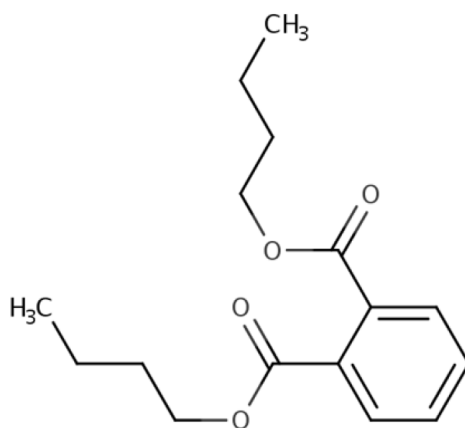

**Data Quality Evaluation and Data Extraction Information for
Dermal Absorption for
Dibutyl Phthalate (DBP)
(1,2-Benzenedicarboxylic acid, 1,2-dibutyl ester)**

Systematic Review Support Document for the Draft Risk Evaluation

CASRN: 84-74-2



December 2025

This supplemental file contains information regarding the data evaluation results for data sources that met the PECO (Population, Exposure, Comparator or Scenario, and Outcomes) screening criteria for the *Risk Evaluation for Dibutyl Phthalate (DBP)* and were used to characterize dermal absorption. EPA conducted data quality evaluations based on author-reported descriptions and results; additional analyses (*e.g.*, statistical analyses performed during data integration for the risk evaluation) potentially conducted by EPA are not contained in this supplemental file. Key parameters and corresponding data for each condition were extracted from the reference. EPA performs data quality evaluation as a part of the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as the '2021 Draft Systematic Review Protocol'). The systematic review steps are further described in the *Systematic Review Protocol for Dibutyl Phthalate (DBP)*.

To evaluate dermal absorption references, EPA consulted several OECD documents when considering quality rankings for individual metrics. Each condition (*e.g.*, individual concentrations tested or different experimental designs) is evaluated independently within a given reference. Therefore each reference may have more than one overall quality determination (OQD) to more appropriately reflect the quality of each condition. No OQD is determined for each reference as a whole, if it contains data from more than one condition. A single reference may evaluate only a limited number of conditions (*e.g.*, use of only the neat compound). If all other methods and results are adequate, the study may be considered acceptable for certain conditions of use. However, the study may still be limited for use in the risk evaluation because it may not address other uses (*e.g.*, lower concentrations, certain solvents/diluents).

Table of Contents

HERO ID	Reference	Page
In vitro		
1323147	Doan, K., Bronaugh, R. L., Yourick, J. J. (2010). In vivo and in vitro skin absorption of lipophilic compounds, dibutyl phthalate, farnesol and geraniol in the hairless guinea pig. Food and Chemical Toxicology 48(1):18-23.	4
2219803	Pan, T. L., Wang, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. F., Fang, J. Y. (2014). Dermal toxicity elicited by phthalates: Evaluation of skin absorption, immunohistology, and functional proteomics. Food and Chemical Toxicology 65:105-114.	12
674473	Scott, R. C., Dugard, P. H., Ramsey, J. D., Rhodes, C. (1987). In vitro absorption of some o-phthalate diesters through human and rat skin. Environmental Health Perspectives 74(0):223-227.	23
3859042	Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17.	30
In vivo - Animal		
1323147	Doan, K., Bronaugh, R. L., Yourick, J. J. (2010). In vivo and in vitro skin absorption of lipophilic compounds, dibutyl phthalate, farnesol and geraniol in the hairless guinea pig. Food and Chemical Toxicology 48(1):18-23.	46
675074	Elsisi, A. E., Carter, D. E., Sipes, I. G. (1989). Dermal absorption of phthalate diesters in rats. Fundamental and Applied Toxicology 12(1):70-77.	49

