chemistry (BUN, creatinine). Histopathology of kidney and urinary				
	bladder (Studies 8 and 9). Absolute a	nd relative kidney weights (Stu	dies 8,9, 10, and 11)Skin/Connective Tissue-Histopathology of skin (Studies 8 and				
	9)Gastrointestinal-Histopathology o	f 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	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)						
Exposure Koute:	Manaa B(C2E1 [manaa] Dath						
Chemical:	Niouse-Doeseri - [iiiouse]-Doui 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 \pm				
			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 pro-				
			vided.				
Additional Comments:	9.DBP 13-week feed study in mice						
Overall Qualit	Overall Quality Determination High						

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	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. 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 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) (Clinical chemistry)-Creatine kinase (Studies: 8, 9, 10, and 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify below) (Clinical chemistry)-Creatine				
Species:	Mouse-B6C3	BF1 - [mouse]-Both			
Chemical:	Dibutyl Phtha	alate- Parent compound			
HERO ID:	680063				
Domain		Metric	Rating	Comments	
Domain 1: Reporting Qu	ıality				
	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.	
Dennein 2. Celestien en	1 D				
Domain 2: Selection and	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					
Continued on next page					

Human Health Hazard Animal Toxicology Evaluation

		cont	tinued from p	revious page		
Study Citation: Health Outcome(s) and Reported	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. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live number of pups/litter. Administered in pups/litter of series of live number of number of pups/litter.					
Health Effect(s):	gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-					
Duration and	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 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).					
Exposure Route:			-)			
Species: Chemical:	Mouse-B6C. Dibutyl Phth	3F1 - [mouse]-Both alate- 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 Re	porting and Att	trition				
	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 M	ethods Sensitiv	ity				
		Con	tinued on ney	ct page		

Human Health Hazard Animal Toxicology Evaluation

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Dibutyl	Phthalate	

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Marsman, I B6C3F1 mix Reproductiv of live pups, gross necrop CoA oxidas dehydrogen: Immune/He histopatholo roids (Studi and spinal c 9)-Ocular/S bladder (Stu 9)Gastroin below) (Clin below) (Gro Oral-Diet-D Mouse-B6C Dibutyl Phtl 680063	D. S. (1995). NTP technical report on the ce. Toxicity Report Series, vol. 30 30:1-G: re/Developmental-No. fetuses/breeding gr/litter, number of pups/sex/litter, Offspring body weights, number of impse activity of dams (Studies 1, 2, 3, and ase, bile acids, and glucose), Histopatho matological-Hematology, thymus weights, bogy of heart (Studies 8 and 9)Other (ple es 8 and 9)-Musculoskeletal-Histopatholocord/sciatic nerve (Studies 8 and 9)Lung/ensory-Histopathology of eyes (Studies 8 and 9).Absolute and relative kidne itestinal-Histopathology of stomach, gall bnical chemistry)-Creatine kinase (Studies: boss necropsy)-Gross necropsy (Study 8 and 9)-Alsolute and puration: Chronic (>90 days)-7-13-week(staftal-Parent compound	toxicity stud 5. roup, Litter w clinical obse lantation sites 4).Serum ch logy of liver histopatholog ase specify be gy of femur a (Respiratory-F and 9)Renal y weights (Stro bladder, large 8, 9, 10, and Study9).	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- emistry (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol (Studies 8 and 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11) gy (thymus, lymph nodes, and spleen) (Studies 8 and 9)Cardiovascular-Heart weight, elow) (Endocrine)-Histopathology of pancreas, pituitary, adrenal gland, and parathy- and thigh muscle (Studies 8 and 9)-Neurological/Behavioral-Histopathology of brain Histopathology of lungs, esophagus, nasal cavity, pharynx, and trachea (Studies 8 and /Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and /Kidney-Clinical chemistry (BUN, creatinine), Histopathology of skin (Studies 8 and intestine, small intestine, and salivary gland (Studies 8 and 9)Other (please specify 11)Thyroid-Histopathology of thyroid (Study 8 and Study 9)Other (please specify	
Domain		Metric	Rating	Comments	
	Metric 6: Metric 7:	Chemical administration and characterization Exposure timing, frequency, and duration	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. Animals were dosed via the diet for 13-weeks. This is consistent with similar study types (OECD 408).	
Domain 6: Outcome M	leasures and Re Metric 8:	sults Display Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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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Human Health Hazard Animal Toxicology Evaluation

	•	continued from p	revious page				
Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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)						
Duration and Exposure Route: Species: Chemical: HERO ID:	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 parathy- roids (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 skiney 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). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s) Mouse-B6C3F1 - [mouse]-Both Dibutyl Phthalate- Parent compound						
Domain	Metric	Rating	Comments				
	Metric 9: Results presentation	Medium	Endpoint summary tables quantitatively reported data for most endpoints as means \pm 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 Qualit	y Determination	High					

Study Citation:	Marsman, D B6C3F1 mic	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-Su	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).					
Duration and Exposure Route:	Oral-Diet-D	uration: Chronic (>90 days)-7-13-week(s)					
Species:	Mouse-B6C	3F1 - [mouse]-Both					
Chemical: HERO ID:	Dibutyl Phth 680063	alate- Parent compound					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Q	uality						
	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 an	d Darformanca						
Domain 2. Selection and	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 2: Confounding	y / Variabla Co	atral					
Domain 3: Confounding	Metric 4:	ttroi 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 Re	porting and Att	rition					
	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 M	ethods Sensitiv	ity					
Continued on next page							

Dibutyl Phthalate

	continued from previous page							
Study Citation:	Marsman, D B6C3F1 mic	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 B6C3E1 mice. Toxicity Report Series, vol. 30.30:1-65						
Health Outcome(s)	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).							
and Reported								
Duration and	Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s)							
Exposure Route:								
Species:	Mouse-B6C	3F1 - [mouse]-Both						
Chemical:	Dibutyl Phth	alate- 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 M	easures and Rev	sulte Dienlay						
Domain 0. Outcome M	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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	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 P6C2E1 mine. Toxicity Panett Series vol. 20 20:1-C5					
Health Outcome(s) and Reported Health Effect(s):	Nutritional/N gain (Studies	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	Oral-Diet-Du	uration: Chronic (>90 days)-7-13-week(s)					
Exposure Route: Species: Chemical: HERO ID:	Mouse-B6C3 Dibutyl Phth 680063	3F1 - [mouse]-Both alate- Parent compound					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Qu	uality 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	d 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	r / Variable Cor	ntrol					
	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 Rep	porting and Att	rition					
	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 Me	ethods Sensitiv	ity					
Continued on next page							

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Dibutyl Phthalate

HERO ID: 680063 Table: 35 of 35

		cont	inued from p	orevious page	
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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 an B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 weig gain (Studies 5, 6, 7, and 12). Oral-Diet-Duration: Chronic (>90 days)-7-13-week(s) Mouse-B6C3F1 - [mouse]-Both Dibutyl Phthalate- Parent compound 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 M	easures and Re	esults Display			
	Metric 8:	Endpoint sensitivity and specificity	High	Aside from USFDA Good Laboratory Practices regulations (21 CFR, Part 58), no par- ticular 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-v	veek feed study in mice			
Overall Quali	ty Deter	mination	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 disconcert phthalate (DINR) in gestation and lactation on male ret sexual development. Reproductive Toxicology 35(Elsevier):70-80
Health Outcome(s) and Reported	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
Health Effect(s):	(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 DND2 surve
Duration and	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Exposure Route:	
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 experi- mental 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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Human Health Hazard Animal Toxicology Evaluation

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) 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 and Reported Health Effect(s): (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 Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14) **Exposure Route:** 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

Domain 4: Selective Reporting and Attrition

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negative control response was adequate for the endpoints assessed.

Human Health Hazard Animal Toxicology Evaluation

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Dibutyl Phthalate

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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
Health Outcome(s)	disononyl phthalate (DINP) in gestation and lactation on male rat sexual development. Reproductive Toxicology 35(Elsevier):/0-80. Nutritional/Metabolic-Body weight, body weight gain, food consumption-Reproductive/Developmental-Number of litters; number of live pups; number
and Reported	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
Health Effect(s):	(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	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Exposure Route:	
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 eval- uation 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 ex- ample, 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 in- fluence 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

Human Health Hazard Animal Toxicology Evaluation

Dibutyl Phthalate

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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)	Nutritional/Metabolic-Body weight, body weight gain, food consumption-Reproductive/Developmental-Number of litters; number of live pups; number
and Reported	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
Health Effect(s):	(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	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Exposure Route:	
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 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 in- terest 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 organo- genesis (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 follow- ing 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 ex- pose 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

Human Health Hazard Animal Toxicology Evaluation

Dibutyl Phthalate

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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
	disononyl phthalate (DINP) in gestation and lactation on male rat sexual development. Reproductive Toxicology 35(Elsevier):70-80.
Health Outcome(s)	Nutritional/Metabolic-Body weight, body weight gain, food consumption-Reproductive/Developmental-Number of litters; number of live pups; number
and Reported	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
Health Effect(s):	(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	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Exposure Route:	
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 eval- uated. 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 af- fected 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 disononyl phthalate (DINP) in gestation and lactation on male rat sexual development. Reproductive Toxicology 35(Elsevier):70-80
Health Outcome(s)	Nutritional/Metabolic-Body weight, body weight gain, food consumption-Reproductive/Developmental-Number of litters: number of live pups: number
and Reported	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
Health Effect(s):	(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	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Exposure Route:	
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1325348

Domain		Metric	Rating	Comments
Domain 1: Reporting Qua	lity			
	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 H	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 experi- mental 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

Human Health Hazard Animal Toxicology Evaluation

Dibutyl Phthalate

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)	Nutritional/Metabolic-Body weight, body weight gain, food consumption-Reproductive/Developmental-Number of litters; number of live pups; number
and Reported	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
Health Effect(s):	(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	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Exposure Route:	
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 in- troduce 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 Repo	orting and At	trition		
	Metric 5:	Selective Reporting and Attrition	Medium	The study reports the results for all prespecified outcomes, exposure groups, and eval- uation 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 groups 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 ex- ample, 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 in- fluence 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.

Human Health Hazard Animal Toxicology Evaluation

... continued from previous page **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) 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 and Reported Health Effect(s): (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 Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14) **Exposure Route:** Species: Rat-Sprague-Dawley - [rat]-Female Chemical: Dibutyl Phthalate- Parent compound **HERO ID:** 1325348 Domain Metric Rating Comments Domain 5: Exposure Methods Sensitivity Chemical administration and Medium Metric 6: 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 characterization 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 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 duration 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;

Continued on next page ...

considered a study deficiency.

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

Human Health Hazard Animal Toxicology Evaluation

Dibutyl Phthalate

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Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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 PDN2 nume:
Duration and	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-23)-F0- lactation (PND 0-14)
Exposure Route:	
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	1325348

Domain		Metric	Rating	Comments
Domain 6: Outcome	Measures and Re	esults 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 eval- uated. 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 af- fected and the total numbers of animals examined.
Additional Comment	s: None			

Overall Quality Determination

Medium

Study Citation:	Furr, J. R., I	ambright, 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		
Health Outcome(s) and Reported	 m the phthalate adverse outcome pathway, to predict disruption of sexual differentiation. Toxicological Sciences 140(2):403-424. Reproductive/Developmental-Male Reproductive - testosterone oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (GD14- GD18) oute: Rat-Sprague-Dawley - [rat]-Both Dibutyl Phthalate- Parent compound 2510906 Linked HERO ID(s): 2510906, 3045543 					
Health Effect(s): Duration and Exposure Route:						
Species: Chemical: HERO ID:						
Domain		Metric	Rating	Comments		
Domain 1: Reporting Qu	uality Metric 1:	Reporting Quality	High	Good. Important information is provided for test animals, exposure methods, experi- mental design, endpoint evaluations, and the presentation of results.		
Domain 2: Selection and Performance						
Domain 2. Selection and	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 normaliza-		
	Metric 3:	Observational Bias / Blinding Changes	Medium	tion procedures were performed to balance important variables across groups. 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	r / Variable Co	ntrol				
	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 1: Selective Re	porting and At	trition				
	Metric 5:	Selective Reporting and Attrition	Medium	Adequate. All endpoints described in methods were reported qualitatively or quantita- tively. 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 Me	ethode Sensitiv					
	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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Dibutyl Phthalate

continued from previous page						
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)	Reproductive/Developmental-Male Reproductive - testosterone					
and Reported						
Health Effect(s):	Oral Causes Duration, Remachative/Davalenmental EQ. sostation (CD14, CD18)					
Exposure Route	Ofal-Gavage	-Duration. Reproductive/Developmental-I	ro - gestation	(0D14- 0D18)		
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 Me	easures and Res	sults 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 indi- vidual 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 validated by	: High confidence. This study was well- authors to have sufficient statistical power	designed to for this anal	evaluate effects on fetal testicular testosterone. The sample size was small, but was ysis. Evidence was presented clearly and transparently.		

Overall Quality Determination

High

Health Outcome(s) and Reported Health Effect(s):	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. Reproductive/Developmental-Fetal testosterone production ex vivo						
Duration and	Oral-Gavag	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD14-GD18)					
Exposure Route: Species:	Rat-Other (Harlan Sprague Dawley)-Female						
Chemical:	Dibutyl Pht	halate- Parent compound					
HERO ID:	9419406 Li	nked HERO ID(s): 9419406, 12162058					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Q	uality 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	d 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 as- sessment. However, the outcome of interest was measured using standard laboratory kits.			
Domain 3: Confounding	a / Variable Co	nntrol					
	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 dis- ruption. 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 poly-carbonate rather than metal cages. The experimental conditions described provided no indication of different practices across treatment groups.			
Domain 4: Selective Re	porting and A	ttrition					
	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.			

Dibutyl Phthalate

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HERO ID: 9419406 Table: 1 of 1

		cont	inued from p	revious page		
Study Citation:	Gray, L. E., Hormonal E Unique Ady	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 Advarse Outcome Pathway. Toxicological Sciences 182(2):105–214				
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Fetal testosterone production ex vivo					
Duration and Exposure Route:	Oral-Gavage	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD14-GD18)				
Species: Chemical: HERO ID:	Rat-Other (Harlan Sprague Dawley)-Female Dibutyl Phthalate- Parent compound 9419406 Linked HERO ID(s): 9419406, 12162058					
Domain	Metric Rating Comments					
Domain 5: Exposure M	ethods Sensitiv	vity	C			
	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 M	easures and Re	esults 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 Quali	ty Deteri	nination	High			

Study Citation: Health Outcome(s) and Reported Health Effect(s):	 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 n phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicolog 105(1):153-165. Health Outcome(s) and Reported Health Effect(s): 						
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 8-18)						
Species:	Rat-Sprague-Dawley - [rat]-Both						
Chemical:	Dibutyl Phth	alate- Parent compound					
	075200						
Domain Domain 1: Reporting Or	ality	Metric	Rating	Comments			
	Metric 1:	Reporting Quality	High	Good. All critical and most important information was reported. Reported informa- tion included information on the test substance (name, source, purity), the test model (species, strain, sex, and source, animal husbandry details (animals per cage, photope- riod, 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. Salastian and	l Daufauman aa						
Domain 2: Selection and	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 normal- ization 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 2. Confounding	Wariahla Ca	ntanl					
	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.			

Dibutyl Phthalate

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Study Citation:	Howdeshell phthalate es 105(1):153-	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 fiv phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicological Science 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: Chemical: HERO ID:	Rat-Sprague-Dawley - [rat]-Both Dibutyl Phthalate- Parent compound 675206						
Domain		Metric	Rating	Comments			
	Metric 5:	Selective Reporting and Attrition	Medium	Adequate. All endpoints described in methods were reported qualitatively or quantita- tively. All dams/litters are accounted for in the maternal weight gain, litter size, resorp- tions, 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 N	Iethods Sensiti	vity					
	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 M	leasures and R a	culte Dieplay					
	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 ana- lyzed or presented. Additional results are provided in a supplemental file.			

Overall Quality Determination

High

		continued from previous page	2			
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)	Reproductive/Developmental-Male reproduct	ive - testosterone				
and Reported						
Health Effect(s):						
Duration and	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 8-18)					
Exposure Route:						
Species:	Rat-Sprague-Dawley - [rat]-Both					
Chemical:	Dibutyl Phthalate- Parent compound					
HERO ID:	675206					
Domain	Metric	Rating	Comments			

Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. Reproductive/Developmental-Fetal testosterone						
Duration and	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (GD19)						
Exposure Route: Species: Chemical: HERO ID:	Rat-Sprague Dibutyl Phth 675949	Rat-Sprague-Dawley - [rat]-Female Dibutyl Phthalate- Parent compound 675949					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Q	uality Metric 1:	Reporting Quality	Medium	The test substance was identified as dibutyl phthalate (DBP). The source of the test sub- stance was identified (Aldrich Chemical Co., Milwaukee, WI). The study states that the purity and concentration of the dosing solutions were verified by gas chromatogra- phy 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. Hus- bandry conditions (temperature, humidity, light cycle) were reported. The number of an- imals/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 in- formation was reported; although some important information was not reported, it is not expected to significantly impact the study evaluation.			
Domain 2: Selection and	d Performance Metric 2: Metric 3:	Allocation Observational Bias / Blinding Changes	Medium 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 fe- tuses/litter were used for analysis; the study authors do not report how the offspring were selected (if random). 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	g / Variable Co	ntrol					
	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 develop- mental and reproductive health problems. This could potentially confound results. Simi- larly, 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 Re	porting and At	trition					
		Contin	ued on next pa	ge			

		cont	inued from previo	ous page			
Study Citation: Health Outcome(s)	Johnson, K. dibutyl phth Reproductiv	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. Reproductive/Developmental-Fetal testosterone					
and Reported Health Effect(s): Duration and	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (GD19)						
Exposure Route:							
Species:	Rat-Sprague-Dawley - [rat]-Female						
Chemical: HERO ID:	Dibutyl Pht 675949	halate- Parent compound					
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 N	Iethods Sensitiv	vity					
	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 M	leasures and Re	esults 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 to	estosterone was evaluated for data quality.					
Overall Ouali	ity Deter	mination	Medium				

Study Citation:	Johnson, K. inhibition of	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	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD12-20)					
Species: Chemical: HERO ID:	Rat-Sprague-Dawley - [rat]-Female Dibutyl Phthalate- Parent compound 788312						
Domain		Metric	Rating	Comments			
Domain 1: Reporting Q	uality Metric 1:	Reporting Quality	Low	All critical and some important information was reported. Reported information in- cluded information on the test substance (name and source), the test model (species, strain, sex, and source), animal husbandry details (food and water availability), ex- posure methods, experimental design, endpoint evaluations, and presentation of re- sults. 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	d 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	g / Variable Co	ntrol					
	Metric 4:	Confounding / Variable Control	Medium	A negative corn oil control group was included. Consistency of other potentially con- founding 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 Re	porting and At	trition					
	Metric 5:	Selective Reporting and Attrition	Medium	The total number of dams included in each test group was not specified in the meth- ods. 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 pro- vide enough information to determine attrition or selective reporting.			
Domain 5: Exposure Mo	ethods Sensitiv	ity					
		Contin	nued on next pa	ge			

Dibutyl Phthalate

	continued from previous page					
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	Johnson, K. inhibition of Reproductiv Oral-Gavage	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. Reproductive/Developmental-Fetal testosterone levels Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD12-20)				
Species:	Rat-Sprague	Rat-Sprague-Dawley - [rat]-Female				
Chemical:	Dibutyl Phtl 788312	halate- Parent compound				
	700312					
Domain		Metric	Rating	Comments		
	Wette 0.	characterization	Low	The test material source (Sigina) was reported. The purity and certificates 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 M	leasures and Re	esults 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 \pm SD. Statistical signifi-		

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

Overall Quality Determination

Medium

cance and sample sizes were noted. There is no indication that the litter was used as the

experimental unit. Individual animal data were not provided.