Study Citation:	Doan, K., Bronaugh, R. L., Yourick, J. J. (2010). In vivo and in vitro skin absorption of lipophilic compounds, dibutyl phthalate, farnesol and geraniol in the hairless guinea pig. Food and Chemical Toxicology 48(1):18-23.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	1323147			
Unique ID:	24-hr duration			
Domain	Metric	Rating	Comments	
Domain 1: Test Substance				
Metric 1:	Test substance identity	Medium	The test substance was identified as dibutyl phthalate (DBP). CASRN: 84-74-2. Physio-chemical properties (MW, Log Kow, water solubility, and solubility in alcohol) were also reported. Unlabeled DBP was spiked with radiolabeled 14C-DBP. A structure showing the site of the radiolabel was not provided.	
Metric 2:	Test substance source	Low	Radiolabeled DBP was purchased from Sigma. This product can no longer be located on the supplier website and the performing laboratory did not analytically verify the test substance identity. Unlabeled DBP was purchased from Acros Organics; the catalogue, or lot/batch number were not reported. A single DBP product currently on the supplier's website has a certificate of analysis; however, because this study is over ten years old, the information currently on the supplier's website may not be applicable to the test material used in this study.	
Metric 3:	Test substance purity	Medium	The radiochemical purity of 14C-DBP was >97% and specific activity was 21.1 mCi/mmol. Impurities were not specified. The purity of the unlabeled material was not specified in the study report. A single DBP product currently on the supplier's website has a purity of ≥99%; however, because this study is over ten years old, the information on the supplier's website may not apply to the test material used in this study.	
Domain 2: Test Design				
Metric 4:	Reference compounds	Low	The study did not include any specified concurrent controls (caffeine, testosterone, or benzoic acid). The study text indicated that the performing laboratory had experience conducting in vitro diffusion cell studies using the skin from the same species and strain used in the current study, and citations were provided.	
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Study Citation: Doan, K., Bronaugh, R. L., Yourick, J. J. (2010). In vivo and in vitro skin absorption of lipophilic compounds, dibutyl phthalate, farnesol and geraniol in the hairless guinea pig. Food and Chemical Toxicology 48(1):18-23. Chemical: Dibutyl Phthalate Exposure Type: Parent compound HERO ID: 1323147 Unique ID: 24-hr duration				
Domain	Metric		Rating	Comments
	Metric 5:	Assay procedures	Medium	Details of the assay procedure were clearly described, with only a few missing details. In brief: skin, in flow-through diffusion cells, was equilibrated for 30 minutes prior to the start of exposure. The temperature of the skin and circulating water were maintained at 32 and 35 degrees C, respectively. The humidity was not reported. The fluid flow rate was 1.5 mL/hour. The diffusion cells were 0.64 cm ² , it is assumed this is the skin surface area (although not explicitly stated). The skin punches (n = 24) were made using a 17 mm circular punch. The receptor fluid was HEPES-buffered Hanks' balanced salt solution containing 4% BSA. The use of BSA is recommended for lipophilic compounds. The test material, prepared in an oil-in-water emulsion, as described in Metric 7.0 was applied to the skin at a dosage of 1 mg/cm ² for 24 or 72 hours. Carbon filter paper was placed on the top of each diffusion cell for 1 hour to trap any volatile test material. Receptor fluid was collected at 6-hour intervals. After exposure, the skin was washed 3 times with a detergent solution and then rinsed twice with distilled water. The skin discs were tape stripped 10 times, and radioactivity in the carbon trap, receptor fluid, the remaining epidermis/dermis, and the tape-stripped sections was measured. It was not specified whether the tape-stripped samples were pooled. Radioactivity in the washes was purportedly not measured and was not included in the determination of recovery. Specific details of scintillation counting (e.g., the time or number of counts) were not provided.
	Metric 6:	Standards for tests	Low	The skin integrity was not assessed prior to the start of the study, and no justification was provided by the study authors. The % recoveries reported were appropriate (96.3% in the 24-hour experiment and 110.9% in the 72-hour experiment); however, based on the data provided, these percentages do not include counts from the carbon traps. The coefficients of variation for radioactivity from all sources and for total recovery were not reported but could be determined based on the information provided.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Some details regarding the preparation of the test solution were described. An oil-in-water emulsion was prepared that contained 7% cold DBP, 3% polyglyceryl disterate, 3% cetyl steryl alcohol, 10% light mineral oil, 5% propylene glycol, 0.5% propyl-p-hydroxybenzoate, 0.5% methyl-p-hydroxybenzoate and 78% water. This formulation was then spiked with radiolabeled DBP and the amount of radioactivity was assayed in triplicate to determine the applied dose. Typically studies use either unlabeled or radiolabeled test substances. OECD TG 28 indicates that, when appropriate, radiolabeled chemicals can be diluted with the non-radiolabeled chemical. It is unclear whether the dilution in this study was appropriate. No explanation was provided for why an oil-in-water emulsion was used, but based on the physical/chemical properties of the test substance, it has a moderately high Log Kow and relatively low water solubility (lipophilic), and solubility is increased in the presence of alcohol. No details on the frequency of the preparation, or mixing to assure homogeneity or storage, or stability in the emulsion were provided. Since a single application was applied to the skin, it is not expected that the lack of details on storage will significantly impact the study results.
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Study Citation:	Doan, K., Bronaugh, R. L., Yourick, J. J. (2010). In vivo and in vitro skin absorption of lipophilic compounds, dibutyl phthalate, farnesol and geraniol in the hairless guinea pig. Food and Chemical Toxicology 48(1):18-23.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	1323147			
Unique ID:	24-hr duration			
Domain		Metric	Rating	Comments
	Metric 8:	Consistency of exposure administration	Medium	This study included a single dose group of 1 mg/cm ² , with 24 or 16 replicates for the 24 hr or 72-hour exposures, respectively. The amount applied to the skin had a specific activity of 0.5 uCi; the volume was not specified. The skin thickness (200-320 um) was reported. The area of the diffusion cell was 0.64 cm ² . There is no indication of significant differences across replicates.
	Metric 9:	Reporting of concentrations	High	The exposure concentration of 1 mg/cm ² was reported without ambiguity, and the specific activity was reported. The doses were based on analytical measurements of the spiked solution. The study authors justified the dosing formulation by indicating that 7% DBP is a concentration typically found in cosmetic products.
	Metric 10:	Exposure frequency	High	The study included two exposure durations, 24 hours, which is standard, and 72 hours, which is an extended time point. These durations were both included to coincide with in vivo experiments at the same durations. OECD TG 156 indicates that skin may start to deteriorate after 24 hours and therefore data generated from longer durations should be considered with caution; however, for lipophilic substances, it may take longer for the chemical to migrate from a skin depot to the receptor fluid.
	Metric 11:	Number of exposure groups and concentration spacing	Low	The purpose of this study was to conduct comparisons between in vitro and in vivo absorption models, and therefore, only a single dose group was used. The concentration used was justified by the study authors.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	Fresh skin samples were excised from female hairless guinea pigs and processed to remove excess subcutaneous fat and were dermatomed to a thickness of 200 - 320 um. 17 mm diameter circular sections were placed in each diffusion cell. The study authors justified the use of guinea pig skin as being similar to humans. The anatomical site of the tissue collections was not specified.
	Metric 13:	Number/Replicates per group	Medium	The study used a total of 24 replicates for the 24-hour experiment and 16 replicates for the 72-hour experiment. The numbers of replicates were adequate for the outcomes measured. It was not specified how many animals were used to generate these samples.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	High	Adherence to a specific guideline was not specified, but the study had some similarities to the OECD TG 428. The outcome assessment methodology was adequately reported and was sensitive for the outcome of interest. The selected concentration was representative of one typically found in cosmetic products. This was presumably a finite dose study (the volume applied was not specified) that was used to determine percent absorption values.
	Metric 15:	Consistency of outcome assessment	Medium	Based on the data available, there is no indication of inconsistencies across replicates in the outcome assessment protocols. Some information was not specified, for example, how soon after the collection of receptor fluids was scintillation counts performed.
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Study Citation:	Doan, K., Bronaugh, R. L., Yourick, J. J. (2010). In vivo and in vitro skin absorption of lipophilic compounds, dibutyl phthalate, farnesol and geraniol in the hairless guinea pig. Food and Chemical Toxicology 48(1):18-23.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	1323147			
Unique ID:	24-hr duration			
Domain	Metric	Rating	Comments	
	Metric 16:	Sampling adequacy and sensitivity	Low	Scintillation counts/sample and/or duration of radioactivity detection, and whether there was an adequate signal-to-noise [i.e., background] ratio for detection were not reported. It is unclear whether these missing details would have a significant impact on the results. All samples from each replicate were analyzed (n = 24, or 16).
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	The study included only a single group. Skin was excised from animals obtained from the same source. The age of the animals was not specified, and the number of animals used to obtain the skin samples was not reported. The standard deviations in the study, including for recovery, were low, indicating low variation among replicates. Skin integrity/quality was not assessed.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	The study did not explicitly demonstrate the solubility of the test substance in the receptor fluid, but the fluid used was compatible with lipophilic substances. There were no reported differences among the replicates that were unrelated to exposure.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	This study did not require any statistical analysis. Total recovery was determined, and was within 100 ± 10%, but did not include skin washes or recovery from the carbon traps, even though they were part of the study protocol; the levels in the charcoal trap were low; skin washes were not measured. The CVs were <25% for all but one end-point evaluated (CV of % in stratum corneum at 72 hours was 26%). Absorption estimates (based on measurements in receptor fluid) were reported across time.
	Metric 20:	Data interpretation	High	Recovery of the applied test substance was adequate. Both the skin compartment and tape stripping measurements were included. The results were correctly interpreted relative to the set-up of the assay.
	Metric 21:	Reporting of data	High	Data were adequately reported as means ± SEM and the sample size "n" was specified.
Overall Quality Determination			Medium	

Study Citation:	Doan, K., Bronaugh, R. L., Yourick, J. J. (2010). In vivo and in vitro skin absorption of lipophilic compounds, dibutyl phthalate, farnesol and geraniol in the hairless guinea pig. Food and Chemical Toxicology 48(1):18-23.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	1323147			
Unique ID:	72-hr duration			
Domain		Metric	Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified as dibutyl phthalate (DBP). CASRN: 84-74-2. Physio-chemical properties (MW, Log Kow, water solubility, and solubility in alcohol) were also reported. Unlabeled DBP was spiked with radiolabeled 14C-DBP. A structure showing the site of the radiolabel was not provided.
	Metric 2:	Test substance source	Low	Radiolabeled DBP was purchased from Sigma. This product can no longer be located on the supplier website and the performing laboratory did not analytically verify the test substance identity. Unlabeled DBP was purchased from Acros Organics; the catalogue, or lot/batch number were not reported. A single DBP product currently on the supplier's website has a certificate of analysis; however, because this study is over ten years old, the information currently on the supplier's website may not be applicable to the test material used in this study.
	Metric 3:	Test substance purity	Medium	The radiochemical purity of 14C-DBP was >97% and specific activity was 21.1 mCi/mmol. Impurities were not specified. The purity of the unlabeled material was not specified in the study report. A single DBP product currently on the supplier's website has a purity of ≥99%; however, because this study is over ten years old, the information on the supplier's website may not apply to the test material used in this study.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	The study did not include any specified concurrent controls (caffeine, testosterone, or benzoic acid). The study text indicated that the performing laboratory had experience conducting in vitro diffusion cell studies using the skin from the same species and strain used in the current study, and citations were provided.
	Metric 5:	Assay procedures	Medium	Details of the assay procedure were clearly described, with only a few missing details. In brief: skin, in flow-through diffusion cells, was equilibrated for 30 minutes prior to the start of exposure. The temperature of the skin and circulating water were maintained at 32 and 35 degrees C, respectively. The humidity was not reported. The fluid flow rate was 1.5 mL/hour. The diffusion cells were 0.64 cm2, it is assumed this is the skin surface area (although not explicitly stated). The skin punches (n = 24) were made using a 17 mm circular punch. The receptor fluid was HEPES-buffered Hanks' balanced salt solution containing 4% BSA. The use of BSA is recommended for lipophilic compounds. The test material, prepared in an oil-in-water emulsion, as described in Metric 7.0 was applied to the skin at a dosage of 1 mg/cm2 for 24 or 72 hours. Carbon filter paper was placed on the top of each diffusion cell for 1 hour to trap any volatile test material. Receptor fluid was collected at 6-hour intervals. After exposure, the skin was washed 3 times with a detergent solution and then rinsed twice with distilled water. The skin discs were tape stripped 10 times, and radioactivity in the carbon trap, receptor fluid, the remaining epidermis/dermis, and the tape-stripped sections was measured. It was not specified whether the tape-stripped samples were pooled. Radioactivity in the washes was purportedly not measured and was not included in the determination of recovery. Specific details of scintillation counting (e.g., the time or number of counts) were not provided.

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Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	1323147			
Unique ID:	72-hr duration			
Domain	Metric	Rating	Comments	
	Metric 6: Standards for tests	Low	The skin integrity was not assessed prior to the start of the study, and no justification was provided by the study authors. The % recoveries reported were appropriate (96.3% in the 24-hour experiment and 110.9% in the 72-hour experiment); however, based on the data provided, these percentages do not include counts from the carbon traps. The coefficients of variation for radioactivity from all sources and for total recovery were not reported but could be determined based on the information provided.	
Domain 3: Exposure Characterization				
	Metric 7: Preparation and storage of test substance (chemical)	Medium	Some details regarding the preparation of the test solution were described. An oil-in-water emulsion was prepared that contained 7% cold DBP, 3% polyglyceryl distearate, 3% cetyl steryl alcohol, 10% light mineral oil, 5% propylene glycol, 0.5% propyl-p- hydroxybenzoate, 0.5% methyl-p- hydroxybenzoate and 78% water. This formulation was then spiked with radiolabeled DBP and the amount of radioactivity was assayed in triplicate to determine the applied dose. Typically studies use either unlabeled or radiolabeled test substances. OECD TG 28 indicates that, when appropriate, radiolabeled chemicals can be diluted with the non-radiolabeled chemical. It is unclear whether the dilution in this study was appropriate. No explanation was provided for why an oil-in-water emulsion was used, but based on the physical/chemical properties of the test substance, it has a moderately high Log Kow and relatively low water solubility (lipophilic), and solubility is increased in the presence of alcohol. No details on the frequency of the preparation, or mixing to assure homogeneity or storage, or stability in the emulsion were provided. Since a single application was applied to the skin, it is not expected that the lack of details on storage will significantly impact the study results.	
	Metric 8: Consistency of exposure administration	Medium	This study included a single dose group of 1 mg/cm2, with 24 or 16 replicates for the 24 hr or 72-hour exposures, respectively. The amount applied to the skin had a specific activity of 0.5 uCi; the volume was not specified. The skin thickness (200-320 um) was reported. The area of the diffusion cell was 0.64 cm2. There is no indication of significant differences across replicates.	
	Metric 9: Reporting of concentrations	High	The exposure concentration of 1 mg/cm2 was reported without ambiguity, and the specific activity was reported. The doses were based on analytical measurements of the spiked solution. The study authors justified the dosing formulation by indicating that 7% DBP is a concentration typically found in cosmetic products.	
	Metric 10: Exposure frequency	High	The study included two exposure durations, 24 hours, which is standard, and 72 hours, which is an extended time point. These durations were both included to coincide with in vivo experiments at the same durations. OECD TG 156 indicates that skin may start to deteriorate after 24 hours and therefore data generated from longer durations should be considered with caution; however, for lipophilic substances, it may take longer for the chemical to migrate from a skin depot to the receptor fluid.	
	Metric 11: Number of exposure groups and concentration spacing	Low	The purpose of this study was to conduct comparisons between in vitro and in vivo absorption models, and therefore, only a single dose group was used. The concentration used was justified by the study authors.	
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Study Citation:	Doan, K., Bronaugh, R. L., Yourick, J. J. (2010). In vivo and in vitro skin absorption of lipophilic compounds, dibutyl phthalate, farnesol and geraniol in the hairless guinea pig. Food and Chemical Toxicology 48(1):18-23.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	1323147			
Unique ID:	72-hr duration			
Domain	Metric	Rating	Comments	
Domain 4: Test Model	Metric 12:	Test model (skin)	High	Fresh skin samples were excised from female hairless guinea pigs and processed to remove excess subcutaneous fat and were dermatomed to a thickness of 200 - 320 um. 17 mm diameter circular sections were placed in each diffusion cell. The study authors justified the use of guinea pig skin as being similar to humans. The anatomical site of the tissue collections was not specified.
	Metric 13:	Number/Replicates per group	Medium	The study used a total of 24 replicates for the 24-hour experiment and 16 replicates for the 72-hour experiment. The numbers of replicates were adequate for the outcomes measured. It was not specified how many animals were used to generate these samples.
Domain 5: Outcome Assessment	Metric 14:	Outcome assessment methodology	High	Adherence to a specific guideline was not specified, but the study had some similarities to the OECD TG 428. The outcome assessment methodology was adequately reported and was sensitive for the outcome of interest. The selected concentration was representative of one typically found in cosmetic products. This was presumably a finite dose study (the volume applied was not specified) that was used to determine percent absorption values.
	Metric 15:	Consistency of outcome assessment	Medium	Based on the data available, there is no indication of inconsistencies across replicates in the outcome assessment protocols. Some information was not specified, for example, how soon after the collection of receptor fluids was scintillation counts performed.
	Metric 16:	Sampling adequacy and sensitivity	Low	Scintillation counts/sample and/or duration of radioactivity detection, and whether there was an adequate signal-to-noise [i.e., background] ratio for detection were not reported. It is unclear whether these missing details would have a significant impact on the results. All samples from each replicate were analyzed (n = 24, or 16).
Domain 6: Confounding/Variable Control	Metric 17:	Confounding variables in test design and procedures	Low	The study included only a single group. Skin was excised from animals obtained from the same source. The age of the animals was not specified, and the number of animals used to obtain the skin samples was not reported. The standard deviations in the study, including for recovery, were low, indicating low variation among replicates. Skin integrity/quality was not assessed.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	The study did not explicitly demonstrate the solubility of the test substance in the receptor fluid, but the fluid used was compatible with lipophilic substances. There were no reported differences among the replicates that were unrelated to exposure.
Domain 7: Data Presentation and Analysis				
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Study Citation:	Doan, K., Bronaugh, R. L., Yourick, J. J. (2010). In vivo and in vitro skin absorption of lipophilic compounds, dibutyl phthalate, farnesol and geraniol in the hairless guinea pig. Food and Chemical Toxicology 48(1):18-23.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	1323147			
Unique ID:	72-hr duration			
Domain	Metric		Rating	Comments
	Metric 19:	Data analysis	Low	This study did not require any statistical analysis. Total recovery was determined, and was within $100 \pm 10\%$, but did not include skin washes or recovery from the carbon traps, even though they were part of the study protocol; the levels in the charcoal trap were low; skin washes were not measured. The CVs were $<25\%$ for all but one end-point evaluated (CV of % in stratum corneum at 72 hours was 26%). Absorption estimates (based on measurements in receptor fluid) were reported across time.
	Metric 20:	Data interpretation	High	Recovery of the applied test substance was adequate. Both the skin compartment and tape stripping measurements were included. The results were correctly interpreted relative to the set-up of the assay.
	Metric 21:	Reporting of data	High	Data were adequately reported as means \pm SEM and the sample size "n" was specified.