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 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. Reproductive/Developmental-Ex vivo fetal testicular testosterone Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD14-18) Rat-Sprague-Dawley - [rat]-Female Dibutyl Phthalate- Parent compound 11785000 			
Domain	molity	Metric	Rating	Comments
Domain 1: Reporting Q	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 an	d Performance			
	Metric 2:	Allocation	High	This study is considered High for Domain 2.1. The dams were weight-ranked and ran- domly 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	g / Variable Cor	ntrol		comes were not subjective and based on the use of automated/computer-driven system (LC-MS).

Dibutyl Phthalate

		cont	inued from previ	ous page		
Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. Reproductive/Developmental-Ex vivo fetal testicular testosterone					
Duration and Exposure Route:	Oral-Gavage	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD14-18)				
Species: Chemical: HERO ID:	Rat-Sprague-Dawley - [rat]-Female Dibutyl Phthalate- Parent compound 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 Re	porting and At	trition				
	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 M	ethods Sensitiv	ity				
	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.		

Dibutyl Phthalate

continued from previous page					
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species:	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. Reproductive/Developmental-Ex vivo fetal testicular testosterone Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD14-18) Pat Sprague Dawlay [rat] Famale				
Chemical:	Dibutyl Phth	alate- Parent compound			
Domain	11785000	Metric	Pating	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 mea- sure 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. How- ever, 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 Me	asures and Res	sults Display			
	Metric 8:	Endpoint sensitivity and specificity	Medium	The study is considered Medium for Domain 6.1. The doses were justified by the au- thors, but only one dose per chemical was used. Outcome assessment methodolo- gies 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 fe- males/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 end- point. Data were analyzed and presented appropriately and included statistical signif- icance. 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: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 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. Reproductive/Developmental-Male Reproductive - testosterone Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 18) Rat-Sprague-Dawley - [rat]-Both Dibutyl Phthalate- Parent compound 1321665 			
Domain		Metric	Rating	Comments
Domain 1: Reporting Qu	uality 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	l 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 Con	trol		

Dibutyl Phthalate

		cor	ntinued from p	revious page	
Study Citation: Health Outcome(s) and Reported	 Kuhl, A. J., Ross, S. M., Gaido, K. W. (2007). CCAAT/enhancer binding protein beta, but not steroidogenic factor-1, modulates the phthalate-induce dysregulation of rat fetal testicular steroidogenesis. Endocrinology 148(12):5851-5864. Reproductive/Developmental-Male Reproductive - testosterone Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 18) Rat-Sprague-Dawley - [rat]-Both 				
Health Effect(s): Duration and Exposure Route: Species:					
Chemical: HERO ID:	Dibutyl Pht 1321665	halate- Parent compound			
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 Re	eporting and Al Metric 5:	ttrition Selective Reporting and Attrition	Low	Deficient. Sample size is not reported for the testosterone concentration results. Re- sults 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 repli- cates 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 M	lethods Sensitiv Metric 6:	vity 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 pre- sumably 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 ver- ified with gas chromatography. Due to the lack of information on test substance purity and preparation methods, this metric is rated as low.	
		Co	ntinued on nex	xt page	

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HERO ID: 1321665 Table: 1 of 1

		cont	inued from p	revious page	
Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. Reproductive/Developmental-Male Reproductive - testosterone				
Duration and Exposure Route:	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 18)				
Species: Chemical: HERO ID:	Rat-Sprague-Dawley - [rat]-Both Dibutyl Phthalate- Parent compound 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 M	easures and Re	esults Display			
	Metric 8:	Endpoint sensitivity and specificity	Medium	Adequate. No concerns were identified regarding the specificity and validity of the pro- tocol used for measuring fetal testosterone concentrations. Testosterone was measured based on an assay method published previously (multiple reports cited) and using a com- mercial radioimmunoassay kit according to the manufacturer's instructions. Timing of endpoint analysis (24 hours after control or test substance treatment) appears to be ap- propriate 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 re- ported 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 treat- ment 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 lit- ters. 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			
Continued on next page				

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Dibutyl Phthalate

HERO ID: 1321665 Table: 1 of 1

continued from previous page					
Study Citation:	Kuhl, A. J., Ross, S. M., Gaido, K. W. (200 dysregulation of rat fetal testicular steroidog	07). CCAAT/enhancer binding prote enesis. Endocrinology 148(12):5851	vin beta, but not steroidogenic factor-1, modulates the phthalate-induced -5864.		
Health Outcome(s)	Reproductive/Developmental-Male Reprodu	ctive - testosterone			
and Reported					
Health Effect(s):					
Duration and	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 18)				
Exposure Route:					
Species:	Rat-Sprague-Dawley - [rat]-Both				
Chemical:	Dibutyl Phthalate- Parent compound				
HERO ID:	1321665				
Domain	Metric	Rating	Comments		

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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 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) Mouse-CD-1 - [mouse]-Both Dibutyl Phthalate- Parent compound 61566			
Domain		Metric	Rating	Comments
Domain 1: Reporting Qu	ality			
	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	Derformance			
Domain 2. Selection and	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 Con Metric 4:	trol 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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HERO ID: 61566 Table: 1 of 7

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Study Citation: Health Outcome(s)	Lamb, J., C Pharmacolo Reproductiv	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. Reproductive/Developmental-Organ weight (testis, epididymis, prostate, seminal vesicles, ovaries including the oviducts, uterus); Histopathology (testis, erididymis, prostate, seminal vesicles). Severe property (arrest of motils energy and arrested of the severe of the se						
Health Effect(s).	abnormal sr	abnormal sperm);Mating and fertility indices (copulatory plug, number of fertile pairs/number cohabitated, litter/pair);F1: live pup body weight, sex ratio,						
Duration and Exposure Route:	abnormal sperm);Mating and fertility indices (copulatory plug, number of fertile pairs/number conabitated, http://pair.jrif.ive.pup body weight, sex ratio, proportion of pups born alive, number of live pups/litter 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-	Mouse-CD-1 - [mouse]-Both						
Chemical:	Dibutyl Pht	halate- 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 M	ethods Sensitiv	vity						
Ţ	Metric 6:	Chemical administration and characterization	Low	The source of the test substance was reported. The purity of the test substance was in- dependently 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 com- pound 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 pre- vious 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 M	essures and Re	eulte Dienlay						
Domain 0. Outcome M	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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HERO ID: 61566 Table: 1 of 7

	continued from previous page						
Study Citation:	Lamb, J., C	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied					
	Pharmacolo	gy 88(2):255-269.					
Health Outcome(s)	Reproductiv	/e/Developmental-Organ weight (testi	s, epididymis, pro	state, seminal vesicles, ovaries including the oviducts, uterus); Histopathology (testis,			
Hoolth Effoct(s):	abnormal sr	prostate, seminal vesicies, ovary, ovar	auci, uterus, and	vagina);Sperm parameters (percent of motife sperm, concentration and percentage of ber of fertile pairs/pumber cohobitated litter/pair);E1: live pup body weight say ratio			
Health Effect(s).	proportion (of pups born alive number of live pup	s/litter	ber of fertile paris/number conabilated, nuer/pari), 11. nve pup body weight, sex failo,			
Duration and	Oral-Diet-D	Duration: Reproductive/Developmenta	1-1-F0- premating	(7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating			
Exposure Route:	(98 days)	1 1	1 0				
Species:	Mouse-CD-	1 - [mouse]-Both					
Chemical:	Dibutyl Pht	halate- 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 \pm 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 Quali	ty Deter	mination	Low				

Study Citation:	Lamb, J., Ch	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (1987). Reproductive effects of four phthalic acid esters in the mouse. Toxicology and Applied					
Health Outcome(s) and Reported	Mortality-Mortality-Hepatic/Liver-Liver weight-Neurological/Behavioral-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight						
Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Oral-Diet-Du (98 days) Mouse-CD- Dibutyl Phth 61566	Dral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating 98 days) Mouse-CD-1 - [mouse]-Both Dibutyl Phthalate- Parent compound 51566					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Qu	uality 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	d 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	g / Variable Cor	ntrol					
	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 plas- ticizers. 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 im- pact 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.			

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Dibutyl Phthalate

		conti	nued from previ	ous page		
Study Citation:	Lamb, J., C Pharmacolo	Chapin, R., Teague, J., Lawton, A., Reel, J.	(1987). Reprodu	active effects of four phthalic acid esters in the mouse. Toxicology and Applied		
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: Species: Chemical: HERO ID:	Oral-Diet-D (98 days) Mouse-CD- Dibutyl Phtl 61566	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) Mouse-CD-1 - [mouse]-Both Dibutyl Phthalate- Parent compound				
Domain	01500	Metric	Dating	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 M	lethods Sensitiv	vity				
Domani J. Exposure M	Metric 6: Metric 7:	Chemical administration and characterization Exposure timing, frequency, and duration	Low Low	The source of the test substance was reported. The purity of the test substance was in- dependently 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 com- pound 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. 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 pre- vious 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 occues to sufficiently detect adverse		
				effects or for males to have adequate time for the maturing of spermatozoa.		
Domain 6: Outcome M	easures and Re	esults 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., C Pharmacolo	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	Oral-Diet-D	Duration: Reproductive/Developmental	I-1-F0- premating (7 day	ys)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating		
Exposure Route:	(98 days)	· ·				
Species:	Mouse-CD-	-1 - [mouse]-Both				
Chemical:	Dibutyl Pht	halate- 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 Quali	ty Deteri	mination	Medium			

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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						
Health Outcome(s) and Reported	Pharmacolog Mortality-M	Pharmacology 88(2):255-269. Mortality-Mortality-Hepatic/Liver-Liver weight-Neurological/Behavioral-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight					
Duration and Exposure Route: Species: Chemical: HERO ID:	Oral-Diet-D (98 days) Mouse-CD- Dibutyl Phth 61566	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) (98 days) Mouse-CD-1 - [mouse]-Both Dibutyl Phthalate- Parent compound 61566					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Qu	uality Metric 1:	Reporting Quality	Medium	The chemical was identified by name (CASRN was not provided). The source and pu- rity (>99%) were reported. Test animal species, strain, sex, age, and source were re- ported. 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 quantita- tive data.			
Domain 2: Selection and	l Performance	Allocation	Hich				
	Methic 2.	Anocation	nigii	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	g / Variable Co	ntrol					
	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.			

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Dibutyl Phthalate

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Study Citation:	Lamb, J., C Pharmacolo	Chapin, R., Teague, J., Lawton, A., Reel, J.	(1987). Reprodu	active effects of four phthalic acid esters in the mouse. Toxicology and Applied		
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: Species: Chemical: HERO ID:	Oral-Diet-D (98 days) Mouse-CD- Dibutyl Phtl 61566	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) Mouse-CD-1 - [mouse]-Both Dibutyl Phthalate- Parent compound				
Domain	01500	Metric	Dating	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 M	lethods Sensitiv	vity				
Domani J. Exposure M	Metric 6: Metric 7:	Chemical administration and characterization Exposure timing, frequency, and duration	Low Low	The source of the test substance was reported. The purity of the test substance was in- dependently 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 com- pound 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. 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 pre- vious 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 occues to sufficiently detect adverse		
				effects or for males to have adequate time for the maturing of spermatozoa.		
Domain 6: Outcome M	easures and Re	esults 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., Cl Pharmacolog	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	Oral-Diet-D	uration: Reproductive/Development	al-1-F0- premating (7 da	ys)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating		
Exposure Route:	(98 days)					
Species:	Mouse-CD-1	l - [mouse]-Both				
Chemical:	Dibutyl Phth	alate- 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						
Health Outcome(s) and Reported	Pharmacolog Mortality-M	Pharmacology 88(2):255-269. Mortality-Mortality-Hepatic/Liver-Liver weight-Neurological/Behavioral-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight					
Duration and Exposure Route: Species: Chemical: HERO ID:	Oral-Diet-D (98 days) Mouse-CD- Dibutyl Phth 61566	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) (98 days) Mouse-CD-1 - [mouse]-Both Dibutyl Phthalate- Parent compound 61566					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Qu	uality Metric 1:	Reporting Quality	Medium	The chemical was identified by name (CASRN was not provided). The source and pu- rity (>99%) were reported. Test animal species, strain, sex, age, and source were re- ported. 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 quantita- tive data.			
Domain 2: Selection and	l Performance	Allocation	Hich				
	Methic 2.	Anocation	nigii	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	g / Variable Co	ntrol					
	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.			

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Dibutyl Phthalate

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Study Citation:	Lamb, J., C Pharmacolo	Chapin, R., Teague, J., Lawton, A., Reel, J.	(1987). Reprodu	active effects of four phthalic acid esters in the mouse. Toxicology and Applied		
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: Species: Chemical: HERO ID:	Oral-Diet-D (98 days) Mouse-CD- Dibutyl Phtl 61566	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) Mouse-CD-1 - [mouse]-Both Dibutyl Phthalate- Parent compound				
Domain	01500	Metric	Dating	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 M	lethods Sensitiv	vity				
Domani J. Exposure M	Metric 6: Metric 7:	Chemical administration and characterization Exposure timing, frequency, and duration	Low Low	The source of the test substance was reported. The purity of the test substance was in- dependently 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 com- pound 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. 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 pre- vious 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 occues to sufficiently detect adverse		
				effects or for males to have adequate time for the maturing of spermatozoa.		
Domain 6: Outcome M	easures and Re	esults 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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Dibutyl Phthalate

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Study Citation:	Lamb, J., Cl Pharmacolog	napin, R., Teague, J., Lawton, A., gy 88(2):255-269.	Reel, J. (1987). Reprodu	ctive effects of four phthalic acid esters in the mouse. Toxicology and Applied	
Health Outcome(s) and Reported Health Effect(s):	Mortality-M	ortality-Hepatic/Liver-Liver weight	t-Neurological/Behavioral	-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight	
Duration and Exposure Route: Species: Chemical:	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) (98 days) Mouse-CD-1 - [mouse]-Both 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						
Health Outcome(s) and Reported	Pharmacolog Mortality-M	Pharmacology 88(2):255-269. Mortality-Mortality-Hepatic/Liver-Liver weight-Neurological/Behavioral-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight					
Duration and Exposure Route: Species: Chemical: HERO ID:	Oral-Diet-D (98 days) Mouse-CD- Dibutyl Phth 61566	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) (98 days) Mouse-CD-1 - [mouse]-Both Dibutyl Phthalate- Parent compound 61566					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Qu	uality Metric 1:	Reporting Quality	Medium	The chemical was identified by name (CASRN was not provided). The source and pu- rity (>99%) were reported. Test animal species, strain, sex, age, and source were re- ported. 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 quantita- tive data.			
Domain 2: Selection and	l Performance	Allocation	Hich				
	Methic 2.	Anocation	nigii	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	g / Variable Co	ntrol					
	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.			