Overall Quality Determination**Medium**

Study Citation:	Pan, T. L., Wang, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. F., Fang, J. Y. (2014). Dermal toxicity elicited by phthalates: Evaluation of skin absorption, immunohistology, and functional proteomics. Food and Chemical Toxicology 65:105-114.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	2219803			
Unique ID:	Mouse-DBP			
Domain	Metric	Rating	Comments	
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as DBP. A CASRN was not provided. The test substance was not radiolabeled.
	Metric 2:	Test substance source	High	The test substance was obtained from Sigma-Aldrich (St. Louis, MO). The batch/lot number was not provided. Test substance identity was not certified by the in the publication but could be verified on manufacturer’s website.
	Metric 3:	Test substance purity	High	The reported purity was >99%
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No reference compound was used and no history of test performance in the laboratory was reported.
	Metric 5:	Assay procedures	Medium	Tests were conducted in a Franz diffusion cell, presumably under static conditions. Freshly excised skin samples were mounted onto the cells (n = 4) leaving a diffusion area of 0.785 cm2. The exposure solution in the donor chamber contained a 5.4mM concentration of the test substance in 40% ethanol, and the receptor fluid was 40% ethanol. It is unclear if this was intended to be an infinite or finite exposure. A magnetic stir bar was used and the receptor was maintained at 37 degrees C. The pH was 7.4. Humidity was not reported, and it was not stated whether the chambers were left open or closed. The exposure duration was 12 hours. During exposure, receptor fluid aliquots were taken every 3 hours, and the volume was replaced with fresh fluid. HPLC was used to analyze the test substance in the receptor fluid and also in homogenized skin at the end of the exposure period. The limits of detection were reported. Tape stripping was mentioned, but may be part of a separate experiment in which concentrations in hair follicles were measured.
	Metric 6:	Standards for tests	Uninformative	This study did not conduct the typical standard tests to determine the validity, reliability, or quality of the experiments. Skin integrity was not tested prior to use, and percent recovery was not determined. The variation across replicates for the reported endpoints can be determined from the information provided, see Metric 19 for more details. There is no text indicating the test met pre-established criteria. Inadequate data were provided in the results to demonstrate that the test conformed to current standards or guidelines.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Limited details on the test substance preparation were provided. No details on stability, homogeneity, mixing, or storage conditions were reported. The test substance was delivered in 40% ethanol, which is often used, and is appropriate as a receptor fluid for lipophilic test substances, but it is unclear if it is also appropriate in the donor chamber. Solubility was not confirmed. Generally, the use of radiolabeled test substances is preferred for penetration studies. This study only used unlabeled test substances. The lack of details could substantially impact the study results.

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Study Citation: Pan, T. L., Wang, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. F., Fang, J. Y. (2014). Dermal toxicity elicited by phthalates: Evaluation of skin absorption, immunohistology, and functional proteomics. Food and Chemical Toxicology 65:105-114. Chemical: Dibutyl Phthalate Exposure Type: Parent compound HERO ID: 2219803 Unique ID: Mouse-DBP				
Domain		Metric	Rating	Comments
	Metric 8:	Consistency of exposure administration	Low	The diffusion area was reported (0.785 cm ²) and consistent across replicates. Each replicate was exposed to a 5.4 mM concentration of the test substance; however, the volume added to each donor chamber and the skin thicknesses were not reported. These missing details could have a substantial impact on the study results.
	Metric 9:	Reporting of concentrations	Low	Insufficient information on dosing was provided. The reported concentration was 5.4 mM, which is presumed to be nominal. There is no indication that the exposure concentration was analytically verified. The mass per skin area (mg/cm ²) or volume per area (mL/cm ²) were not reported. It is unclear if conditions were met for an infinite exposure.
	Metric 10:	Exposure frequency	High	The exposure duration of 12 hours was not justified by the study authors. It may reflect an appropriate 'in-use' practice and is acceptable according to OECD test guidelines. The timepoint was used for flux measurements.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Fewer than three concentrations were tested. This study only tested one concentration and it was not justified by the study authors.
Domain 4: Test Model	Metric 12:	Test model (skin)	Low	Full-thickness skin was excised from the dorsal regions of 8-week-old mice and 1-week-old pigs. It was not specified how many animals were used to obtain the samples. Mice are not a typical species for dermal absorption studies, and it is unclear whether this species is appropriate for this study type. However, the authors justified the use of nude mouse skin by indicating that it has a similar number of layers (3-4 cell layers) as the epidermis of infants. They also noted that nude mouse skin has greater permeability than human skin, but it may be a good model for human facial skin, which has a 4-fold higher permeability than other sites. Pigs are an acceptable model for dermal absorption studies. The source of the animals was reported. Full-thickness skin can be used when properly justified and if the thickness is not excessive. However, OECD TG 156 specifies that full-thickness skin should not be used for calculating fluxes, which was the main outcome of this study. A flux for DBP could not be determined because no test substance was detected in the receptor fluid, underscoring that full-thickness skin was likely, not appropriate. Viable skin was used, but no details of its preparation prior to being placed in the diffusion cells were provided. Skin integrity was not tested. The skin thickness was not reported. There was no information on storage, but it appears that the skin was used immediately. The missing details are likely to have a substantial impact on the study results.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was not explicitly reported in the study methods and there is some lack of clarity. The data results indicate an n = 4, suggesting that there were at least four samples/ replicates of the single concentration tested. This is the minimum number of replicates required as per OECD TG 428. However, there were 4 replicates in which the entire skin sample was homogenized for analysis, yet there are also data measuring concentrations in hair follicles following tape stripping (also noted as 4 replicates). It is presumed that these are two separate experiments, but the reporting details were not clear.

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Study Citation:	Pan, T. L., Wang, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. F., Fang, J. Y. (2014). Dermal toxicity elicited by phthalates: Evaluation of skin absorption, immunohistology, and functional proteomics. Food and Chemical Toxicology 65:105-114.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	2219803			
Unique ID:	Mouse-DBP			
Domain	Metric	Rating	Comments	
Domain 5: Outcome Assessment				
Metric 14:	Outcome assessment methodology	Low	The outcome assessment methodology deviated significantly from OECD TG 428 recommendations. This study did not determine a mean mass balance recovery. This study analyzed concentrations of the test substance in the receptor fluid and in the skin at the end of the study using HPLC. Based on the figures provided, receptor fluid was sampled every 2 hours for the duration of the study. Flux was specified as an outcome, but Kp was not reported. The study did not report total absorption or percentage applied. Insufficient information on dosing was provided to determine whether an appropriate (infinite) exposure condition was used. Possibly in a separate experiment, some samples were tape stripped 20 times to remove the stratum corneum, to allow concentration analysis in hair follicles. The missing details make it difficult to determine the appropriateness of the outcome assessments and have a substantial impact on results.	
Metric 15:	Consistency of outcome assessment	High	Based on the available information, the same duration of exposure, and receptor fluid collection times were applied to all of the replicates. All replicates had the same donor vehicle and receptor fluid. Based on the information provided, there is no indication that there were significant differences between replicates.	
Metric 16:	Sampling adequacy and sensitivity	Medium	All data were derived from an n = 4. Details of HLPC, including the LOD were reported. It is unclear whether the sampling intervals for the receptor fluid were sufficient to allow at least 4 data points at steady state for calculation of flux.	
Domain 6: Confounding/Variable Control				
Metric 17:	Confounding variables in test design and procedures	Low	Insufficient information was provided to determine confounding. The number of donors, skin integrity, and skin thicknesses were not reported. % Recovery was not assessed.	
Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	There were no reported differences among the study replicates that were unrelated to exposure. It was not specified whether the test substance was soluble in the receptor fluid; however, a 50% ethanol solution (this study used 40%) is common and acceptable, particularly for lipophilic compounds.	
Domain 7: Data Presentation and Analysis				
Metric 19:	Data analysis	Low	Limited details on data analysis were provided. Flux was calculated from the slope of the permeated amount vs. time. It was not specified that it was a linear portion of the curve. No data were reported as percentage estimates. The standard deviations relative to the mean for skin accumulation were <25%. For flux, the coefficient of variance was <25% for nude mice, but for pig, was 27%. Standard deviations were provided which will allow for EPA to calculate an alternate upper end value to account for variability in the results.	
Metric 20:	Data interpretation	Medium	The lack of exposure details, and deviations from guideline in outcome assessments make this study difficult to interpret. The authors do not make any unreasonable claims, but also do not report standard outcomes (e.g., % recovery, % absorption, Kp). It is also unclear if dosing was infinite or finite.	

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Study Citation:	Pan, T. L., Wang, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. F., Fang, J. Y. (2014). Dermal toxicity elicited by phthalates: Evaluation of skin absorption, immunohistology, and functional proteomics. Food and Chemical Toxicology 65:105-114.
Chemical:	Dibutyl Phthalate
Exposure Type:	Parent compound
HERO ID:	2219803
Unique ID:	Mouse-DBP

Domain	Metric	Rating	Comments
	Metric 21: Reporting of data	Low	Data for some specified outcomes were adequately reported as means \pm SD. Permeation The study did not report concentrations in receptor fluid by time. A figure showing the plotted data with a corresponding linear slope was not provided.

Overall Quality DeterminationUninformative

Study Citation:	Pan, T. L., Wang, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. F., Fang, J. Y. (2014). Dermal toxicity elicited by phthalates: Evaluation of skin absorption, immunohistology, and functional proteomics. Food and Chemical Toxicology 65:105-114.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	2219803			
Unique ID:	Pig-DBP			
Domain	Metric	Rating	Comments	
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as DBP. A CASRN was not provided. The test substance was not radiolabeled.
	Metric 2:	Test substance source	High	The test substance was obtained from Sigma-Aldrich (St. Louis, MO). The batch/lot number was not provided. Test substance identity was not certified by the in the publication but could be verified on manufacturer’s website.
	Metric 3:	Test substance purity	High	The reported purity was >99%
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No reference compound was used and no history of test performance in the laboratory was reported.
	Metric 5:	Assay procedures	Medium	Tests were conducted in a Franz diffusion cell, presumably under static conditions. Freshly excised skin samples were mounted onto the cells (n = 4) leaving a diffusion area of 0.785 cm2. The exposure solution in the donor chamber contained a 5.4mM concentration of the test substance in 40% ethanol, and the receptor fluid was 40% ethanol. It is unclear if this was intended to be an infinite or finite exposure. A magnetic stir bar was used and the receptor was maintained at 37 degrees C. The pH was 7.4. Humidity was not reported, and it was not stated whether the chambers were left open or closed. The exposure duration was 12 hours. During exposure, receptor fluid aliquots were taken every 3 hours, and the volume was replaced with fresh fluid. HPLC was used to analyze the test substance in the receptor fluid and also in homogenized skin at the end of the exposure period. The limits of detection were reported. Tape stripping was mentioned, but may be part of a separate experiment in which concentrations in hair follicles were measured.
	Metric 6:	Standards for tests	Uninformative	This study did not conduct the typical standard tests to determine the validity, reliability, or quality of the experiments. Skin integrity was not tested prior to use, and percent recovery was not determined. The variation across replicates for the reported endpoints can be determined from the information provided, see Metric 19 for more details. There is no text indicating the test met pre-established criteria. Inadequate data were provided in the results to demonstrate that the test conformed to current standards or guidelines.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Limited details on the test substance preparation were provided. No details on stability, homogeneity, mixing, or storage conditions were reported. The test substance was delivered in 40% ethanol, which is often used, and is appropriate as a receptor fluid for lipophilic test substances, but it is unclear if it is also appropriate in the donor chamber. Solubility was not confirmed. Generally, the use of radiolabeled test substances is preferred for penetration studies. This study only used unlabeled test substances. The lack of details could substantially impact the study results.