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Dibutyl Phthalate

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Study Citation:	Lamb, J., C Pharmacolo	Chapin, R., Teague, J., Lawton, A., Reel, J.	(1987). Reprodu	active effects of four phthalic acid esters in the mouse. Toxicology and Applied			
Health Outcome(s) and Reported Health Effect(s):	Mortality-M	Mortality-Mortality-Hepatic/Liver-Liver weight-Neurological/Behavioral-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight					
Duration and Exposure Route: Species: Chemical: HERO ID:	Oral-Diet-D (98 days) Mouse-CD- Dibutyl Phtl 61566	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) (98 days) Mouse-CD-1 - [mouse]-Both Dibutyl Phthalate- Parent compound					
Domain	01500	Metric	Dating	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 M	lethods Sensitiv	vity					
Domani J. Exposure M	Metric 6: Metric 7:	Chemical administration and characterization Exposure timing, frequency, and duration	Low Low	The source of the test substance was reported. The purity of the test substance was in- dependently 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 com- pound 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. 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 pre- vious 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 occues to sufficiently detect adverse			
				effects or for males to have adequate time for the maturing of spermatozoa.			
Domain 6: Outcome M	easures and Re	esults 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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Dibutyl Phthalate

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Study Citation:	Lamb, J., Cl Pharmacolog	napin, R., Teague, J., Lawton, A., I 3y 88(2):255-269.	Reel, J. (1987). Reprodu	ctive effects of four phthalic acid esters in the mouse. Toxicology and Applied
Health Outcome(s) and Reported Health Effect(s):	Mortality-M	ortality-Hepatic/Liver-Liver weight	-Neurological/Behaviora	-Brain weight-Other (please specify below) (Endocrine)-Pituitary weight
Duration and	Oral-Diet-D	uration: Reproductive/Development	al-1-F0- premating (7 da	ys)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating
Exposure Route:	(98 days)			
Species:	Mouse-CD-1	l - [mouse]-Both		
Chemical:	Dibutyl Phth	alate- 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

Health Outcome(s)	Pharmacolog	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.					
and Reported	Other (please specify below) (Clinical signs)-Clinical signs of toxicity						
Duration and Exposure Route: Species: Chemical:	Oral-Diet-Du (98 days) Mouse-CD-1 Dibutyl Phtha	ration: Reproductive/Developmental-1-F0- - [mouse]-Both alate- Parent compound	premating (7 da	ys)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating			
HERO ID:	01500						
Domain	1;+	Metric	Rating	Comments			
	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 H	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 Con	trol					
	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 plas- ticizers. 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 im- pact 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.			

Dibutyl Phthalate

		conti	nued from previ	ous page		
Study Citation: Health Outcome(s)	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. Other (please specify below) (Clinical signs)-Clinical signs of toxicity					
and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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) Mouse-CD-1 - [mouse]-Both Dibutyl Phthalate- Parent compound 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 Me	ethods Sensitiv	vity				
	Metric 6:	Chemical administration and characterization	Low	The source of the test substance was reported. The purity of the test substance was in- dependently 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 com- pound 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 pre- vious 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.		
Demain (, Outerma M.						
Domani o. Outcome Me	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					

Dibutyl Phthalate

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Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A., Reel, J. (19	87). Reproductive effects of four	phthalic acid esters in the mouse. Toxicology and Applied
	Pharmacology 88(2):255-269.		
Health Outcome(s)	Other (please specify below) (Clinical signs)-Clinical signs	of toxicity	
and Reported			
Health Effect(s):			
Duration and	Oral-Diet-Duration: Reproductive/Developmental-1-F0- pr	remating (7 days)-F0- mating (98	days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating
Exposure Route:	(98 days)		
Species:	Mouse-CD-1 - [mouse]-Both		
Chemical:	Dibutyl Phthalate- Parent compound		
HERO ID:	61566		
Domain	Metric	Rating	Comments
		_	

Overall Quality Determination

Medium

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HERO ID: 61566 Table: 7 of 7

Study Citation:	Lamb, J., C Pharmacolo	hapin, R., Teague, J., Lawton, A., Reel, J. 99, 88(2):255-269.	(1987). Re	productive effects of four phthalic acid esters in the mouse. Toxicology and Applied			
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight and food intake						
Duration and Exposure Route: Species:	Oral-Diet-D (98 days) Mouse-CD- Dibutyl Phtl	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) (98 days) Mouse-CD-1 - [mouse]-Both					
HERO ID:	61566	larate- i arent compound					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Q	Juality						
	Metric 1:	Reporting Quality	Medium	The chemical was identified by name (CASRN was not provided). The source and pu- rity (>99%) were reported. Test animal species, strain, sex, age, and source were re- ported. 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 quantita- tive data.			
Domain 2: Selection an	d Performance						
Domain 2. Selection an	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: Confoundin	σ / Variable Co	ntrol					
	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 plas- ticizers. 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 im- pact 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: Salaativa Da	morting and At	trition					
Domain 4. Selective Re	porting and At						

		con	tinued from p	revious page		
Study Citation:	Lamb, J., C Pharmacolo	hapin, R., Teague, J., Lawton, A., Reel, 9y 88(2):255-269	J. (1987). Rej	productive effects of four phthalic acid esters in the mouse. Toxicology and Applied		
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight and food intake					
Duration and Exposure Route: Species:	Oral-Diet-D (98 days) Mouse-CD-	Puration: Reproductive/Developmental-1-	F0- premating	(7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating		
HERO ID:	61566	nalate- Parent compound				
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 N	Iethods Sensitiv	vity				
·	Metric 6:	Chemical administration and characterization	Low	The source of the test substance was reported. The purity of the test substance was in- dependently 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 com- pound 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 pre- vious 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 M	leasures and Re	sults 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.		
		Cor	ntinued on nex	cessive death was not observed at the highest dose and adverse effec at the lowest dose. Outcome methodologies were not adequately rep measurements for food intake and body weights were not reported. ct page		

		continued from p	revious page		
Study Citation:	Lamb, J., Chapin, R., Teague, J., Lawton, A. Pharmacology 88(2):255-269	, Reel, J. (1987). Rep	productive effects of four phthalic acid esters in the mouse. Toxicology and Applied		
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight and food intake				
Duration and	Oral-Diet-Duration: Reproductive/Developme	ntal-1-F0- premating	(7 days)-F0- mating (98 days)-F0 - gestation (21)-F0- premating (7 days)-F0- mating		
Exposure Route:	(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 Qualit	ty Determination	Low			

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Lee, K. Y., Sl both sexes of Reproductive preputial sepa lobe of the pr thyroid gland istry was per (FSH), and pr Oral-Diet-Du Rat-Other (C Dibutyl Phtha 676278	hibutani, M., Takagi, H., Kato, N., Takigami rat offspring after maternal exposure during /Developmental-Number of pups, body wei aration, estrous cyclicity. Organs weighed: br rostate and seminal vesicles were weight at I ls, liver, kidneys, adrenals, testes, epidiymide formed on the pituitary gland on offspring s rolactin. aration: Reproductive/Developmental-F0 - ge D (SD) IGS)-Female alate- Parent compound	i, S., Uneyama, the period fron ghts, sex ratio, rain, liver, kidno PNW 11 and Pl es, prostate, sen sacrificed on Pl estation (GD15	C., Hirose, M. (2004). Diverse developmental toxicity of di-n-butyl phthalate in a late gestation through lactation. Toxicology 203(1-3):221-238. anogenital distance, number of nipples/areolae, day of vaginal opening, day of eys, adrenals, testes, epidiymides, ovaries and uterus; in addition, pituitary, ventral NW 20. Histopathology was performed on the following tissues: brain, pituitary, ninal vesicles, ovaries, uterus, vagina, and mammary glands. Immunohistochem- ND 21 and PNW 11 for luteinizing hormone (LH), follicle-stimulating hormone to delivery)-F0- lactation (until weaning (PND21))
Domain		Metric	Rating	Comments
Domain 1: Reporting Q	uality			
	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	d 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	g / Variable Con	trol		

Human Health Hazard Animal Toxicology Evaluation

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	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. 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, 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. Oral-Diet-Duration: Reproductive/Developmental-F0 - gestation (GD15 to delivery)-F0- lactation (until weaning (PND21))						
Species:	Rat-Other (Rat-Other (CD (SD) IGS)-Female					
Chemical:	Dibutyl Pht	halate- 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 con- tainer 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 con- founding variable. Husbandry conditions were consistent between the groups. A concur- rent 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 R	eporting and A Metric 5:	ttrition 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 N	Methods Sensiti Metric 6:	vity Chemical administration and	Low	Animals were fed a soy-free diet containing DBP (>98% pure) at various concentra-			
		characterization		tions. The study does not describe how the diet was prepared or how often. Informa- tion 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

Human Health Hazard Animal Toxicology Evaluation

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	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. 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. Immunohistochem- istry 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. Oral-Diet-Duration: Reproductive/Developmental-F0 - gestation (GD15 to delivery)-F0- lactation (until weaning (PND21))			
Snecies	Rat-Other (TD (SD) IGS)-Female		
Chemical:	Dibutyl Pht	halate- 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, partic- ularly 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 Qualit	ty Deteri	nination	Medium	

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HERO ID: 676278 Table: 2 of 2

Study Citation: Health Outcome(s) and Reported	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. Nutritional/Metabolic-Body weight and food intake of pregnant dams				
Health Effect(s): Duration and Exposure Route:	Oral-Diet-D	uration: Reproductive/Developmental-F0 - g	estation (GD15	to delivery)-F0- lactation (until weaning (PND21))	
Species: Chemical: HERO ID:	Rat-Other (C Dibutyl Phth 676278	CD (SD) IGS)-Female alate- Parent compound			
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	uality 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	d 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	g / Variable Co	ntrol			
	Metric 4:	Confounding / Variable Control	Medium	The study does not report if plastic or glass water bottles were used or the type of con- tainer 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 con- founding variable. Husbandry conditions were consistent between the groups. A concur- rent 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 ($<0.05 \text{ mg}/100g$ 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 Re	porting and Att	rition			
	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.	
Continued on next page					

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HERO ID: 676278 Table: 2 of 2

		conti	inued from previ	ous page			
Study Citation:	Lee, K. Y., both sexes of	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)	Nutritional/	Metabolic-Body weight and food intake of	pregnant dams				
Health Effect(s).							
Duration and	Oral-Diet-D	ouration: Reproductive/Developmental-F0 -	gestation (GD15	to delivery)-F0- lactation (until weaping (PND21))			
Exposure Route:							
Species:	Rat-Other (CD (SD) IGS)-Female					
Chemical:	Dibutyl Pht	halate- Parent compound					
HERO ID:	676278						
Domain		Metric	Rating	Comments			
Domain 5: Exposure M	ethods Sensitiv	vity					
	Metric 6:	Chemical administration and characterization	Low	Animals were fed a soy-free diet containing DBP (>98% pure) at various concentra- tions. The study does not describe how the diet was prepared or how often. Informa- tion 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 Me	easures and Re	esults 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, partic- ularly 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 Quali	ty Deteri	mination	Medium				

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Lehmann, K. the fetal tester Reproductive, genes and pro Oral-Gavage- Rat-Sprague- Dibutyl Phtha 674382	P., Phillips, S., Sar, M., Foster, D., P.M., C s of male rats exposed to di (n-butyl) phtha /Developmental-Testicular levels of testost teins involved in cholesterol transport and Duration: Reproductive/Developmental-1-1 Dawley - [rat]-Female ilate- Parent compound	Gaido, K. W. (20 late. Toxicologic erone (radioimm steroidogenesis (F0 - gestation (G	04). Dose-dependent alterations in gene expression and testosterone synthesis in eal Sciences 81(1):60-68. nunoassay) and lipid content (oil red O staining)Gene and protein expression of RT-PCR, Western Blot, and immunohistochemistry) D 12-19)
Domain		Metric	Rating	Comments
Domain 1: Reporting Qu	nality 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., Milwau- kee, 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, dura- tion, and route of exposure were reported. Endpoint evaluation methods were reported along with quantitative data. All critical information is provided and although some im- portant information is missing, the missing information is not expected to significantly impact the study evaluation.
Domain 2: Selection and	l Performance Metric 2:	Allocation	High	Pregnant dams were assigned to a treatment group by body weight randomization using Provantis.
	M (')		N / 1'	

	Metric 5:	Observational Blas / Blinding Changes	Medium	endpoints evaluated were either not subjective in nature (e.g., testosterone levels, body weight).
Domain 3: Confounding	g / Variable Co	ntrol		
	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 polycar- bonate cages. Polycarbonate contains BPA, which have been linking to developmental and reproductive health problems. Similarly, it is unclear if glass or plastic water bot- tles 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 Re	porting and Att Metric 5:	trition 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

Dibutyl Phthalate

Human Health Hazard Animal Toxicology Evaluation

HERO ID: 674382 Table: 1 of 2

		conti	nued from previ	ous page
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HEPO ID:	Lehmann, F the fetal tes Reproductiv genes and p Oral-Gavag Rat-Spragu Dibutyl Pht	K. P., Phillips, S., Sar, M., Foster, D., P.M., tes of male rats exposed to di (n-butyl) phth ve/Developmental-Testicular levels of testor roteins involved in cholesterol transport and e-Duration: Reproductive/Developmental-1 e-Dawley - [rat]-Female halate- Parent compound	Gaido, K. W. (20 alate. Toxicologi sterone (radioimr l steroidogenesis -F0 - gestation (C	004). Dose-dependent alterations in gene expression and testosterone synthesis in cal Sciences 81(1):60-68. nunoassay) and lipid content (oil red O staining)Gene and protein expression of (RT-PCR, Western Blot, and immunohistochemistry) GD 12-19)
Domain	074382	Metric	Rating	Comments
2.511411	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 deter- mined. 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 N	Aeasures and Re	esults 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,

Additional Comments: None

Overall Quality Determination

Medium

experimental findings.

rather than as litter means, has the potential to overestimate the statistical significance of

Study Citation:	Lehmann, K	. P., Phillips, S., Sar, M., Foster, D., P.M., Gai	ido, K. W. (2004). Dose-	dependent alterations in gene expression and testosterone synthesis in			
Health Outcome(s) and Reported Health Effect(s):	Nutritional/N	Metabolic-Body weight of dams	e. Toxicological Sciences	\$ 81(1).00-08.			
Duration and Exposure Route:	Oral-Gavage	-Duration: Reproductive/Developmental-1-F0	- gestation (GD 12-19)				
Species: Chemical: HERO ID:	Rat-Sprague Dibutyl Phth 674382	Rat-Sprague-Dawley - [rat]-Female Dibutyl Phthalate- Parent compound 674382					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Q	uality						
	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., Milwau- kee, 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, dura- tion, and route of exposure were reported. Endpoint evaluation methods were reported along with quantitative data. All critical information is provided and although some im- portant information is missing, the missing information is not expected to significantly impact the study evaluation.			
Domain 2: Selection an	d Performance						
Domain 2. Selection and	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	g / Variable Coi	ntrol					
	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 polycar- bonate cages. Polycarbonate contains BPA, which have been linking to developmental and reproductive health problems. Similarly, it is unclear if glass or plastic water bot- tles 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: Salaatiya Da	norting and Att	trition					
	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 M	ethods Sensitiv	ity					
		Со	ntinued on next page				

Human Health Hazard Animal Toxicology Evaluation

HERO ID: 674382 Table: 2 of 2

		••	. continued from previous pa	nge		
Study Citation: Health Outcome(s) and Reported Health Effect(s):	Lehmann, K the fetal test Nutritional/	K. P., Phillips, S., Sar, M., Foster, D., P.M., tes of male rats exposed to di (n-butyl) phtl Metabolic-Body weight of dams	, Gaido, K. W. (2004). Dose-(halate. Toxicological Sciences	dependent alterations in gene expression and testosterone synthesis in \$81(1):60-68.		
Duration and Exposure Route:	Oral-Gavage	Oral-Gavage-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12-19)				
Species: Chemical: HERO ID:	Rat-Sprague Dibutyl Phtl 674382	e-Dawley - [rat]-Female halate- Parent compound				
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 M	leasures and Re	sults Display				
2 shun or outcome in	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 Quali	ity Deteri	mination	Uninformative			

Study Citation:	Marsman, D	D. S. (1995). NTP technical report on the t	oxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species:	Reproductiv of live pups/ gross necrop CoA oxidase nase, bile ac Terminal bo 12). Oral-Diet-D Rat-Fischer	e/Developmental-No. fetuses/breeding gro litter, number of pups/sex/litter, Offspring c osy, offspring body weights, number of impla e activity of dams (Studies 1, 2, 3, and 4).Ser ids, and glucose), Histopathology of liver (S dy weights (Studies 1, 2, 3, and 4).Body we uration: Reproductive/Developmental-1-F0 344 - [rat]-Female	up, Litter w clinical obse intation sites um chemistr tudies 8 and ight, feed co - gestation (regisht; Gestation length, number of pups/litter, number of live pups/litter, percentage grvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, s, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- y (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydroge- 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)Nutritional/Metabolic- onsumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and (20 days)
Chemical:	Dibutyl Phtl	nalate- Parent compound		
HERO ID:	680063			
Domain		Metric	Rating	Comments
Domain 1: Reporting Q	uality			
	Metric 1:	Reporting Quality	Medium	All critical and most important information was reported in this study. The study in- cluded identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (tempera- ture, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (fre- quency 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 an	d 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 mod- ifying factors across groups were noted by the study authors. In addition, for this ex- periment, 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	g / Variable Co	ntrol		
	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.
		Contin	nued on ney	xt page

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Human Health Hazard Animal Toxicology Evaluation

HERO ID: 680063 Table: 1 of 34

		con	tinued from p	revious page
Study Citation: Health Outcome(s) and Reported Health Effect(s):	Marsman, D B6C3F1 mid Reproductiv of live pups/ gross necrop CoA oxidase nase, bile ac Terminal bo 12). Oral-Diet-D	D. S. (1995). NTP technical report on the ce. Toxicity Report Series, vol. 30 30:1-C e/Developmental-No. fetuses/breeding g litter, number of pups/sex/litter, Offsprin sy, offspring body weights, number of imp e activity of dams (Studies 1, 2, 3, and 4).S ids, and glucose), Histopathology of liver dy weights (Studies 1, 2, 3, and 4).Body weights uration: Reproductive/Developmental-1-	e toxicity stud 55. group, Litter w g clinical obse plantation sites erum chemistr (Studies 8 and weight, feed co	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- y (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydroge- 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)Nutritional/Metabolic- nsumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 20 days)
Exposure Route: Species: Chemical: HERO ID:	Rat-Fischer Dibutyl Phth 680063	344 - [rat]-Female aalate- Parent compound	gestation (
Domain		Metric	Rating	Comments
Domain 4: Selective Ro	eporting and At Metric 5:	trition 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 N	lethods Sensitiv	ity		
Domain of Exposure in	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 M	leasures and Re	sults Display		

Continued on next page ...