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Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	2219803			
Unique ID:	Pig-DBP			
Domain	Metric	Rating	Comments	
	Metric 8: Consistency of exposure administration	Low	The diffusion area was reported (0.785 cm ²) and consistent across replicates. Each replicate was exposed to a 5.4 mM concentration of the test substance; however, the volume added to each donor chamber and the skin thicknesses were not reported. These missing details could have a substantial impact on the study results.	
	Metric 9: Reporting of concentrations	Low	Insufficient information on dosing was provided. The reported concentration was 5.4 mM, which is presumed to be nominal. There is no indication that the exposure concentration was analytically verified. The mass per skin area (mg/cm ²) or volume per area (mL/cm ²) were not reported. It is unclear if conditions were met for an infinite exposure.	
	Metric 10: Exposure frequency	High	The exposure duration of 12 hours was not justified by the study authors. It may reflect an appropriate 'in-use' practice and is acceptable according to OECD test guidelines. The timepoint was used for flux measurements.	
	Metric 11: Number of exposure groups and concentration spacing	Low	Fewer than three concentrations were tested. This study only tested one concentration and it was not justified by the study authors.	
Domain 4: Test Model	Metric 12: Test model (skin)	Low	Full-thickness skin was excised from the dorsal regions of 8-week-old mice and 1-week-old pigs. It was not specified how many animals were used to obtain the samples. Mice are not a typical species for dermal absorption studies, and it is unclear whether this species is appropriate for this study type. However, the authors justified the use of nude mouse skin by indicating that it has a similar number of layers (3-4 cell layers) as the epidermis of infants. They also noted that nude mouse skin has greater permeability than human skin, but it may be a good model for human facial skin, which has a 4-fold higher permeability than other sites. Pigs are an acceptable model for dermal absorption studies. The source of the animals was reported. Full-thickness skin can be used when properly justified and if the thickness is not excessive. However, OECD TG 156 specifies that full-thickness skin should not be used for calculating fluxes, which was the main outcome of this study. A flux for DBP could not be determined because no test substance was detected in the receptor fluid, underscoring that full-thickness skin was likely, not appropriate. Viable skin was used, but no details of its preparation prior to being placed in the diffusion cells were provided. Skin integrity was not tested. The skin thickness was not reported. There was no information on storage, but it appears that the skin was used immediately. The missing details are likely to have a substantial impact on the study results.	
	Metric 13: Number/Replicates per group	Medium	The number of replicates was not explicitly reported in the study methods and there is some lack of clarity. The data results indicate an n = 4, suggesting that there were at least four samples/ replicates of the single concentration tested. This is the minimum number of replicates required as per OECD TG 428. However, there were 4 replicates in which the entire skin sample was homogenized for analysis, yet there are also data measuring concentrations in hair follicles following tape stripping (also noted as 4 replicates). It is presumed that these are two separate experiments, but the reporting details were not clear.	

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Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	2219803			
Unique ID:	Pig-DBP			
Domain	Metric	Rating	Comments	
Domain 5: Outcome Assessment				
Metric 14:	Outcome assessment methodology	Low	The outcome assessment methodology deviated significantly from OECD TG 428 recommendations. This study did not determine a mean mass balance recovery. This study analyzed concentrations of the test substance in the receptor fluid and in the skin at the end of the study using HPLC. Based on the figures provided, receptor fluid was sampled every 2 hours for the duration of the study. Flux was specified as an outcome, but Kp was not reported. The study did not report total absorption or percentage applied. Insufficient information on dosing was provided to determine whether an appropriate (infinite) exposure condition was used. Possibly in a separate experiment, some samples were tape stripped 20 times to remove the stratum corneum, to allow concentration analysis in hair follicles. The missing details make it difficult to determine the appropriateness of the outcome assessments and have a substantial impact on results.	
Metric 15:	Consistency of outcome assessment	High	Based on the available information, the same duration of exposure, and receptor fluid collection times were applied to all of the replicates. All replicates had the same donor vehicle and receptor fluid. Based on the information provided, there is no indication that there were significant differences between replicates.	
Metric 16:	Sampling adequacy and sensitivity	Medium	All data were derived from an n = 4. Details of HPLC, including the LOD were reported. It is unclear whether the sampling intervals for the receptor fluid were sufficient to allow at least 4 data points at steady state for calculation of flux.	
Domain 6: Confounding/Variable Control				
Metric 17:	Confounding variables in test design and procedures	Low	Insufficient information was provided to determine confounding. The number of donors, skin integrity, and skin thicknesses were not reported. % Recovery was not assessed.	
Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	There were no reported differences among the study replicates that were unrelated to exposure. It was not specified whether the test substance was soluble in the receptor fluid; however, a 50% ethanol solution (this study used 40%) is common and acceptable, particularly for lipophilic compounds.	
Domain 7: Data Presentation and Analysis				
Metric 19:	Data analysis	Low	Limited details on data analysis were provided. Flux was calculated from the slope of the permeated amount vs. time. It was not specified that it was a linear portion of the curve. No data were reported as percentage estimates. The standard deviations relative to the mean for skin accumulation were <25%. For flux, the coefficient of variance was <25% for nude mice, but for pig, was 27%. Standard deviations were provided which will allow for EPA to calculate an alternate upper end value to account for variability in the results.	
Metric 20:	Data interpretation	Medium	The lack of exposure details, and deviations from guideline in outcome assessments make this study difficult to interpret. The authors do not make any unreasonable claims, but also do not report standard outcomes (e.g., % recovery, % absorption, Kp). It is also unclear if dosing was infinite or finite.	

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Study Citation:	Pan, T. L., Wang, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. F., Fang, J. Y. (2014). Dermal toxicity elicited by phthalates: Evaluation of skin absorption, immunohistology, and functional proteomics. Food and Chemical Toxicology 65:105-114.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	2219803			
Unique ID:	Pig-DBP			
Domain	Metric	Rating	Comments	
	Metric 21: Reporting of data	Low	Data for some specified outcomes were adequately reported as means \pm SD. Permeation The study did not report concentrations in receptor fluid by time. A figure showing the plotted data with a corresponding linear slope was not provided.	

Overall Quality Determination	Uninformative
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Study Citation:	Pan, T. L., Wang, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. F., Fang, J. Y. (2014). Dermal toxicity elicited by phthalates: Evaluation of skin absorption, immunohistology, and functional proteomics. Food and Chemical Toxicology 65:105-114.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	2219803			
Unique ID:	Strat-M membrane-DBP			
Domain	Metric	Rating	Comments	
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as DBP. A CASRN was not provided. The test substance was not radiolabeled.
	Metric 2:	Test substance source	High	The test substance was obtained from Sigma-Aldrich (St. Louis, MO). The batch/lot number was not provided. Test substance identity was not certified by the in the publication but could be verified on manufacturer’s website.
	Metric 3:	Test substance purity	High	The reported purity was >99%
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No reference compound was used and no history of test performance in the laboratory was reported.
	Metric 5:	Assay procedures	Medium	Tests were conducted in a Franz diffusion cell, presumably under static conditions. Freshly excised skin samples were mounted onto the cells (n = 4) leaving a diffusion area of 0.785 cm2. The exposure solution in the donor chamber contained a 5.4mM concentration of the test substance in 40% ethanol, and the receptor fluid was 40% ethanol. It is unclear if this was intended to be an infinite or finite exposure. A magnetic stir bar was used and the receptor was maintained at 37 degrees C. The pH was 7.4. Humidity was not reported, and it was not stated whether the chambers were left open or closed. The exposure duration was 12 hours. During exposure, receptor fluid aliquots were taken every 2 hours, and the volume was replaced with fresh fluid. HPLC was used to analyze the test substance in the receptor fluid and also in homogenized skin at the end of the exposure period. The limits of detection were reported.
	Metric 6:	Standards for tests	Uninformative	This study did not conduct the typical standard tests to determine the validity, reliability, or quality of the experiments. Skin integrity was not tested prior to use, and percent recovery was not determined. The variation across replicates for the reported endpoints was acceptable (SD <25%). There is no text indicating the test met pre-established criteria. Inadequate data were provided in the results to demonstrate that the test conformed to current standards or guidelines.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Limited details on the test substance preparation were provided. No details on stability, homogeneity, mixing, or storage conditions were reported. The test substance was delivered in 40% ethanol, which is often used, and is appropriate as a receptor fluid for lipophilic test substances, but it is unclear if it is also appropriate in the donor chamber. Solubility was not confirmed. Generally, the use of radiolabeled test substances is preferred for penetration studies. This study only used unlabeled test substances. The lack of details could substantially impact the study results.
	Metric 8:	Consistency of exposure administration	Low	The diffusion area was reported (0.785 cm2) and consistent across replicates. Each replicate was exposed to a 5.4 mM concentration of the test substance; however, the volume added to each donor chamber and the skin thicknesses were not reported. These missing details could have a substantial impact on the study results.

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Study Citation:		Pan, T. L., Wang, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. F., Fang, J. Y. (2014). Dermal toxicity elicited by phthalates: Evaluation of skin absorption, immunohistology, and functional proteomics. Food and Chemical Toxicology 65:105-114.		
Chemical:		Dibutyl Phthalate		
Exposure Type:		Parent compound		
HERO ID:		2219803		
Unique ID:		Strat-M membrane-DBP		
Domain	Metric	Rating	Comments	
	Metric 9:	Reporting of concentrations	Low	Insufficient information on dosing was provided. The reported concentration was 5.4 mM, which is presumed to be nominal. There is no indication that the exposure concentration was analytically verified. The mass per skin area (mg/cm ²) or volume per area (mL/cm ²) were not reported. It is unclear if conditions were met for an infinite exposure.
	Metric 10:	Exposure frequency	High	The exposure duration of 12 hours was not justified by the study authors. It may reflect an appropriate 'in-use' practice and is acceptable according to OECD test guidelines. The timepoint was used for flux measurements.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Fewer than three concentrations were tested. This study only tested one concentration and it was not justified by the study authors.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Uninformative	Experiments were conducted on Strat-M membrane, a synthetic, non-animal-based model for transdermal diffusion testing. The membrane was obtained from Merk-Millipore, although these standardized membranes are sold by multiple vendors. The thickness was not reported in the study. Some vendors note the thickness to be 25 mm. All vendors provide additional information and certificates of quality upon request. These certificates are likely to assure integrity. Integrity was not confirmed by the performing laboratory. Synthetic membranes are not mentioned in the current OECD TG, and although these are sold as an adequate model for humans, it is not clear they are currently accepted as an appropriate model system. There was no information on storage. The missing details are likely to have a substantial impact on the study results.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was not explicitly reported in the study methods and there is some lack of clarity. The data results indicate an n = 4, suggesting that there were at least four samples/replicates of the single concentration tested. This is the minimum number of replicates required as per OECD TG 428.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Low	The outcome assessment methodology deviated significantly from OECD TG 428 recommendations. This study did not determine a mean mass balance recovery. This study analyzed concentrations of the test substance in the receptor fluid using HPLC. Based on the figures provided, receptor fluid was sampled every 2 hours for the duration of the study. Flux was specified as an outcome, but Kp was not reported. Insufficient information on dosing was provided to determine whether an appropriate (infinite) exposure condition was used. The missing details make it difficult to determine the appropriateness of the outcome assessments and have a substantial impact on results.
	Metric 15:	Consistency of outcome assessment	High	Based on the available information, the same duration of exposure, and receptor fluid collection times were applied to all of the replicates. All replicates had the same donor vehicle and receptor fluid. Based on the information provided, there is no indication that there were significant differences between replicates.
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Study Citation:	Pan, T. L., Wang, P. W., Aljuffali, I. A., Hung, Y. Y., Lin, C. F., Fang, J. Y. (2014). Dermal toxicity elicited by phthalates: Evaluation of skin absorption, immunohistology, and functional proteomics. Food and Chemical Toxicology 65:105-114.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	2219803			
Unique ID:	Strat-M membrane-DBP			
Domain	Metric	Rating	Comments	
	Metric 16:	Sampling adequacy and sensitivity	Medium	All data were derived from an n = 4. Details of HPLC, including the LOD were reported. It is unclear whether the sampling intervals for the receptor fluid were sufficient to allow at least 4 data points at steady state for calculation of flux.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	Insufficient information was provided to determine confounding; however, the use of a standardized synthetic membrane removes several confounding factors related to donors, donor sites, thickness, integrity, etc..
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	There were no reported differences among the study replicates that were unrelated to exposure. It was not specified whether the test substance was soluble in the receptor fluid; however, a 50% ethanol solution (this study used 40%) is common and acceptable, particularly for lipophilic compounds.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Limited details on data analysis were provided. Flux was purportedly calculated from the slope of the permeated amount vs. time, but a value was not provided. It was not specified that it was a linear portion of the curve. No data were reported as percentage estimates. A Kp was not reported. An independent analysis could be done based on the information provided. Standard deviations were plotted on a graphical representation of the data and appeared to be appropriate (<25%)
	Metric 20:	Data interpretation	Medium	A quantitative flux value was not actually reported, it was only stated in the study text that the data were consistent with what was observed in ex vivo model systems.
	Metric 21:	Reporting of data	High	Data were graphically reported showing permeated amount vs. time. Points represented means ± SD.