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Human Health Hazard Animal Toxicology Evaluation

	continued from previous page
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)	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage
and Reported	of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues,
Health Effect(s):	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 dehydroge-
	nase, 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	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)
Exposure Route:	
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063
D :	

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 \pm 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 Sup	o study in utero in rats		
Overall Qualit	y Deter	mination	Low	

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Marsman, D B6C3F1 mic Reproductive of live pups/I gross necrops CoA oxidase nase, bile aci Terminal bod 12). Oral-Diet-Du Rat-Fischer 3 Dibutyl Phth 680063	S. (1995). NTP technical report on the t e. Toxicity Report Series, vol. 30 30:1-G5. e/Developmental-No. fetuses/breeding gro litter, number of pups/sex/litter, Offspring of sy, offspring body weights, number of impla activity of dams (Studies 1, 2, 3, and 4).Ser ds, and glucose), Histopathology of liver (S ly weights (Studies 1, 2, 3, and 4).Body we uration: Reproductive/Developmental-1-F0 344 - [rat]-Female alate- Parent compound	toxicity stud bup, Litter w clinical obse antation sites um chemistr tudies 8 and ight, feed co - gestation (ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues, , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- y (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydroge- 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)Nutritional/Metabolic- nsumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 20 days)
Domain		Metric	Rating	Comments
Domain 1: Reporting Qu	uality Metric 1:	Reporting Quality	Medium	All critical and most important information was reported in this study. The study in- cluded identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (tempera- ture, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (fre- quency 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	l Performance Metric 2: Metric 3:	Allocation Observational Bias / Blinding Changes	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 mod- ifying factors across groups were noted by the study authors. In addition, for this ex- periment, 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. 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 Cor Metric 4:	ntrol 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 Rep	porting and Att	rition		
		Conti	nued on nex	t page

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Dibutyl Phthalate

Human Health Hazard Animal Toxicology Evaluation

HERO ID: 680063 Table: 2 of 34

		сог	ntinued from p	revious page
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and	Marsman, I B6C3F1 mi Reproductiv of live pups gross necrop CoA oxidas nase, bile ac Terminal bo 12). Oral-Diet-F	D. S. (1995). NTP technical report on the ce. Toxicity Report Series, vol. 30 30:1-0 ve/Developmental-No. fetuses/breeding s /litter, number of pups/sex/litter, Offspring psy, offspring body weights, number of im e activity of dams (Studies 1, 2, 3, and 4). cids, and glucose), Histopathology of liver body weights (Studies 1, 2, 3, and 4).Body Duration: Reproductive/Developmental-1-	ne toxicity stud: G5. group, Litter w ng clinical obse uplantation sites Serum chemistr r (Studies 8 and weight, feed co	es of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and eight; Gestation length, number of pups/litter, number of live pups/litter, percentage rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues , mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl- y (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydroge- 9). Absolute and relative liver weight (Studies 8, 9, 10, and 11)Nutritional/Metabolic- nsumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 20 days)
Exposure Route:	Of al-Dict-L	Juration. Reproductive/Developmental-1-	-1 0 - gestation (20 days)
Species:	Rat-Fischer	344 - [rat]-Female		
Chemical: HERO ID:	Dibutyl Pht 680063	halate- Parent compound		
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 N	Aethods Sensitiv	vity		
Domain 3. Exposure w	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

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Human Health Hazard Animal Toxicology Evaluation

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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)	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage					
and Reported	of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues,					
Health Effect(s):	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 dehydroge-					
	nase, 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	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)					
Exposure Route:						
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 \pm 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	o study in utero in rats		
Overall Qualit	y Deter	mination	Low	

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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 dehydroge-nase, 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days) Rat-Fischer 344 - [rat]-Female Dibutyl Phthalate- Parent compound 680063						
Domain		Metric	Rating	Comments			
Domain 1: Reporting Qu	uality Metric 1:	Reporting Quality	Medium	All critical and most important information was reported in this study. The study in- cluded identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (tempera- ture, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (fre- quency 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	l Performance Metric 2: Metric 3:	Allocation Observational Bias / Blinding Changes	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 mod- ifying factors across groups were noted by the study authors. In addition, for this ex- periment, 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. Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.			
Domain 3: Confounding	g / Variable Cor Metric 4:	ntrol 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							
Continued on next page							
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Dibutyl Phthalate

Human Health Hazard Animal Toxicology Evaluation

HERO ID: 680063 Table: 3 of 34

		cor	ntinued from p	revious page			
Study Citation: Health Outcome(s) and Reported	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. 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.						
Health Effect(s):	gross necrop CoA oxidase nase, bile ac Terminal bo 12).	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 dehydroge- nase, 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-D	uration: Reproductive/Developmental-1-	·F0 - gestation (20 days)			
Species:	Rat-Fischer	344 - [rat]-Female					
Chemical: HERO ID:	Dibutyl Phthalate- Parent compound 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 N	lathada Sanaitir	-iter					
Domain 3: Exposure M	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.			
			Madium	For this study, the route, fragmency, and duration of avacuum ware appropriate for the			

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Human Health Hazard Animal Toxicology Evaluation

	continued from previous page					
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)	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage					
and Reported	of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues,					
Health Effect(s):	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 dehydroge-					
	nase, 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	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)					
Exposure Route:						
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 \pm 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	o study in utero in rats		
Overall Qualit	y Deteri	mination	Low	

Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity studies of dibutyl B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.				
Health Outcome(s) and Reported	Other (please	e specify below) (Clinical observat	ions)-Clinical Observations		
Health Effect(s):					
Duration and	Oral-Diet-Du	aration: Reproductive/Developmer	ntal-1-F0 - gestation (20 days)		
Exposure Route:					
Species:	Rat-Fischer 3	344 - [rat]-Female			
Chemical:	Dibutyl Phth	alate- Parent compound			
HERO ID:	680063				
Domain		Metric	Rating		
Domain 1: Reporting Q	Juality				
	Metric 1:	Reporting Quality	Medium		
Domain 2: Selection an	d Performance				
	Metric 2:	Allocation	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						
Health Outcome(s)	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Other (please specify below) (Clinical observations)-Clinical Observations						
and Reported	o aler (pieda						
Health Effect(s):							
Duration and	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (20 days)						
Exposure Route:							
Species:	Rat-Fischer	344 - [rat]-Female					
Chemical:	Dibutyl Phth	alate- Parent compound					
	080005						
Domain	mality	Metric	Rating	Comments			
Domain 1: Reporting Q	Metric 1:	Reporting Quality	Medium	All critical and most important information was reported in this study. The study in-			
	Wether 1.	Reporting Quanty	Weenum	cluded identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (tempera- ture, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (fre- quency 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 an	d Performance						
Domain 2. Selection al	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 mod- ifying factors across groups were noted by the study authors. In addition, for this ex- periment, 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: Confoundin	g / Variable Cor	ntrol					
	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 Re	porting and Att	trition					
	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.			
		Cont	inued on next page				

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Dibutyl Phthalate

HERO ID: 680063 Table: 4 of 34

			continued from previous pa	age				
Study Citation:	Marsman, E B6C3F1 mi	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)	Other (please specify below) (Clinical observations)-Clinical Observations							
Health Effect(s):								
Duration and	Oral-Diet-D	uration: Reproductive/Developmental-1-F	0 - gestation (20 days)					
Exposure Route:	Rat-Fischer	344 - [rat] Female						
Chemical: HERO ID:	Dibutyl Phtl 680063	nalate- Parent compound						
Domain		Metric	Rating	Comments				
Domain 5: Exposure M	ethods Sensitiv	vity						
	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 Me	easures and Re	sults 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 Qualit	ty Detern	nination	Uninformative					

PUBLIC RELEASE DRAFT May 2025 Human Health Hazard Animal Toxicology Evaluation

Study Citation:	Marsman, D	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					
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)						
Chemical:	Dibutyl Phth	alate- Parent compound					
HERO ID:	680063	ľ					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Q	uality						
	Metric 1.	Reporting Quanty	Medium	An entrear and most important information was reported in this study. The study in- cluded identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (tempera- ture, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (fre- quency 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 an	d Darformanca						
Domain 2. Selection and	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	y / Variable Cou	ntrol					
	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 Re	porting and Att	trition					
Continued on next page							

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Human Health Hazard Animal Toxicology Evaluation

		con	tinued from p	revious page			
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and	Marsman, I B6C3F1 mi Reproductiv of live pups gross necrop CoA oxidas nase, bile ac Terminal bo 12). Oral-Diet-F	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. 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).					
Exposure Route:							
Species:	Rat-Fischer	344 - [rat]-Female					
Chemical: HERO ID:	Dibutyl Pht 680063	halate- Parent compound					
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 N	Aethods Sensitiv	vity					
Domain J. Exposure .	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 N	lessures and D						
	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.			
		Con	tinued on nex	NOAEL/LOAEL values. The sample sizes were sufficient for conducting statistical analysis.			

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HERO ID: 680063 Table: 5 of 34

		. continued from p	revious page		
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				
Health Outcome(s)	Reproductive/Developmental-No. fetuses/breed	ing group. Litter w	eight: Gestation length, number of pups/litter, number of live pups/litter, percentage		
and Reported	of live pups/litter, number of pups/sex/litter, Off	spring clinical obse	rvations, mortality, feed consumption, histologic examinations on >30 organs/tissues,		
Health Effect(s):	gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitovl-				
	CoA oxidase activity of dams (Studies 1, 2, 3, and	14).Serum chemistr	y (ALP, ALT, total protein, albumin, total cholesterol, triglycerides, sorbitol dehydroge-		
	nase, 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).B	ody weight, feed co	nsumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and		
	12).				
Duration and	Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)				
Exposure Route:					
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 \pm 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 Quali	ty Determination	Low			

Dibutyl Phthalate

PUBLIC RELEASE DRAFT May 2025 Human Health Hazard Animal Toxicology Evaluation

Study Citation:	Marsman, D	D. S. (1995). NTP technical report on the t	oxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and			
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 dehydroge- nase, 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days) Rat-Fischer 344 - [rat]-Female Dibutyl Phthalate- Parent compound						
Domain	080003	Metric	Rating	Comments			
Domain 1: Reporting O	uality	Methe	Katilig	Comments			
	Metric 1:	Reporting Quality	Medium	All critical and most important information was reported in this study. The study in- cluded identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (tempera- ture, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (fre- quency 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: Salastion an	d Darfarmanaa						
Domain 2. Selection an	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	a / Variable Co	ntrol					
	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 Re	porting and At	trition					
		Conti	nued on nex	xt page			

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Dibutyl Phthalate

HERO ID: 680063 Table: 6 of 34

		cont	tinued from p	revious page			
Study Citation: Health Outcome(s) and Reported Health Effect(s):	Marsman, I B6C3F1 mi Reproductiv of live pups gross necrop CoA oxidas nase, bile ac Terminal bo 12).	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. 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 dehydroge-nase, 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 Poute:	Oral-Diet-D	Puration: Reproductive/Developmental-I-F	$^{\circ}$ 0- lactation (2	21 days)			
Species: Chemical: HERO ID:	Rat-Fischer Dibutyl Phtl 680063	344 - [rat]-Female halate- Parent compound					
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 ex- planation was provided. The methods state there should have been data for 24 controls. There is no indication of animal attrition.			
Domain 5: Exposure N	Aethods Sensitiv	vity					
Domain 5. Exposule iv	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 M	leasures and De	sults 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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Human Health Hazard Animal Toxicology Evaluation

HERO ID: 680063 Table: 6 of 34

	continued from previous page					
Study Citation:	Marsman, D. S. (1995). NTP technical report	t on the toxicity studi	es of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and			
Health Outcome(s) and Reported Health Effect(s):	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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					
Duration and	Oral-Diet-Duration: Reproductive/Developme	ntal-1-F0- lactation (2	1 days)			
Exposure Route:	Rat-Fischer 311 - [rat]-Female					
Chemical:	Dibutyl Phthalate- Parent compound					
HERO ID:	680063					
Domain	Metric	Rating	Comments			
	Metric 9: Results presentation	Medium	Quantitative data (mean \pm 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 ox- idase activity in dam livers, and terminal body weights of dams. Statistical signifi- cance 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 Qualit	ty Determination	Low				

PUBLIC RELEASE DRAFT May 2025 Human Health Hazard Animal Toxicology Evaluation

Study Citation:	Marsman, D	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					
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 dehydroge-nase, 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days) Rat-Fischer 344 - [rat]-Female Dibutyl Phthalate- Parent compound						
Domain	080003	Matric	Dating	Comments			
Domain 1: Reporting O	uality	Metric	Katilig	Comments			
Q	Metric 1:	Reporting Quality	Medium	All critical and most important information was reported in this study. The study in- cluded identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (tempera- ture, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (fre- quency 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 an	d Darformanca						
Domain 2. Selection an	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	a / Variable Co	atrol					
	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 Re	porting and At	trition					
		Conti	nued on nex	at page			

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Human Health Hazard Animal Toxicology Evaluation

		cont	inued from p	revious page				
Study Citation: Health Outcome(s)	Marsman, I B6C3F1 mic Reproductiv	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. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter of pups/litter. Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage of live pups/litter.						
Health Effect(s):	gross necrop CoA oxidase nase, bile ac Terminal bo 12).	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 dehydroge-nase, 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-D	uration: Reproductive/Developmental-1-F	0- lactation (2	21 days)				
Species:	Rat-Fischer	344 - [rat]-Female						
Chemical:	Dibutyl Phtl	nalate- 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 ex- planation was provided. The methods state there should have been data for 24 controls. There is no indication of animal attrition.				
Domain 5: Exposure M	ethods Sensitiv	vity						
Domani J. Exposure M	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 M	easures and Re	sults 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.				
	Continued on next page							

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HERO ID: 680063 Table: 7 of 34

	continued from previous page						
Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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 dehydroge-nase, 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	Oral-Diet-Duration: Reproductive/Developme	ental-1-F0- lactation (2)	l days)				
Exposure Route:	Pat Fischer 344 [rat] Female						
Chemical:	Dibutyl Phthalate- Parent compound						
HERO ID:	680063						
Domain	Metric	Rating	Comments				
	Metric 9: Results presentation	Medium	Quantitative data (mean \pm 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 ox- idase activity in dam livers, and terminal body weights of dams. Statistical signifi- cance 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 Quali	ty Determination	Low					

Study Citation:	Marsman, D	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					
Health Outcome(s) and Reported	Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)						
Duration and							
Species:	Rat-Fischer	344 - [rat]-Female					
Chemical: HERO ID:	Dibutyl Phth 680063	nalate- Parent compound					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Q	Quality						
	Metric 1:	Reporting Quality	Medium	All critical and most important information was reported in this study. The study in- cluded identification of the test substance DBP, and source (Chem Central); test animal characteristics (source, strain, sex, age); general animal husbandry conditions (tempera- ture, humidity, diet, water availability, number of animals per cage); exposure methods (test substance source, purity, method of administration); experimental design (fre- quency 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 ar	nd Performance						
2011111 21 0010000 m	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 2: Confoundin	va / Variabla Ca	ntrol					
Domain 5. Confoundin	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 R	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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Dibutyl Phthalate

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Dibutyl Phthalate

HERO ID: 680063 Table: 8 of 34

		(continued from previous j	page			
Study Citation: Health Outcome(s)	Marsman, I B6C3F1 mi Other (pleas	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.					
and Reported Health Effect(s): Duration and Exposure Route:	Oral-Diet-Duration: Reproductive/Developmental-1-F0- lactation (21 days)						
Species: Chemical: HERO ID:	Rat-Fischer Dibutyl Pht 680063	344 - [rat]-Female halate- Parent compound					
Domain		Metric	Rating	Comments			
Domain 5: Exposure M	ethods Sensitiv Metric 6:	vity 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 mate- rial 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 char- acterization 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 Me	easures and Re	sults 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	o study lactational in rats					
Overall Quali	ty Deteri	nination	Uninformative	<u>)</u>			

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HERO ID: 680063 Table: 9 of 34

Study Citation:	Marsman, I B6C3E1 mi	D. S. (1995). NTP technical report on the to	xicity studies o	f dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and			
Health Outcome(s) and Reported	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).						
Health Effect(s): Duration and Exposure Route:	Oral-Diet-D	uration: Reproductive/Developmental-1-F0 -	gestation (3 we	eeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)			
Species: Chemical: HERO ID:	Rat-Fischer Dibutyl Pht	344 - [rat]-Female nalate- Parent compound					
Domain	000005	Metric	Rating	Comments			
Domain 1: Reporting Q	uality Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); test animal characteristics (source, strain, age, sex, starting body weight); gen- eral 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 an- imals 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 an	d Performance						
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a com- puter 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	g / Variable Co	ntrol					
	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 re- quired. 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 Re	porting and At	trition					
		Contin	ued on next pa	ge			

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Dibutyl Phthalate

	continued from previous page
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)	Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).
and Reported	
Health Effect(s):	
Duration and	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Exposure Route:	
Species:	Rat-Fischer 344 - [rat]-Female
Chemical:	Dibutyl Phthalate- Parent compound
HERO ID:	680063
Demein	

Domain	Metric	Rating	Comments
Metric 5: Domain 5: Exposure Methods Sensit	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/171 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.
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,

Domain 6: Outcome Measures and Results Display

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Dibutyl Phthalate

		conti	nued from previo	us page			
Study Citation:	Marsman, I B6C3F1 mi	D. S. (1995). NTP technical report on the technical report on the technical report Series, vol. 30 30:1-G5	toxicity studies of	dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and			
Health Outcome(s)	Mortality-S	urvival (Studies 5, 6, 7, 8, 9, 10, 11, and 12)).				
and Reported Health Effect(s):							
Duration and	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)						
Exposure Route:							
Species:	Rat-Fischer 344 - [rat]-Female						
HERO ID:	680063	nalate- Parent compound					
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						
Additional Comments.	5.001 1111	,, ,					

PUBLIC RELEASE DRAFT May 2025 Human Health Hazard Animal Toxicology Evaluation

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks) Rat-Fischer 344 - [rat]-Female Dibutyl Phthalate- Parent compound 680062						
Domain		Metric	Rating	Comments			
Domain 1: Reporting Q	aality Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); test animal characteristics (source, strain, age, sex, starting body weight); gen- eral 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 an- imals 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	l Performance Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a com-			
	Metric 3:	Observational Bias / Blinding Changes	Medium	puter program. Litters were randomly culled; however, the method was not reported. Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.			
Domain 3: Confounding	y / Variable Co	ntrol					
	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 re- quired. 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.			

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Dibutyl Phthalate

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks) Rat-Fischer 344 - [rat]-Female Dibutyl Phthalate- Parent compound 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 Me	thods Sensitivi	ty					
	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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Dibutyl Phthalate

		conti	inued from previ	ous page			
Study Citation:	Marsman, 1 B6C3F1 mi	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)	Reproducti	ve/Developmental-No. fetuses/breeding gro	oup, Litter weigh	t; Gestation length, number of pups/litter, number of live pups/litter, percentage			
and Reported	of live pups	of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues,					
Health Effect(s):	gross necro	gross necropsy, offspring body weights, number of implantation sites, mating index, fertility index-Nutritional/Metabolic-Terminal body weights (Studies					
	1, 2, 3, and	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	Oral-Diet-I	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)					
Exposure Route:							
Species:	Rat-Fischer	r 344 - [rat]-Female					
Chemical:	Dibutyl Pht	thalate- Parent compound					
HERO ID:	680063	L					
Domain		Metric	Rating	Comments			
Domain 6: Outcome M	leasures and R	esults Display					
	Metric 8:	Endpoint sensitivity and specificity	Medium	This study was conducted to identify the maximum prenatal exposure (MPE) concen- tration 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 / Devel- opmental 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 devel- opmental 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 pos- itive dams/treatment group) is slightly less than the preferred 20 pregnant dams/group for most developmental studies. For some endpoints, there were unexplained inconsis- tencies 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 determina- tion of a NOAEL and a LOAEL.			
	Metric 9:	Results presentation	Low	Quantitative data (mean \pm SEM) were provided for most of the specified endpoints. Statistical methods were described. Statistical significance was provided for these end- points. 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 lacta- tion. This is expected to substantially impact the interpretation of the results. Pup body			

Additional Comments: 5.DBP MPE Determination study in rats

Overall Quality Determination

Medium

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.

PUBLIC RELEASE DRAFT May 2025 Human Health Hazard Animal Toxicology Evaluation

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Marsman, E B6C3F1 mic Reproductiv of live pups/ gross necrop 1, 2, 3, and 4 Oral-Diet-D Rat-Fischer Dibutyl Phth 680063	 D. S. (1995). NTP technical report on the to ce. Toxicity Report Series, vol. 30 30:1-G5. e/Developmental-No. fetuses/breeding grouy/litter, number of pups/sex/litter, Offspring cl osy, offspring body weights, number of impla 4). Body weight, feed consumption (Studies 5 uration: Reproductive/Developmental-1-F0 - 344 - [rat]-Female nalate- Parent compound 	xicity studies o p, Litter weigh inical observati ntation sites, m , 6, 7, 8, 9, 10, gestation (3 we	f dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and t; Gestation length, number of pups/litter, number of live pups/litter, percentage ons, mortality, feed consumption, histologic examinations on >30 organs/tissues, ating index, fertility index-Nutritional/Metabolic-Terminal body weights (Studies 11, and 12).Body weight gain (Studies 5, 6, 7, and 12). weks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Domain		Metric	Rating	Comments
Domain 1: Reporting Q	uality Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); test animal characteristics (source, strain, age, sex, starting body weight); gen- eral 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 an- imals 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	d Performance Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a com-
	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	g / Variable Co	ntrol		
	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 re- quired. 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.

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Dibutyl Phthalate

		cont	inued from previ	ous page			
Study Citation:	Marsman, D B6C3E1 mi	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): Duration and Exposure Route:	BoC3F1 mice. Toxicity Report Series, vol. 50-50: 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). 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	Rat-Fischer 344 - [rat]-Female					
HERO ID:	680063	lalate- Parent compound					
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 M	ethods Sensitiv	vity					
	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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Dibutyl Phthalate

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks) Rat-Fischer 344 - [rat]-Female Dibutyl Phthalate- Parent compound 680063			
Domain		Metric	Rating	Comments
Domain 6: Outcome M	leasures and Re Metric 8:	esults Display Endpoint sensitivity and specificity	Medium	This study was conducted to identify the maximum prenatal exposure (MPE) concen- tration 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 / Devel- opmental 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 devel- opmental 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 pos- itive dams/treatment group) is slightly less than the preferred 20 pregnant dams/group for most developmental studies. For some endpoints, there were unexplained inconsis- tencies 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 determina- tion of a NOAEL and a LOAEL.
	Metric 9:	Results presentation	Low	Quantitative data (mean \pm SEM) were provided for most of the specified endpoints. Statistical methods were described. Statistical significance was provided for these end- points. 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 lacta- tion. 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

Additional Comments: 5.DBP MPE Determination study in rats

Overall Quality Determination

Medium

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.

PUBLIC RELEASE DRAFT May 2025 Human Health Hazard Animal Toxicology Evaluation

Study Citation:	Marsman, D	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 R6C3E1 mine. Toxicity Report Series yel 20:30:1.65				
Health Outcome(s) and Reported Health Effect(s):	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Other (please specify below) (Clinical observations)-Clinical Observations Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (3 weeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)					
Duration and						
Exposure Route:						
Species:	Rat-Fischer 344 - [rat]-Female					
HERO ID:	680063					
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality					
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); test animal characteristics (source, strain, age, sex, starting body weight); gen- eral 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 an- imals 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	d Performance					
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a com- puter 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	g / Variable Co	ntrol				
	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 re- quired. 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 Re	porting and At	trition				

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Dibutyl Phthalate

	C	ontinued from previous page	9
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)	Other (please specify below) (Clinical observations)-Clinical Observations	
and Reported			
Health Effect(s):			
Duration and	Oral-Diet-Duration: Reproductive/Developmental-	1-F0 - gestation (3 weeks)-F0-	lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Exposure Route:			
Species:	Rat-Fischer 344 - [rat]-Female		
Chemical:	Dibutyl Phthalate- Parent compound		
HERO ID:	680063		
Domain	Metric	Rating	Comments

Domain		methe	rtating	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	e Methods Sensitiv Metric 6:	vity 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	High	This was an extended exposure study. Exposure was conducted in utero (from GD 0) through lactation, and for 4 weeks after weaping as part of a collection of studies assess-

Domain 6: Outcome Measures and Results Display

Human Health Hazard Animal Toxicology Evaluation

HERO ID: 680063 Table: 12 of 34

continued from previous page				
Study Citation:	Marsman, E B6C3F1 mi	D. S. (1995). NTP technical report on the ce. Toxicity Report Series, vol. 30 30:1-G5	toxicity studies o	f dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s)	Other (pleas	e specify below) (Clinical observations)-Cl	linical Observatio	ns
Health Effect(s):				
Duration and	Oral-Diet-D	uration: Reproductive/Developmental-1-F0) - gestation (3 we	eeks)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)
Exposure Route: Species: Chemical: HFRO ID:	Rat-Fischer 344 - [rat]-Female Dibutyl Phthalate- Parent compound			
Domain	000005	Metric	Rating	Comments
	Metric 8:	Endpoint sensitivity and specificity	Medium	Dams were assessed for clinical signs. The frequency of clinical observations was re- ported, 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 im- pact the interpretation of the results. The test animals (rats) and sex (females) were ap- propriate 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

Dibutyl Phthalate

Medium

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HERO ID: 680063 Table: 13 of 34

Study Citation:	Marsman, D	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 P6C3E1 mine. Toxicity Perpert Series, vol. 30, 2011 C5					
Health Outcome(s) and Reported Health Effect(s):	Mortality-Su	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).					
Duration and Exposure Route:	Oral-Diet-D	uration: Reproductive/Developmental-1-F0 -	gestation (17 d	ays)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)			
Species: Chemical: HERO ID:	Mouse-B6C Dibutyl Phth 680063	3F1 - [mouse]-Female halate- Parent compound					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Q	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); test animal characteristics (source, strain, age, sex, starting body weight); gen- eral 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 an- imals 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 an	d Performance Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a com- puter 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	g / Variable Co	ntrol					
	Metric 4:	Confounding / Variable Control	Low	The study included a negative control group, which received undosed feed. Control re- sponses 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 lacta- tion. It is unclear whether reductions in dam body weights or weight gain were related to altered food consumption or palatability issues; however, offspring food consump- tion 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 Re	porting and At	trition					
Continued on next page							

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Dibutyl Phthalate

		cont	inued from previ	ious page	
Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12).				
Duration and Exposure Route:	Oral-Diet-D	uration: Reproductive/Developmental-1-F	0 - gestation (17 d	lays)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)	
Species: Chemical: HERO ID:	Mouse-B6C Dibutyl Phtl 680063	3F1 - [mouse]-Female halate- Parent compound			
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 dif- fers 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 end- points. 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 exclu- sion 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.	
Dennain 5. Ennerman	[-4]				
Domain 5: Exposure M	Iethods Sensitiv 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: Outcom - M	and D-	culta Dieplay			
	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 in- terpretation of the results. The test animals (mice) and sex (females) were appropri- ate 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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Dibutyl Phthalate

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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)	Mortality-S	urvival (Studies 5, 6, 7, 8, 9, 10, 11, a	and 12).		
and Reported Health Effect(s):					
Duration and	Oral-Diet-D	Ouration: Reproductive/Developmenta	al-1-F0 - gestation (17 day	ys)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)	
Exposure Route:					
Species:	Mouse-B6C	C3F1 - [mouse]-Female			
Chemical:	Dibutyl Pht	halate- 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	E Determination study in mice			
Overall Qualit	y Deteri	mination	Medium		

PUBLIC RELEASE DRAFT May 2025 Human Health Hazard Animal Toxicology Evaluation

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks) Mouse-B6C3F1 - [mouse]-Female Dibutyl Phthalate- Parent compound 680063				
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	uality Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); test animal characteristics (source, strain, age, sex, starting body weight); gen- eral 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 an- imals 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 an	d Performance				
Domain 2. Sciection an	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a com- puter 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	a / Variable Co	ntrol			
	Metric 4:	Confounding / Variable Control	Low	LOW: The study included a negative control group, which received undosed feed. Con- trol 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 ex- posure 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 plasticiz- ers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.	
Domain 4: Selective Re	porting and Att	trition			

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Human Health Hazard Animal Toxicology Evaluation

Dibutyl Phthalate

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Study Citation: Health Outcome(s)	Marsman, D B6C3F1 mic Reproductive	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. Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage					
and Reported	of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues,						
Health Effect(s):	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 (Studi	es 5, 6, 7, 8, 9,	10, 11, and 12).Body weight gain (Studies 5, 6, 7, and 12).			
Duration and	Oral-Diet-Di	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)					
Exposure Koute:	Mana D(C)						
Species:	Mouse-BoC.	olate Depend compound					
Unennical:	680063	arate- Parent compound					
	080005						
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 dif- fers 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 end- points. 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 exclu- sion 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 M	ethods Sensitiv	ity					
	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 Mo	easures and Res	sults Display					

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks) Mouse-B6C3F1 - [mouse]-Female Dibutyl Phthalate- Parent compound 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 consump- tion. The frequency of body weight and food consumption measurements of dams were provided. Dams and pups were assessed for select Reproductive/Developmental end- points. 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 appro- priate 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 \pm SEM) were provided for most of the specified endpoints. Statistical methods were described. Statistical significance was provided for these end- points. 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. Addi- tionally, no individual animal data were provided.		
			tohan, no marriada anna data were provided.		
Additional Comments:	6.DBP MPE Determination study in mice				

Overall Quality Determination

Low

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks) Mouse-B6C3F1 - [mouse]-Female Dibutyl Phthalate- Parent compound 680063				
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	uality Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); test animal characteristics (source, strain, age, sex, starting body weight); gen- eral 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 an- imals 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 an	d Performance				
Domain 2. Sciection an	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a com- puter 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	a / Variable Co	atrol			
	Metric 4:	Confounding / Variable Control	Low	LOW: The study included a negative control group, which received undosed feed. Con- trol 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 ex- posure 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 plasticiz- ers, and the materials used for caging and to dispense water were not reported. The test chemical is a known endocrine disruptor.	
Domain 4: Selective Re	porting and Att	rition			

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Dibutyl Phthalate

		con	tinued from p	revious page	
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks) Mouse-B6C3F1 - [mouse]-Female Dibutyl Phthalate- Parent compound 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 dif- fers 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 end- points. 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 exclu- sion 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. Expansion M	athada Canaitir	····			
Domain 5: Exposure M	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 Mo	easures and Re	sults Display			

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Human Health Hazard Animal Toxicology Evaluation

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (17 days)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks) Mouse-B6C3F1 - [mouse]-Female Dibutyl Phthalate- Parent compound 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 consump- tion. The frequency of body weight and food consumption measurements of dams were provided. Dams and pups were assessed for select Reproductive/Developmental end- points. 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 appro- priate 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 \pm 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
PUBLIC RELEASE DRAFT May 2025 Human Health Hazard Animal Toxicology Evaluation

HERO ID: 680063 Table: 16 of 34

Study Citation:	Marsman, D	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 R6C3E1 mice. Toxicity Penert Series, vol. 30 30:1 C5				
Health Outcome(s) and Reported Health Effect(s):	Other (pleas	Other (please specify below) (Clinical observations)-Clinical Observations				
Duration and Exposure Route:	Oral-Diet-D	uration: Reproductive/Developmental-1-F0 -	gestation (17 d	ays)-F0- lactation (4 weeks)-F1- premating (4 weeks)-F1- premating (4 weeks)		
Species:	Mouse-B6C	3F1 - [mouse]-Female				
Chemical:	Dibutyl Phth	nalate- Parent compound				
HERO ID:	680063					
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality					
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); test animal characteristics (source, strain, age, sex, starting body weight); gen- eral 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 an- imals 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 an	d Performance					
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a com- puter 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	g / Variable Co	ntrol				
	Metric 4:	Confounding / Variable Control	Low	The study included a negative control group, which received undosed feed. Control re- sponses 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 lacta- tion. It is unclear whether reductions in dam body weights or weight gain were related to altered food consumption or palatability issues; however, offspring food consump- tion 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 Re	porting and At	trition				
	Continued on next page					

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Dibutyl Phthalate

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Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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: HERO ID:	Dibutyl Phth 680063	nalate- Parent compound				
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 dif- fers 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 end- points. 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 exclu- sion 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 M	ethods Sensitiv	<i>ity</i>				
Domain 3. Exposure in	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.		

Dibutyl Phthalate

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HERO ID: 680063 Table: 16 of 34

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Study Citation:	Marsman, I B6C3F1 mi	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: Chemical: HERO ID:	Mouse-B60 Dibutyl Pht 680063	3F1 - [mouse]-Female halate- Parent compound			
Domain		Metric	Rating	Comments	
	Metric 8:	Endpoint sensitivity and specificity	Medium	Dams were assessed for clinical signs. The frequency of clinical observations was re- ported, 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 im- pact 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 MPI	E Determination study in mice			
Overall Qualit	ty Deter	nination	Medium		

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HERO ID: 680063 Table: 17 of 34

Study Citation:	Marsman, D B6C3E1 mi	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 B6C3E1 mice. Toxicity Report Series, vol. 30, 30:1-65					
Health Outcome(s) and Reported Health Effect(s):	BocsF1 inter. Toxicity Report Series, vol. 50 50.1-03. Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12). 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)) and (3 weeks (at 0 or 10000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm)) Provide the state of th						
Duration and Exposure Route:							
Species:	Rat-Fischer	ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm)) Rat-Fischer 344 - [rat]-Female					
Chemical: HERO ID:	Dibutyl Phth 680063	halate- Parent compound					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Qu	uality						
	Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); test animal characteristics (source, strain, age, sex, starting body weight); gen- eral 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 an- imals 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	d Performance Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a com-			
	Metric 3:	Observational Bias / Blinding Changes	Medium	puter program. Litters were randomly culled; however, the method was not reported. Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.			
Domain 3: Confounding	g / variable Co Metric 4:	ntroi Confounding / Variable Control	Medium	The study included a negative control group, which received undosed feed. Control re- sponses 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 con- sumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry condi- tions 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 disrup- tor.			
Domain 4: Selective Re	porting and At	trition					

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Dibutyl Phthalate

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Marsman, D B6C3F1 mic Mortality-Su Oral-Diet-Du ing (17 week ppm; 13 wee Rat-Fischer 3 Dibutyl Phth 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. Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12). 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)) Rat-Fischer 344 - [rat]-Female Dibutyl Phthalate- Parent compound 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, ani- mals 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 selec- tive reporting and this is expected to notably impact the interpretation of the results.	
Domain 5: Exposure M	ethods Sensitiv	ity			
Domain 5. Exposure im	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 Me	easures and Res	sults Display			

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Dibutyl Phthalate

continued from previous page				
Study Citation:	Marsman, D. B6C3F1 mice	S. (1995). NTP technical report on the e. Toxicity Report Series, vol. 30 30:1-G5	toxicity studies of	dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and
Health Outcome(s) and Reported	Mortality-Sur	rvival (Studies 5, 6, 7, 8, 9, 10, 11, and 12)).	
Health Effect(s): Duration and	Oral-Diet-Du	ration: Reproductive/Developmental-1-F0) - gestation (3 wee	eks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premat-
Exposure Route:	ing (17 week	s (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 weel	ks at 0, 2500, 5000, 10000, 20000, or 4000	00 ppm))	
Species:	Rat-Fischer 3	44 - [rat]-Female		
Chemical:	Dibutyl Phtha	alate- Parent compound		
	080005			
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 in- terpretation 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 termina- tion."
Additional Comments:	7.DBP 13-we	eek feed study w/ perinatal in rats		

Overall Quality Determination

Medium

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Marsman, D B6C3F1 mic Nutritional/I gain (Studie: Oral-Diet-D ing (17 weel ppm; 13 wee Rat-Fischer Dibutyl Phth 680063	 D. S. (1995). NTP technical report on the to be. Toxicity Report Series, vol. 30 30:1-G5. Metabolic-Terminal body weights (Studies 1, s 5, 6, 7, and 12). uration: Reproductive/Developmental-1-F0 - ks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 344 - [rat]-Female halate- Parent compound 	xicity studies o 2, 3, and 4).Bo gestation (3 we 0, 2500, 5000, ppm))	f dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and ody weight, feed consumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight eks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premat- 10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000
Domain		Metric	Rating	Comments
Domain 1: Reporting Q	uality Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); test animal characteristics (source, strain, age, sex, starting body weight); gen- eral 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 an- imals 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	d Performance Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a com-
	Metric 3:	Observational Bias / Blinding Changes	Medium	puter program. Litters were randomly culled; however, the method was not reported. Blinding or other measures to reduce observational bias were not reported. However, the endpoints of interest were objective or simple measures.
Demein 2. Conformation				
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received undosed feed. Control re- sponses 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 con- sumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry condi- tions 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 disrup- tor.
Domain 4: Selective Rep	porting and At	trition		

Human Health Hazard Animal Toxicology Evaluation

Dibutyl Phthalate

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Study Citation:	Marsman, E B6C3F1 mie	D. S. (1995). NTP technical report on the ce. Toxicity Report Series, vol. 30 30:1-G5	toxicity studies o	f dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
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))-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))-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))-F1- premating (17 weeks (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 ppm))				
Chemical: HERO ID:	Dibutyl Phtl 680063	halate- Parent compound			
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, ani- mals 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 selec- tive reporting and this is expected to notably impact the interpretation of the results.	
Domain 5: Exposure M	ethods Sensitiv	vity			
	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 M	easures and Re	sults Display			

Human Health Hazard Animal Toxicology Evaluation

Dibutyl Phthalate

HERO ID: 680063 Table: 18 of 34

	continued from previous page				
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 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. 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). 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))-F1- premating (17 weeks (4 - [rat]-Female Dibutyl Phthalate- Parent compound 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 \pm 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-w	veek feed study w/ perinatal in rats			
Overall Quali	ty Deteri	nination	Medium		

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Marsman, D B6C3F1 mic Reproductive of live pups/ gross necrop Oral-Diet-Di ing (17 weel ppm; 13 wee Rat-Fischer Dibutyl Phth 680063	S. (1995). NTP technical report on the total report of the total report Report Series, vol. 30 30:1-G5. e/Developmental-No. fetuses/breeding group litter, number of pups/sex/litter, Offspring clissy, offspring body weights, number of implaturation: Reproductive/Developmental-1-F0 - cs (4 weeks at 0 or 10,000 ppm; 13 weeks at 0, 2500, 5000, 10000, 20000, or 40000 344 - [rat]-Female alate- Parent compound	xicity studies o p, Litter weight inical observation ntation sites, ma gestation (3 we 0, 2500, 5000, ppm))	f dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and c; Gestation length, number of pups/litter, number of live pups/litter, percentage cons, mortality, feed consumption, histologic examinations on >30 organs/tissues, ating index, fertility index eks (at 0 or 10000 ppm))-F0- lactation (4 weeks (at 0 or 10000 ppm))-F1- premat- 10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000
Domain		Metric	Rating	Comments
Domain 1: Reporting Qu	uality Metric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); test animal characteristics (source, strain, age, sex, starting body weight); gen- eral 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 an- imals 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	l Performance			
	Metric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a com- puter 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	y / Variable Cor	ntrol		
	Metric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received undosed feed. Control re- sponses 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 con- sumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry condi- tions 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 disrup- tor.

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Dibutyl Phthalate

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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 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;)) Rat-Fischer 344 - [rat]-Female Dibutyl Phthalate- Parent compound 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, ani- mals 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 selec- tive reporting and this is expected to notably impact the interpretation of the results.
Domain 5: Exposure M	ethods Sensitiv	ity		
	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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Dibutyl Phthalate

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		conti	nued from previo	us page		
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Marsman, E B6C3F1 mid Reproductiv of live pups, gross necrop Oral-Diet-D ing (17 wee ppm; 13 wee Rat-Fischer Dibutyl Phtl 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. 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 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)) Rat-Fischer 344 - [rat]-Female Dibutyl Phthalate- Parent compound 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 observa- tions 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 end- points 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 be- tween 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 ex- posed 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 \pm 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-w	eek feed study w/ perinatal in rats				
Overall Qualit	y Deteri	nination	Medium			

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HERO ID: 680063 Table: 20 of 34

Health Outcome(s) Of and Reported Health Effect(s):	Other (please sp	10					
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 at 0 or 10 000 ppm)) F1- premating (17 weeks (18 ppm)) F1- premating (17 weeks at 0 or 10 000 ppm)) F1- premating (17 weeks at 0 or 10 000 ppm)) F1- premating (17 weeks at 0 or 10 000 ppm)) F1- premating (17 weeks at 0 or 10 000 ppm)) F1- premating (17 weeks at 0 or 10 000 ppm)) F1- premating (17 weeks at 0 or 10 000 ppm)) F1- premating (17 weeks at 0 or 10 000 ppm)) F1- premating (17 weeks at 0 or 10 000 ppm)) F1- premating (17 weeks at 0						
pp	ppm; 13 weeks	at 0, 2500, 5000, 10000, 20000, or 40000	ppm))	10000, 20000, 01 40000 ppin/)-1 1- premaining (17 weeks (4 weeks at 0 01 10,000			
Species: Ra	Rat-Fischer 344	4 - [rat]-Female					
HERO ID: 68	80063	ite- i arent compound					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Qualit	ity Aetric 1:	Reporting Quality	Medium	All critical and most important information were reported in this study. The study in- cluded identification of the test substance (Dibutyl phthalate), and source (Chem Cen- tral); test animal characteristics (source, strain, age, sex, starting body weight); gen- eral 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 an- imals 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 Per M	erformance Aetric 2:	Allocation	Medium	The study authors state that animals were weighed and were randomized using a com-			
M	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 / Va	Variable Contro	bl					
M	Aetric 4:	Confounding / Variable Control	Medium	The study included a negative control group, which received undosed feed. Control re- sponses 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 con- sumption or palatability issues; however, offspring food consumption was consistent across groups and no issues with palatability were observed. Animal husbandry condi- tions 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 disrup- tor.			

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Dibutyl Phthalate

		con	tinued from previo	ous page		
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and	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. Other (please specify below) (Clinical observations)-Clinical Observations 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- premat-					
Exposure Route: Species: Chemical: HERO ID:	ing (17 weel ppm; 13 wee Rat-Fischer Dibutyl Phth 680063	cs (4 weeks at 0 or 10,000 ppm; 13 week eks at 0, 2500, 5000, 10000, 20000, or 40 344 - [rat]-Female halate- Parent compound	s at 0, 2500, 5000, 000 ppm))	10000, 20000, or 40000 ppm))-F1- premating (17 weeks (4 weeks at 0 or 10,000		
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, ani- mals 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 selec- tive reporting and this is expected to notably impact the interpretation of the results.		
Domain 5: Exposure M	ethods Sensitiv	ity				
Domain 5. DAposare in	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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Dibutyl Phthalate

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Study Citation: Health Outcome(s) and Reported Health Effect(s):	Marsman, I B6C3F1 mi Other (pleas	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 36C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. Other (please specify below) (Clinical observations)-Clinical Observations				
Duration and Exposure Route: Species: Chemical: HERO ID:	Oral-Diet-D ing (17 wee ppm; 13 we Rat-Fischer Dibutyl Phtl 680063	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- premat- ing (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)) Rat-Fischer 344 - [rat]-Female Dibutyl Phthalate- Parent compound 680063				
Domain		Metric	Rating	Comments		
	Metric 8:	Endpoint sensitivity and specificity	Medium	Dams were assessed for clinical signs. The frequency of clinical observations was re- ported, 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-w	veek 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				
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 dehydroge-nase, 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). 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))-F1- gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- gestation (3 weeks)-F0- prem				
Species: Chemical:	Rat-Sprague	-Dawley - [rat]-Both alate- Parent compound			
HERO ID:	680063	mane i arene compound			
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	uality				
	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 an	d 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 mea- sures or initial histopathology.	
Domain 3: Confounding	g / Variable Co	ntrol			
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropri- ate. 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 Re	porting and At	trition			
	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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Dibutyl Phthalate

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Study Citation:	Marsman, E	D. S. (1995). NTP technical report on the	toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 dehydroge-nase, 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). Oral-Diet-Duration: Reproductive/Developmental-2-F0- premating (1 week)-F0- mating-F0 - gestation (3 weeks)-F0- lactation (4 weeks (F1e litter only))-				
~ .	litter only))-	F1- mating (7 days (F1e only))	(, aujs (110		
Species: Chemical: HERO ID:	Rat-Sprague Dibutyl Phtl 680063	e-Dawley - [rat]-Both nalate- Parent compound			
Domain		Metric	Rating	Comments	
	Metric 6: Metric 7:	Chemical administration and characterization	High High	DBP was sourced from Chem Central. The test material and purity (99%) was analyt- ically 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. The exposure frequency and duration were clearly instified by the study authors and	
	Wette 7.	duration	Ingli	were appropriate for the study type.	
Domain 6: Outcome Me	easures and Re	sults 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 \pm 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 Cor	ntinuous breeding study in rats			
Overall Qualit	ty Deteri	nination	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				
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 dehydroge-nase, 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). 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 only))-F1- mating (7 days (F1e only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e only))-F1- mating (7 days (F1e only))-F1 - mating (7 days (F1e only))-F1 - mating (7 days (F1e only))-F1 - mating (7 days (F1e only))				
Chemical: HERO ID:	Dibutyl Phth 680063	alate- Parent compound			
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	uality 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 an	d Performance				
	Metric 2: Metric 3:	Allocation Observational Bias / Blinding Changes	Medium Medium	No method of animal allocation into study groups was provided. Blinding was not reported, but the endpoints were not subjective or were simple mea- sures or initial histopathology.	
Domain 3: Confounding	• / Variable Co	ntrol			
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropri- ate. 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 Re	porting and At Metric 5:	trition 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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Dibutyl Phthalate

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continued from previous page					
Study Citation:	Marsman, E	D. S. (1995). NTP technical report on the	toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
Health Outcome(s) and Reported Health Effect(s): Duration and	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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).				
Exposure Route:	F1- premati	ng (77 days (F1e litter only))-F1- mating ((7 days (F1e	only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e	
Species: Chemical: HERO ID:	litter only))-F1- mating (7 days (F1e only)) Rat-Sprague-Dawley - [rat]-Both Dibutyl Phthalate- Parent compound 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 analyt- ically 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 /:	duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.	
Domain & Outcome Ma	agunag and Da				
Domain 0. Outcome Me	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 \pm 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 Cor	ntinuous breeding study in rats			
Overall Qualit	ty Deteri	nination	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				
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 dehydroge-nase, 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). 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))-F1- gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e litter only))-F1- gestation (3 weeks)-F0- prem				
Species: Chemical:	Rat-Sprague	-Dawley - [rat]-Both alate- Parent compound			
HERO ID:	680063	mane i arene compound			
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	uality				
	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 an	d 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 mea- sures or initial histopathology.	
Domain 3: Confounding	g / Variable Co	ntrol			
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropri- ate. 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 Re	porting and At	trition			
	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					
Continued on next page					

Dibutyl Phthalate

May 2025 Human Health Hazard Animal Toxicology Evaluation

continued from previous page					
Study Citation:	Marsman, E	D. S. (1995). NTP technical report on the	toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
Health Outcome(s) and Reported Health Effect(s): Duration and	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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).				
Exposure Route:	F1- premati	ng (77 days (F1e litter only))-F1- mating ((7 days (F1e	only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e	
Species: Chemical: HERO ID:	litter only))-F1- mating (7 days (F1e only)) Rat-Sprague-Dawley - [rat]-Both Dibutyl Phthalate- Parent compound 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 analyt- ically 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 /:	duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.	
Domain & Outcome Ma	agunag and Da				
Domain 0. Outcome Me	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 \pm 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 Cor	ntinuous breeding study in rats			
Overall Qualit	ty Deteri	nination	High		

Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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 dehydroge-				
Duration and	nase, 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).				
Exposure Route:	F1- prematir	ng (77 days (F1e litter only))-F1- mating (7	days (F1e	only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e	
Species: Chemical: HERO ID:	litter only))- Rat-Sprague Dibutyl Phth 680063	F1- mating (7 days (F1e only)) -Dawley - [rat]-Both alate- Parent compound	, (
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	uality	metric	Runng		
	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	d 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 mea- sures or initial histopathology.	
Domain 3: Confounding	y / Variable Co	ntrol			
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropri- ate. 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 Re	porting and Att	rition			
	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					
Continued on next page					

Dibutyl Phthalate

May 2025 Human Health Hazard Animal Toxicology Evaluation

continued from previous page					
Study Citation:	Marsman, E	D. S. (1995). NTP technical report on the	toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
Health Outcome(s) and Reported Health Effect(s): Duration and	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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).				
Exposure Route:	F1- premati	ng (77 days (F1e litter only))-F1- mating ((7 days (F1e	only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e	
Species: Chemical: HERO ID:	litter only))-F1- mating (7 days (F1e only)) Rat-Sprague-Dawley - [rat]-Both Dibutyl Phthalate- Parent compound 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 analyt- ically 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 /:	duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.	
Domain & Outcome Ma	agunag and Da				
Domain 0. Outcome Me	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 \pm 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 Cor	ntinuous breeding study in rats			
Overall Qualit	ty Deteri	nination	High		

Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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 dehydroge-				
Duration and	nase, 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).				
Exposure Route:	F1- prematir	ng (77 days (F1e litter only))-F1- mating (7	days (F1e	only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e	
Species: Chemical: HERO ID:	litter only))- Rat-Sprague Dibutyl Phth 680063	F1- mating (7 days (F1e only)) -Dawley - [rat]-Both alate- Parent compound	, (
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	uality	metric	Runng		
	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	d 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 mea- sures or initial histopathology.	
Domain 3: Confounding	y / Variable Co	ntrol			
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropri- ate. 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 Re	porting and Att	rition			
	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					
Continued on next page					

Dibutyl Phthalate

May 2025 Human Health Hazard Animal Toxicology Evaluation

continued from previous page							
Study Citation:	Marsman, E	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					
Health Outcome(s) and Reported Health Effect(s): Duration and	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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).						
Exposure Route:	F1- premati	ng (77 days (F1e litter only))-F1- mating ((7 days (F1e	only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e			
Species: Chemical: HERO ID:	litter only))-F1- mating (7 days (F1e only)) Rat-Sprague-Dawley - [rat]-Both Dibutyl Phthalate- Parent compound 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 analyt- ically 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 /:	duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.			
Domain & Outcome Ma	agunag and Da						
Domain 0. Outcome Me	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 \pm 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 Cor	ntinuous breeding study in rats					
Overall Quality Determination			High				

Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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 dehydroge-					
Duration and	nase, 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).					
Exposure Route:	F1- prematir	ng (77 days (F1e litter only))-F1- mating (7	days (F1e	only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e		
Species: Chemical: HERO ID:	litter only))- Rat-Sprague Dibutyl Phth 680063	F1- mating (7 days (F1e only)) -Dawley - [rat]-Both alate- Parent compound	, (
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality	metric	Runng			
	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	d 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 mea- sures or initial histopathology.		
Domain 3: Confounding	y / Variable Co	ntrol				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropri- ate. 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 Re	porting and Att	rition				
	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						
Continued on next page						

Dibutyl Phthalate

May 2025 Human Health Hazard Animal Toxicology Evaluation

continued from previous page							
Study Citation:	Marsman, E	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					
Health Outcome(s) and Reported Health Effect(s): Duration and	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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).						
Exposure Route:	F1- premati	ng (77 days (F1e litter only))-F1- mating ((7 days (F1e	only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e			
Species: Chemical: HERO ID:	litter only))-F1- mating (7 days (F1e only)) Rat-Sprague-Dawley - [rat]-Both Dibutyl Phthalate- Parent compound 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 analyt- ically 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 /:	duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.			
Domain & Outcome Ma	agunag and Da						
Domain 0. Outcome Me	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 \pm 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 Cor	ntinuous 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					
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 dehydroge-nase, 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). 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 only))-F1- mating (7 days (F1e only))-F1- mating (7 days (F1e only))-F1- mating (7 days (F1e only)))-F1- mating (7 days (F1e only))-F1- mating (7 days (
Species: Chemical:	Rat-Sprague	-Dawley - [rat]-Both alate- Parent compound				
HERO ID:	680063	mane i arene compound				
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality					
	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 an	d 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 mea- sures or initial histopathology.		
Domain 3: Confounding	g / Variable Co	ntrol				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropri- ate. 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 Re	porting and At	trition				
	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						
Continued on next page						

Dibutyl Phthalate

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continued from previous page							
Study Citation:	Marsman, E	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					
Health Outcome(s) and Reported Health Effect(s): Duration and	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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).						
Exposure Route:	F1- premati	ng (77 days (F1e litter only))-F1- mating ((7 days (F1e	only))-F1 - gestation (3 weeks)-F0- premating (1 week)-F1- premating (77 days (F1e			
Species: Chemical: HERO ID:	litter only))-F1- mating (7 days (F1e only)) Rat-Sprague-Dawley - [rat]-Both Dibutyl Phthalate- Parent compound 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 analyt- ically 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 /:	duration	High	The exposure frequency and duration were clearly justified by the study authors and were appropriate for the study type.			
Domain & Outcome Ma	agunag and Da						
Domain 0. Outcome Me	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 \pm 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 Cor	ntinuous breeding study in rats					
Overall Quality Determination			High				

Study Citation:	Marsman, I	D. S. (1995). NTP technical report on the t	toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and		
Health Outcome(s) and Reported Health Effect(s): Duration and	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)					
Exposure Route:						
Species:	Mouse-CD-	1 - [mouse]-Both				
Chemical:	Dibutyl Phtl	halate- Parent compound				
HERO ID:	680063					
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality					
	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 an	d 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 mea- sures or initial histopathology.		
Domain 3: Confounding	g / Variable Co	ontrol				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropri- ate. 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 Re	porting and At	ttrition				
	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 M	ethods Sensitiv	vity				
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	continued from previous page
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 B6C3E1 mice. Toxicity Report Series, vol. 30 30:1-G5

.3F1 mice. 10x1city Report Series, vol. 30 30:1-G5. Health Outcome(s) Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage and Reported of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues, Health Effect(s): 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 Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days) **Exposure Route: 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 analyt- ically 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 pro- vided; 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 Mo	easures and Re	sults 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 \pm 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 Cor	ntinuous breeding study in mice		
Overall Quality Determination High				

Study Citation:	Marsman, I	D. S. (1995). NTP technical report on the t	toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and		
Health Outcome(s) and Reported Health Effect(s): Duration and	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)					
Exposure Route:						
Species:	Mouse-CD-	1 - [mouse]-Both				
Chemical:	Dibutyl Phtl	halate- Parent compound				
HERO ID:	680063					
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality					
	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 an	d 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 mea- sures or initial histopathology.		
Domain 3: Confounding	g / Variable Co	ontrol				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropri- ate. 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 Re	porting and At	ttrition				
	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 M	ethods Sensitiv	vity				
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Dibutyl Phthalate	

Study Citation:	Marsman, D.	S. (1995). NTP technical report on the tox	icity studi	es of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and		
Health Outcome(s) and Reported Health Effect(s): Duration and	 B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- premating (
Exposure Route:						
Species:	Mouse-CD-1	- [mouse]-Both				
Chemical:	Dibutyl Phtha	late- 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 analyt- ically 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 pro- vided; 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 Mea	asures and Resu	ılts 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 \pm SE. Sample sizes were specified. Statis-		

Additional Comments: 11.DBP Continuous breeding study in mice

Overall Quality Determination

High

provided in HERO 061570

tical 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

Study Citation:	Marsman, I	D. S. (1995). NTP technical report on the t	toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and		
Health Outcome(s) and Reported Health Effect(s): Duration and	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)					
Exposure Route:						
Species:	Mouse-CD-	1 - [mouse]-Both				
Chemical:	Dibutyl Phtl	halate- Parent compound				
HERO ID:	680063					
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality					
	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 an	d 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 mea- sures or initial histopathology.		
Domain 3: Confounding	g / Variable Co	ontrol				
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropri- ate. 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 Re	porting and At	ttrition				
	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 M	ethods Sensitiv	vity				
Continued on next page						

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Dibutyl Phthalate

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route:	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. 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 dehydroge-nase, 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). 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 analyt- ically 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 pro- vided; 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 \pm 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 Cor	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						
Health Outcome(s) and Reported Health Effect(s): Duration and	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 dehydroge-nase, 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)						
Exposure Route:							
Species:	Mouse-CD-1 - [mouse]-Both Dibutyl Phthalate Parent compound						
HERO ID:	680063	arate- I arent compound					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Q	uality 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 mea- sures 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 appropri- ate. 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							
Continued on next page							
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	continued from
Study Citation:	Marsman, D. S. (1995). NTP technical report on the toxicity s B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5.

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	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. 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 dehydroge-nase, 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days) Mouse-CD-1 - [mouse]-Both Dibutyl Phthalate- Parent compound				
Domain		Metric	Rating	Comments	
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analyt- ically 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 pro- vided; 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 Mo	easures and Re	sults 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 \pm 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 Cor	ntinuous 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 P6C3E1 mice. Toxicity Perpert Series, vol. 20 20:1 C5.					
Health Outcome(s)	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage					
and Reported	of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues,					
Health Effect(s):	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 dehydroge-					
	nase, 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 boo	ly weights (Studies 1, 2, 3, and 4).Body we	ight, feed co	nsumption (Studies 5, 6, 7, 8, 9, 10, 11, and 12).Body weight gain (Studies 5, 6, 7, and		
	12)Other (p	blease specify below) (Clinical observation	s)-Clinical (Diservations-Mortality-Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12)Renal/Kidney-		
	10 and 11)	Other (place specify below) (Clinical cher	n kluney and	tine kinese (Studies: 8, 0, 10, and 11)		
Duration and	Oral-Diet-Di	aration: Reproductive/Developmental-1-F0	- premating	(7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)		
Exposure Route:		I I I I I I I I I I I I I I I I I I I	1 0			
Species:	Mouse-CD-1	- [mouse]-Both				
Chemical:	Dibutyl Phth	alate- Parent compound				
HERO ID:	680063					
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality					
	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 dura-		
				tion, 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: Salastion and	d Darfarmanaa					
Domain 2. Selection and	Metric 2.	Allocation	Medium	HERO ID 061570 provided a study protocol that specifies animals were to be matched		
	Wietrie 2.	Allocation	Wiedium	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 mea-		
				sures or initial histopathology.		
Domain 3: Confounding	v / Variable Cor	atrol				
Domain 5. Comountuing	Metric 4.	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropri-		
	Methe 1.	contouriding / variable control	Wiedrum	ate. 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 Re	porting and Att	rition				
	Metric 5:	Selective Reporting and Attrition	High	The study provided quantitative or qualitative results for all endpoints (also see HERO		
			C	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		
				sciecuve reporting.		
Domain 5: Exposure Me	ethods Sensitiv	ity				
		Conti	nued on nex	xt page		
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Dibutyl Phthalate	

		co	ntinued from p	previous page		
Study Citation:	Marsman, 1	D. S. (1995). NTP technical report on t	he toxicity stud	lies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and		
	B6C3F1 mi	ce. Toxicity Report Series, vol. 30 30:1-	G5.			
Health Outcome(s)	Reproductive/Developmental-No. fetuses/breeding group, Litter weight; Gestation length, number of pups/litter, number of live pups/litter, percentage					
and Reported	of live pups/litter, number of pups/sex/litter, Offspring clinical observations, mortality, feed consumption, histologic examinations on >30 organs/tissues,					
Health Effect(s):	gross necro	psy, offspring body weights, number of in	nplantation sites	s, mating index, fertility index-Hepatic/Liver-Absolute liver weights of dams, palmitoyl-		
	CoA oxidas	e activity of dams (Studies 1, 2, 3, and 4).	Serum chemisti	(ALP, ALI, total protein, albumin, total cholesterol, triglycerides, sorbitol denydroge-		
	Tarminal h	dy weights (Studies 1, 2, 3, and 4) Redy	r (Studies 8 and	9). Adsolute and relative liver weight (Studies 8, 9, 10, and 11)Nutritional/Metabolic-		
	12) Other	(please specify below) (Clinical observation)	tions)-Clinical	Diservations Mortality Survival (Studies 5, 6, 7, 8, 9, 10, 11, and 12). Benal/Kidney		
	Clinical che	mistry (BUN creatinine) Historiatholog	gy of kidney an	d 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	Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)					
Exposure Route:						
Species:	Mouse-CD-	1 - [mouse]-Both				
Chemical:	Dibutyl Pht	halate- Parent compound				
HERO ID:	680063					
Domain		Metric	Rating	Comments		
	Metric 6:	Chemical administration and	High	DBP was sourced from Chem Central. The test material and purity (99%) was analyt-		
		characterization		ically verified using GC. Preparation and storage details of the test formulations were		
				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 pro- vided; 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 Mo	easures and Re	sults 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 \pm 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 Cor	tinuous breeding study in mice		

Overall Quality Determination

High

Study Citation:	Marsman, I	D. S. (1995). NTP technical report on the t	toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
Health Outcome(s) and Reported Health Effect(s): Duration and	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 dehydroge-nase, 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)				
Exposure Route:					
Species:	Mouse-CD-	1 - [mouse]-Both			
Chemical:	Dibutyl Phtl	halate- Parent compound			
HERO ID:	680063				
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	uality				
	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 an	d 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 mea- sures or initial histopathology.	
Domain 3: Confounding	g / Variable Co	ontrol			
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropri- ate. 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 Re	porting and At	ttrition			
	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					
Continued on next page					

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Human Health Hazard Animal Toxicology Evaluation

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HERO ID: 680063 Table: 33 of 34

Dibutyl Phthalate

Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. 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				
	Clinical che	mistry (BUN, creatinine), Histopathology	of kidney and	d urinary bladder (Studies 8 and 9). Absolute and relative kidney weights (Studies 8,9,	
Duration and Exposure Route:	10, and 11). Oral-Diet-D	Other (please specify below) (Clinical che uration: Reproductive/Developmental-1-F(emistry)-Crea 0- premating	tine kinase (Studies: 8, 9, 10, and 11). (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)	
Species:	Mouse-CD-	I - [mouse]-Both			
HERO ID:	680063	larate- Farent compound			
Domain		Metric	Rating	Comments	
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analyt- ically 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 pro- vided; 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 Mo	easures and Re	sults 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 \pm 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, I	D. S. (1995). NTP technical report on the t	toxicity stud	ies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and	
Health Outcome(s) and Reported Health Effect(s): Duration and	B6C3F1 mice. Toxicity Report Series, vol. 30 30:1-G5. 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 dehydroge-nase, 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0- gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days)				
Exposure Route:					
Species:	Mouse-CD-	1 - [mouse]-Both			
Chemical:	Dibutyl Phtl	halate- Parent compound			
HERO ID:	680063				
Domain		Metric	Rating	Comments	
Domain 1: Reporting Q	uality				
	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 an	d 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 mea- sures or initial histopathology.	
Domain 3: Confounding	g / Variable Co	ontrol			
	Metric 4:	Confounding / Variable Control	Medium	Control animals were administered un-dosed feed and control responses were appropri- ate. 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 Re	porting and At	ttrition			
	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					
Continued on next page					

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Human Health Hazard Animal Toxicology Evaluation

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HERO ID: 680063 Table: 34 of 34

Dibutyl Phthalate

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): Duration and Exposure Route: Species: Chemical:	BoCsPT lince. Toxicity Report Series, vol. 50 50:1-05. 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 dehydroge-nase, 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). Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (7 days)-F0 - gestation (17 days)-F0- lactation (28 days)-F0- premating (7 days) Mouse-CD-1 - [mouse]-Both				
HERO ID:	680063	arace r arent compound			
Domain		Metric	Rating	Comments	
	Metric 6:	Chemical administration and characterization	High	DBP was sourced from Chem Central. The test material and purity (99%) was analyt- ically 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 pro- vided; 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 Me	asures and Res	sults 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 \pm 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 Con	tinuous breeding study in mice			

Overall Quality Determination

High

Study Citation: Health Outcome(s)	Martino-And of active phtl Reproductive	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. Reproductive/Developmental-Testicular testosterone levels					
and Reported Health Effect(s): Duration and Exposure Route:	Oral-Gavage	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (GD13-GD21)					
Species:	Rat-Wistar -	[rat]-Female					
Chemical: HERO ID:	Dibutyl Phth 676281	alate- Parent compound					
Domain		Metric	Rating	Comments			
Domain 1: Reporting Qu	aality Metric 1:	Reporting Quality	Medium	All critical and most important information was reported. Reported information in- cluded information on the test substance (name, CASRN, purity and source), the test model (species, strain, sex, and source), animal husbandry details (photoperiod, tem- perature, 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	l Performance Metric 2:	Allocation	Low	No details on the allocation of dams into study groups or on the selection of fetuses for			
	Metric 3:	Observational Bias / Blinding Changes	Medium	outcome analysis were provided. Blinding was not specified but the outcome was measured using a standard laboratory kit.			
Demain 2: Conformation	Westehle Com	1					
	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 Rej	porting and Att Metric 5:	rition 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 Me	ethods Sensitivi	ity Contin	nued on next pa	ge			

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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 Phtl	halate- 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 Me	easures and Re	sults Display					
	Metric 8:	Endpoint sensitivity and specificity	High	Testosterone levels were measured using an ELISA assay from presumably pooled sam- ples 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 \pm 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						

Study Citation:	Moody, S., Goh, H., Bielanowicz, A., Rippon, P., Loveland, K. L., Itman, C. (2013). Prepubertal mouse testis growth and maturation and androgen					
Health Outcome(s) and Reported Health Effect(s):	production are acutely sensitive to di-n-butyl phthalate. Endocrinology 154(9):3460-3475. 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,					
Duration and	oral-Gavage-Duration: Reproductive/Developmental-F1- post-natal (PND4-21)					
Exposure Route:	Mouse-C57	RI - [mouse] Male				
Chemical: HERO ID:	Dibutyl Phth 1639195	nalate- Parent compound				
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality 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 an	d 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	g / Variable Co	ntrol				
	Metric 4:	Confounding / Variable Control	Medium	The negative control group was included and appropriate. Gavage volume was appropri- ate (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. Phtha- lates may leach into water from plastic, thereby potentially confounding the results (if plastic was used).		
Domain 4: Selective Re	porting and At	trition				
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Dibutyl Phthalate

HERO ID: 1639195 Table: 1 of 1

		contin	nued from previ	ious page		
Study Citation:	Moody, S.,	Moody, S., Goh, H., Bielanowicz, A., Rippon, P., Loveland, K. L., Itman, C. (2013). Prepubertal mouse testis growth and maturation and androgen				
Health Outcome(s) and Reported Health Effect(s):	production a Reproductiv testosterone Sertoli cells of spermato	production are acutely sensitive to di-n-butyl phthalate. Endocrinology 154(9):3460-3475. 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,				
Duration and	alpha-tubulin, cleaved caspase 3. Oral-Gayage-Duration: Reproductive/Developmental-F1- post-natal (PND4-21)					
Exposure Route:	Orar-Oavage-Duration. Reproductive/Developmentai-11- post-natal (110D+-21)					
Species:	Mouse-C57	BL - [mouse]-Male				
Chemical: HERO ID:	Dibutyl Phtl 1639195	halate- Parent compound				
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 M	lethods Sensitiv	vity				
-	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 M	easures and Re	sults 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 Quali	ty Deteri	nination	Medium			

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Mylchreest, I rats exposed Reproductive weights, AGI vas deferens, Oral-Gavage- Rat-Sprague- Dibutyl Phtha 673305	E., Wallace, D. G., Cattley, R. C., Foster, P to di(n-butyl) phthalate during late gestatio //Developmental-F0: Organ weights (uterus D, male nipple/areolae count, vaginal openin ventral prostate, levator ani-bulbocavernos -Duration: Reproductive/Developmental-F(Dawley - [rat]-Female alate- Parent compound	M. (2000). n. Toxicolog s, ovaries), i ng or preput us muscle),) - gestation	Dose-dependent alterations in androgen-regulated male reproductive development in gical Sciences 55(1):143-151. Implantation sites. F1:numbers of live and dead pups, sex, pups signs of toxicity, pup ial separation, necropsy, organ weights (ovaries, testes, seminal vesicles, epididymides, histopathology of male reproductive tissues (12-21)
Domain 1: Reporting O	uality	Weute	Raing	Commento
	Metric 1:	Reporting Quality	High	Test substance was reported as DBP (99.8% pure) from Aldrich chem. No CAS or struc- ture were reported. Doses were administered via gavage and doses were reported appro- priately (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: hus- bandry 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 previ- ously identified LOAEL and less power was needed. Exposure via gavage was adminis- tered daily to dams (during gestation GD 12-21) to encompass the period of male sexual differentiation. Endpoint evaluation methods were reported and qualitative or quantita- tive results were reported for most endpoints.
Domain 2: Selection and	d 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	a / Variable Con	trol		
	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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Human Health Hazard Animal Toxicology Evaluation

HERO ID: 673305 Table: 1 of 5

		cont	tinued from p	revious page		
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development is rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151. Reproductive/Developmental-F0: Organ weights (uterus, ovaries), implantation sites. F1:numbers of live and dead pups, sex, pups signs of toxicity, pu weights, AGD, male nipple/areolae count, vaginal opening or preputial separation, necropsy, organ weights (ovaries, testes, seminal vesicles, epididymide vas deferens, ventral prostate, levator ani-bulbocavernosus muscle), histopathology of male reproductive tissues Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21) Rat-Sprague-Dawley - [rat]-Female Dibutyl Phthalate- Parent compound 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 N	Iethods Sensitiv	vity				
·	Metric 6:	Chemical administration and characterization	Medium	The chemical source (Aldrich chemical Co.) and purity (99.8%) were reported. No in- dependent 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 M	leasures and Re	esulte Dienlay				
2 cintan o. Outcome iv	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.		

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Dibutyl Phthalate

HERO ID: 673305 Table: 1 of 5

		continued from previous pag	e			
Study Citation:	Mylchreest, E., Wallace, D. G., Cattley, R. C rats exposed to di(n-butyl) phthalate during	C., Foster, P. M. (2000). Dose-depe late gestation. Toxicological Science	ndent alterations in androgen-regulated male reproductive development in es 55(1):143-151.			
Health Outcome(s)	Reproductive/Developmental-F0: Organ we	ights (uterus, ovaries), implantation	sites. F1:numbers of live and dead pups, sex, pups signs of toxicity, pup			
and Reported	weights, AGD, male nipple/areolae count, va	ginal opening or preputial separatio	n, necropsy, organ weights (ovaries, testes, seminal vesicles, epididymides,			
Health Effect(s):	vas deferens, ventral prostate, levator ani-bulbocavernosus muscle), histopathology of male reproductive tissues					
Duration and	Oral-Gavage-Duration: Reproductive/Develo	opmental-F0 - gestation (12-21)				
Exposure Route:						
Species:	Rat-Sprague-Dawley - [rat]-Female					
Chemical:	Dibutyl Phthalate- Parent compound					
HERO ID:	673305					
Domain	Metric	Rating	Comments			
Overall Quali	ty Determination	High				

Study Citation:	Mylchreest,	Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in							
Health Outcome(s) and Reported Health Effect(s):	Nutritional/I	Nutritional/Metabolic-Dam body weight, body weight gain, food consumption							
Duration and Exposure Route:	Oral-Gavage	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21)							
Species: Chemical: HERO ID:	Rat-Sprague-Dawley - [rat]-Female Dibutyl Phthalate- Parent compound 673305								
Domain		Metric	Rating	Comments					
Domain 1: Reporting Q	uality Metric 1:	Reporting Quality	High	Test substance was reported as DBP (99.8% pure) from Aldrich chem. No CAS or struc- ture were reported. Doses were administered via gavage and doses were reported appro- priately (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: hus- bandry 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 guide- line 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 ad- ministered 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	d 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	g / Variable Co	ntrol							
	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 Re	porting and At Metric 5:	trition 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.					
		Conti	nued on ney	xt page					

		con	tinued from p	revious page			
Study Citation:	Mylchreest, rats exposed	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 Poute:	Oral-Gavag	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21)					
Species: Chemical: HERO ID:	Rat-Sprague Dibutyl Phtl 673305	e-Dawley - [rat]-Female halate- Parent compound					
Domain		Metric	Rating	Comments			
Domain 5: Exposure M	ethods Sensitiv	vity					
	Metric 6:	Chemical administration and characterization	Medium	The chemical source (Aldrich chemical Co.) and purity (99.8%) were reported. No in- dependent 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 Me	easures and Re	sults 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 ap- propriate 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 Qualit	ty Deteri	nination	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	rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151.					
Health Outcome(s)	Hepatic/Live	Hepatic/Liver-Liver weight-Renal/Kidney-Kidney weight-Other (please specify below) (endocrine)-adrenal gland weight					
and Reported							
Health Effect(s):							
Duration and	Oral-Gavage	e-Duration: Reproductive/Developmental-F0	- gestation (12-	21)			
Exposure Route:							
Species:	Rat-Sprague-Dawley - [rat]-Female						
Chemical:	Dibutyl Phthalate- Parent compound						
HERO ID:	673305	-					
Domain		Metric	Rating	Comments			
Domain 1: Reporting (Quality		0				
	Metric 1:	Reporting Quality	High	Test substance was reported as DBP (99.8% pure) from Aldrich chem. No CAS or struc-			
				ture were reported. Doses were administered via gavage and doses were reported appro- priately (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: hus- bandry 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 guide- line 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 ad- ministered 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 an	nd 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: Contoundin	ng / Variable Co	ntrol					
	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 1. Salastiva D	enorting and A+	trition					
Domain 4. Selective R	Metric 5	Selective Reporting and Attrition	High	The number of deaths was low and explained (lack of pregnancy or debudgetion). The			
	wieuric 5:	Selective Reporting and Authon	nigii	results were reported quantitatively or with a qualitative statement for each outcome and there was no evidence of selective reporting.			
		Contin	ued on next na	ge			
		Contin		0			

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Study Citation: Health Outcome(s) and Reported Health Effect(c)	Mylchreest, rats exposed Hepatic/Liv	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. Hepatic/Liver-Liver weight-Renal/Kidney-Kidney weight-Other (please specify below) (endocrine)-adrenal gland weight						
Duration and	Oral-Gavage	Oral-Gavage-Duration: Reproductive/Developmental-F0 - gestation (12-21)						
Exposure Route: Species:	Rat-Sprague	e-Dawley - [rat]-Female						
Chemical: HERO ID:	Dibutyl Phtl 673305	nalate- Parent compound						
Domain		Metric	Rating	Comments				
Domain 5: Exposure Me	ethods Sensitiv	vity						
	Metric 6:	Chemical administration and characterization	Medium	The chemical source (Aldrich chemical Co.) and purity (99.8%) were reported. No in- dependent 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 Me	easures and Re	sults 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 Qualit	ty Deteri	nination	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					
Health Outcome(s)	rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151. Henatic/Liver-Liver weight-Renal/Kidney-Kidney weight-Other (please specify below) (endocrine)-adrenal gland weight					
and Reported	Thepatic/Erver-Erver weight-Kenal/Kluney-Kluney weight-Onler (please speen y below) (endocrine)-adrenal grand weight					
Health Effect(s):						
Duration and	Oral-Gavage	e-Duration: Reproductive/Developmental-F0	- gestation (12-	21)		
Exposure Route:		I I I I I I I I I I I I I I I I I I I	8	,		
Species:	Rat-Sprague	e-Dawley - [rat]-Female				
Chemical:	Dibutyl Phth	nalate- 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 struc- ture were reported. Doses were administered via gavage and doses were reported appro- priately (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: hus- bandry 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 guide- line 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 ad- ministered 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 as	nd Performance Metric 2:	Allocation	Medium	The method of allocation to study groups was reported as "using randomization of body		
	fileane 2.		inculum	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: Confoundir	ng / Variable Co	ntrol				
	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 P	enorting and At	trition				
Domain 4. Selective K	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.		
		Contin	ued on next pa	nge		

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		cont	inued from previo	us page		
Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. Hepatic/Liver-Liver weight-Renal/Kidney-Kidney weight-Other (please specify below) (endocrine)-adrenal gland weight					
Duration and Exposure Route:	Oral-Gavage	e-Duration: Reproductive/Developmental-I	F0 - gestation (12-2	21)		
Species: Chemical: HERO ID:	Rat-Sprague Dibutyl Pht 673305	e-Dawley - [rat]-Female halate- Parent compound				
Domain		Metric	Rating	Comments		
Domain 5: Exposure Me	ethods Sensitiv	vity				
ľ	Metric 6:	Chemical administration and characterization	Medium	The chemical source (Aldrich chemical Co.) and purity (99.8%) were reported. No in- dependent 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 Me	easures and Re	sults 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 Qualit	ty Deteri	nination	Medium			

Study Citation:	Mylchreest,	Mylchreest, E., Wallace, D. G., Cattley, R. C., Foster, P. M. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in				
Health Outcome(s)	rats exposed	rats exposed to di(n-butyl) phthalate during late gestation. Toxicological Sciences 55(1):143-151. Henatic/LiveryLiveryLiveryLiveryLidney-Kidney weight-Other (please specify below) (endocrine)-adrenal gland weight				
and Reported	riepatie/Liw	er-Liver weight-Kenal/Kluney-Kluney weight	t-Other (please	specify below) (endoernie)-adrenar grand weight		
Health Effect(s):						
Duration and	Oral-Gavage	e-Duration: Reproductive/Developmental-F0	- gestation (12-	21)		
Exposure Route:		I I I I I I I I I I I I I I I I I I I	8	,		
Species:	Rat-Sprague	e-Dawley - [rat]-Female				
Chemical:	Dibutyl Phth	nalate- 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 struc- ture were reported. Doses were administered via gavage and doses were reported appro- priately (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: hus- bandry 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 guide- line 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 ad- ministered 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 as	nd Performance Metric 2:	Allocation	Medium	The method of allocation to study groups was reported as "using randomization of body		
	fileane 2.		inculum	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: Confoundir	ng / Variable Co	ntrol				
	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 P	enorting and At	trition				
Domain 4. Selective K	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.		
		Contin	ued on next pa	nge		

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		cont	inued from previo	bus page		
Study Citation: Health Outcome(s) and Reported Health Effect(s):	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. Hepatic/Liver-Liver weight-Renal/Kidney-Kidney weight-Other (please specify below) (endocrine)-adrenal gland weight					
Duration and	Oral-Gavag	e-Duration: Reproductive/Developmental-I	F0 - gestation (12-2	21)		
Exposure Route:	Det Comercia	Develop [ast] Formale				
Chemical:	Dibutyl Pht	halate- Parent compound				
HERO ID:	673305					
Domain		Metric	Rating	Comments		
Domain 5: Exposure Me	ethods Sensitiv	vity				
	Metric 6:	Chemical administration and characterization	Medium	The chemical source (Aldrich chemical Co.) and purity (99.8%) were reported. No in- dependent 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 Me	easures and Re	esults 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 Qualit	ty Deteri	mination	Medium			

Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Salazar, V., Castillo, C., Ariznavarreta, C., Campón of Long Evans rats and pre-pubertal development of Reproductive/Developmental-Percentage of pregna weights of pups (PND2, PND6); Days to eyes' ope (PND14); Thymus relative weight of male pups (PN to pre-putial separation in male pups-Nutritional/Me Oral-Diet-Duration: Reproductive/Developmental- premating (PND 22 - up to PND 41) Rat-Long-Evans - [rat]-Female Dibutyl Phthalate- Parent compound 673308	, R., Tresguerres, F., J.A. (200 f their offspring. Toxicology 2 nt rats; Litter size (PND0, 2, ning (assessed PND6 onward VD14); Plasma of male pups (etabolic-Dam body weights; T 1-F0- premating (unclear 2-2.	04). Effect of oral intake of dibutyl phthalate on reproductive parameters 205(1-2):131-137. and 6); Pup survival; Female:male ratio of pups (PND2, PND6); Body ls); Male pup body weight (PND14); Testis relative weight of male pups (PND14); Days to vaginal opening and first estrous in female pups; Days Total dam body weight gain (g/3 months) .5 months)-F0- mating (NR)-F0 - gestation (NR)-F0- lactation (NR)-F1-
Domain	Metric	Rating	Comments
Domain 1: Reporting Q	Quality	C	
	Metric 1: Reporting Quality	Low	All critical and most important information was reported in this study. The study in- cluded 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 end- point 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 an- imals 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 in- formation is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation. However, un- certainties 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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Human Health Hazard Animal Toxicology Evaluation

HERO ID: 673308 Table: 1 of 2

		cont	inued from previou	s page	
Study Citation:	Salazar, V.,	Castillo, C., Ariznavarreta, C., Campón, R., Tre	sguerres, F., J.A. (20	004). Effect of oral intake of dibutyl phthalate on reproductive parameters	
Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 of Long Evans rats and pre-pubertal development of their offspring. Toxicology 205(1-2):131-137. ne(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 s): (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) Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (unclear 2-2.5 months)-F0- mating (NR)-F0- gestation (NR)-F0- lactation (NR)-F1- te: premating (PND 22 - up to PND 41) Rat-Long-Evans - [rat]-Female Dibutyl Phthalate- Parent compound 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: Confoundin	ng / Variable Co Metric 4:	ntrol 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 R	enorting and At	trition			
	Metric 5:	Selective Reporting and Attrition	Low	Quantitative or qualitative results were reported for most, but not all outcomes de- scribed 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 M	1ethods Sensitiv	vity			
Continued on next page					

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Human Health Hazard Animal Toxicology Evaluation

HERO ID: 673308 Table: 1 of 2

		•••	continued from previous p	age		
Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Salazar, V., of Long Eva Reproductiv weights of p (PND14); T to pre-putial Oral-Diet-D premating (Rat-Long-E Dibutyl Phtl 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. 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) 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) Rat-Long-Evans - [rat]-Female Dibutyl Phthalate- Parent compound 673308				
Domain		Metric	Rating	Comments		
	Metric 6: Metric 7:	Chemical administration and characterization Exposure timing, frequency, and duration	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. 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 M	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 $\leq 81.8\%$ of females became pregnant.		
			Continued on next page			

Human Health Hazard Animal Toxicology Evaluation

HERO ID: 673308 Table: 1 of 2

		continued from previous	s page		
Study Citation:	Salazar, V., Castillo, C., Ariznavarreta, C., Campón, of Long Evans rats and pre-pubertal development of	R., Tresguerres, F., J.A. (20)	04). Effect of oral intake of dibutyl phthalate on reproductive parameters 205(1-2):131-137		
Health Outcome(s)	Reproductive/Developmental-Percentage of pregnant rats: Litter size (PND0, 2, and 6): Pup survival: Female:male ratio of pups (PND2, PND6): Body				
and Reported	weights of pups (PND2, PND6): Days to eves' oper	ning (assessed PND6 onward	ds): Male pup body weight (PND14): Testis relative weight of male pups		
Health Effect(s):	(PND14): Thymus relative weight of male pups (PN	D14): Plasma of male pups	(PND14): Days to vaginal opening and first estrous in female pups: Days		
	to pre-putial separation in male pups-Nutritional/Me	tabolic-Dam body weights:	Total dam body weight gain ($g/3$ months)		
Duration and	Oral-Diet-Duration: Reproductive/Developmental-1	-F0- premating (unclear 2-2	.5 months)-F0- mating (NR)-F0 - gestation (NR)-F0- lactation (NR)-F1-		
Exposure Route:	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 \pm 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 lit- ters 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 inde- pendent 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: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	 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. 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) Oral-Diet-Duration: Reproductive/Developmental-1-F0- premating (unclear 2-2.5 months)-F0- mating (NR)-F0- lactation (NR)-F1- premating (PND 22 - up to PND 41) Rat-Long-Evans - [rat]-Female Dibutyl Phthalate- Parent compound 673308 			
Domain	Metric	Rating	Comments	
Domain 1: Reporting Q	uality			
	Metric 1: Reporting Quality	Low	All critical and most important information was reported in this study. The study in- cluded 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 end- point 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 an- imals 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 in- formation is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation. However, un- certainties 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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Human Health Hazard Animal Toxicology Evaluation

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Salazar, V., C of Long Eva Reproductive weights of p (PND14); TH to pre-putial Oral-Diet-Du premating (F Rat-Long-Ev Dibutyl Phth 673308	Castillo, C., Ariznavarreta, C., Campón, R., Tre ns rats and pre-pubertal development of their of e/Developmental-Percentage of pregnant rats; I ups (PND2, PND6); Days to eyes' opening (as nymus relative weight of male pups (PND14); F separation in male pups-Nutritional/Metabolic- uration: Reproductive/Developmental-1-F0- pro PND 22 - up to PND 41) vans - [rat]-Female alate- Parent compound	ssguerres, F., J.A. (20) fspring. Toxicology Litter size (PND0, 2, sessed PND6 onward Plasma of male pups Dam body weights; emating (unclear 2-2)	04). Effect of oral intake of dibutyl phthalate on reproductive parameters 205(1-2):131-137. , and 6); Pup survival; Female:male ratio of pups (PND2, PND6); Body ds); Male pup body weight (PND14); Testis relative weight of male pups (PND14); Days to vaginal opening and first estrous in female pups; Days Total dam body weight gain (g/3 months) .5 months)-F0- mating (NR)-F0 - gestation (NR)-F0- lactation (NR)-F1-	
Domain	075500	Metric	Rating	Comments	
Domain	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: Confoundin	og / Variable Cou	ntrol			
	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 coexposures 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 de- scribed 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 M	lethods Sensitiv	ity			
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Human Health Hazard Animal Toxicology Evaluation

HERO ID: 673308 Table: 2 of 2

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Study Citation: Health Outcome(s) and Reported Health Effect(s): Duration and Exposure Route: Species: Chemical: HERO ID:	Salazar, V., of Long Eva Reproductiv weights of p (PND14); T to pre-putial Oral-Diet-D premating (Rat-Long-E Dibutyl Phtl 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. 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) 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) Rat-Long-Evans - [rat]-Female Dibutyl Phthalate- Parent compound 673308				
Domain		Metric	Rating	Comments		
	Metric 6: Metric 7:	Chemical administration and characterization Exposure timing, frequency, and duration	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. 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 M	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 $\leq 81.8\%$ of females became pregnant.		
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Human Health Hazard Animal Toxicology Evaluation

HERO ID: 673308 Table: 2 of 2

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Study Citation:	Salazar, V., Castillo, C., Ariznavarreta, C., Campón, of Long Evans rats and pre-pubertal development of	R., Tresguerres, F., J.A. (20)	04). Effect of oral intake of dibutyl phthalate on reproductive parameters 205(1-2):131-137		
Health Outcome(s)	Reproductive/Developmental-Percentage of pregnant rats: Litter size (PND0, 2, and 6): Pup survival: Female:male ratio of pups (PND2, PND6): Body				
and Reported	weights of pups (PND2, PND6): Days to eves' oper	ning (assessed PND6 onward	ds): Male pup body weight (PND14): Testis relative weight of male pups		
Health Effect(s):	(PND14): Thymus relative weight of male pups (PN	D14): Plasma of male pups	(PND14): Days to vaginal opening and first estrous in female pups: Days		
	to pre-putial separation in male pups-Nutritional/Me	tabolic-Dam body weights:	Total dam body weight gain ($g/3$ months)		
Duration and	Oral-Diet-Duration: Reproductive/Developmental-1	-F0- premating (unclear 2-2	.5 months)-F0- mating (NR)-F0 - gestation (NR)-F0- lactation (NR)-F1-		
Exposure Route:	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 \pm 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 lit- ters 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 inde- pendent 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: Health Outcome(s) and Reported Health Effect(s):	Struve, M. F. and pharmac Reproductive Reproductive	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. Reproductive/Developmental-Fetal testosterone				
Duration and Exposure Route:	Oral-Diet-Du	ration: Reproductive/Developmental-1-F0 -	gestation (GD	12- GD 19)		
Species: Chemical: HERO ID:	Rat-Sprague- Dibutyl Phth 684035	Dawley - [rat]-Female alate- Parent compound				
Domain		Metric	Rating	Comments		
Domain 1: Reporting Q	uality 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	d 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	y / Variable Cor	atrol				
	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 Re	norting and Att	rition				
	Metric 5:	Selective Reporting and Attrition	High	All animals were accounted for in the results. There is no indication of selective report- ing or attrition.		
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Human Health Hazard Animal Toxicology Evaluation

HERO ID: 684035 Table: 1 of 1

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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)	Reproductive/Developmental-Fetal testosterone			
and Reported		•		
Health Effect(s):				
Duration and	Oral-Diet-Duration: Reproductive/Developmental-1-F0 - gestation (GD 12- GD 19)			
Exposure Route:				
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 ho- mogeneity of all DBP-containing diets were verified using an Agilent 6890 gas chro- matograph with 5973 mass spectrometer". These data were not reported. Study au- thors 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 M	easures and Re	esults 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