Overall Quality Determination**Uninformative**

Study Citation:	Scott, R. C., Dugard, P. H., Ramsey, J. D., Rhodes, C. (1987). In vitro absorption of some o-phthalate diesters through human and rat skin. Environmental Health Perspectives 74(0):223-227.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	674473			
Unique ID:	DBP-Human skin			
Domain	Metric	Rating	Comments	
Domain 1: Test Substance				
Metric 1:	Test substance identity	Medium	The test substance was identified as DBP. No CASRN or structure was provided. The study included a table reporting physical/chemical properties. The test substance was unlabeled.	
Metric 2:	Test substance source	Low	The unlabeled test substance was obtained from Aldrich Chemical Co. The identity of the test substance was not verified by the performing laboratory and certificates of analysis were not provided. The chemicals used in this 1987 study cannot be verified on the manufacturer's website.	
Metric 3:	Test substance purity	High	The purity of the unlabeled compound was 99%.	
Domain 2: Test Design				
Metric 4:	Reference compounds	Low	A concurrent reference compound was not tested along with the test substance and the authors did not specify previous experience with dermal absorption studies. One of the papers cited for preparation of epidermal layers was conducted by the same group of authors.	
Metric 5:	Assay procedures	Medium	In this study, epidermal membrane samples were placed in a static glass diffusion cell; details of the setup were cited to Dugard et al. 1984, which is open access and was viewed for this review. The number of donors or samples was not reported in the methods. After permeability testing using tritiated water (day 1), receptor chambers were filled with 4.5 mL of 50% v/v aqueous ethanol. The authors did not provide justification for the receptor fluid used, but aqueous ethanol is considered to be appropriate (OECD 156). A 0.5mL volume of unlabelled DBP was applied neat to the donor compartment (radiolabelled is preferred); the loading rate (mg/cm2) was not specified; however, the skin diameter was given (3 cm), and the area was calculated for this review to be 7.07 cm2. Diffusion cells were maintained at 30 ± 1°C. The system was left uncovered; humidity was not reported. Samples of receptor fluid (0.5mL) were "taken frequently" (number and frequency not specified) and replaced with equal volumes of fresh receptor fluid. DBP was detected in receptor fluid using GC analysis, although minimal details were provided. At the end of the experiment, the skin was washed (washing method not specified), and a second permeability test was conducted. This allowed the determination of a damage ratio.	
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Study Citation:	Scott, R. C., Dugard, P. H., Ramsey, J. D., Rhodes, C. (1987). In vitro absorption of some o-phthalate diesters through human and rat skin. Environmental Health Perspectives 74(0):223-227.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	674473			
Unique ID:	DBP-Human skin			
Domain	Metric	Rating	Comments	
	Metric 6:	Standards for tests	Medium	The skin integrity was determined using tritiated water. Integrity was determined before the application of the test substance. Membranes with permeability constants >1.5 x 10^-3 (human), and >2.5 x 10^-2 (rat) were rejected. Another tritiated water permeability test was conducted at the end of the study and a damage ratio was calculated. A slight increase in human skin permeability occurred over the course of the study. The damage ratio was 1.8.Percent recovery was not reported, but this is not expected for an infinite exposure study. Coefficients of variation for Kp and steady-state flux could be calculated using the data provided. CV values were >50% and an adjustment should be applied.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Storage of test substance was not adequately reported; however, this is not likely to substantially impact results. The substance is not very volatile. The test substance was used neat; therefore, a discussion of preparation was not necessary.
	Metric 8:	Consistency of exposure administration	Medium	Epidermal membranes 3cm in diameter were used (7.07 cm2). The thickness of the heat-isolated epidermis is not typically reported. The application volume was reported as approximately 0.5mL; given the application is an infinite dose slight deviation in volume are unlikely to substantially impact results. The available information suggests consistency of application across replicates.
	Metric 9:	Reporting of concentrations	Medium	The test substance was studied neat. The dose (mg/cm2) was not reported, only a volume of 0.5mL. It is possible the density of DBP could be used to calculate an approximate dose (mg). Based on the application area (7.07 cm2, calculated based on a given diameter of 3 cm), the loading rate was 70 uL/cm2.
	Metric 10:	Exposure frequency	Low	Human epidermis studies were continued for up to 30 hours. The authors noted a lag time of 2.9 hours, but it is unclear why exposure beyond 24 hours was needed. Absorption curves were not provided to visualize what time-frames a linear portion of the curve was obtained.
	Metric 11:	Number of exposure groups and concentration spacing	Low	The study only tested a single dose (neat).
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	Human abdominal skin was obtained from cadavers. Donors were reported as mostly females aged ≥55 years. The number of donors and number of skin samples per donor were not reported. The epidermis was separated from the dermis after immersing the skin into water at 60 degrees C for 40 to 45 seconds. The skin was stored at 4 degrees C; it was used within 7 days of preparation. The integrity of the skin was evaluated by measuring the permeability of tritiated water at both the beginning and end of the experiment. Split-thickness skin is preferred because the use of epidermal membranes may overestimate human in vivo skin absorption (OECD 156).
	Metric 13:	Number/Replicates per group	Medium	The number of replicates at the start of the study was not reported; absorption data were obtained from an n = 15, which was sufficient.

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Study Citation:	Scott, R. C., Dugard, P. H., Ramsey, J. D., Rhodes, C. (1987). In vitro absorption of some o-phthalate diesters through human and rat skin. Environmental Health Perspectives 74(0):223-227.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	674473			
Unique ID:	DBP-Human skin			
Domain	Metric	Rating	Comments	
Domain 5: Outcome Assessment				
Metric 14:	Outcome assessment methodology	Medium	The study used approximately 70 uL/cm2 (calculated for this review, based on skin diameter and volume applied). This is less than the 100 uL/cm2 recommended for infinite dose scenarios. Steady-state absorption rates were calculated from linear portions of the curve. The study cited Dugard et al. (1984) for details on calculating permeability constants.	
Metric 15:	Consistency of outcome assessment	Medium	Details regarding the execution of the study protocol were mostly reported. The duration of exposure and the same receptor fluid composition were used across replicates. The same volume of receptor fluid was removed at each collection, although the frequency of collections was not specified (see metric 16).	
Metric 16:	Sampling adequacy and sensitivity	Low	Details regarding sampling were insufficiently reported. Samples of receptor fluid (0.5uL) were “taken frequently” (number and frequency not specified).	
Domain 6: Confounding/Variable Control				
Metric 17:	Confounding variables in test design and procedures	Medium	The study did not report the thickness of the skin studied; therefore, it is unclear how much variation existed between the samples. Skin integrity was evaluated prior to the start of the study using tritiated water. Human membranes with values greater than 1.5 x 10-3 were excluded which is acceptable. Actual measurements were not reported. The authors noted that human skin epidermal layers prepared and stored as reported “have been shown to maintain their permeability parameters.” Integrity was also measured at the end of the study. The authors noted that there was a ”slight increase in the permeability of human skin.” The number of donors and skin samples per donor was not reported.	
Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	Solubility in the receptor fluid was not demonstrated, although solubility in water was reported. OECD guidelines recommend that with very lipophilic substances, such as DBP, that BSA or 6% polyethylene glycol 20 oleyl ether be added to the receptor fluid to overcome solubility restrictions. This study used 50% v/v aqueous ethanol which is also acceptable according to OECD TG 28.	
Domain 7: Data Presentation and Analysis				
Metric 19:	Data analysis	Low	Methods for the calculation of the permeability constant was cited to Dugard et al. (1984; available open access). The coefficients of variation, calculated for this review, were 101 and 102% for Kp and the steady-state absorption rate, respectively. Sufficient information is available for EPA to calculate an upper-end value to account for variability in the results.	
Metric 20:	Data interpretation	High	Data were properly interpreted. Permeability (Kp) was calculated using infinite concentration. Recovery was not reported, but this is not an important endpoint for infinite exposures.	
Metric 21:	Reporting of data	Medium	Calculated absorption rate and permeability constant are reported. The study does not graphically show the permeation curves.	

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Study Citation:	Scott, R. C., Dugard, P. H., Ramsey, J. D., Rhodes, C. (1987). In vitro absorption of some o-phthalate diesters through human and rat skin. Environmental Health Perspectives 74(0):223-227.
Chemical:	Dibutyl Phthalate
Exposure Type:	Parent compound
HERO ID:	674473
Unique ID:	DBP-Human skin

Domain	Metric	Rating	Comments
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Overall Quality Determination	Medium
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Study Citation:	Scott, R. C., Dugard, P. H., Ramsey, J. D., Rhodes, C. (1987). In vitro absorption of some o-phthalate diesters through human and rat skin. Environmental Health Perspectives 74(0):223-227.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	674473			
Unique ID:	DBP-Rat skin			
Domain	Metric		Rating	Comments
Domain 1: Test Substance	Metric 1:	Test substance identity	Medium	The test substance was identified as DBP. No CASRN or structure was provided. The study included a table reporting physical/chemical properties. The test substance was unlabeled.
	Metric 2:	Test substance source	Low	The unlabeled test substance was obtained from Aldrich Chemical Co. The identity of the test substance was not verified by the performing laboratory and certificates of analysis were not provided. The chemicals used in this 1987 study cannot be verified on the manufacturer’s website.
	Metric 3:	Test substance purity	High	The purity of the unlabeled compound was 99%.
Domain 2: Test Design	Metric 4:	Reference compounds	Low	A concurrent reference compound was not tested along with the test substance and the authors did not specify previous experience with dermal absorption studies. One of the papers cited for preparation of epidermal layers was conducted by the same group of authors.
	Metric 5:	Assay procedures	Medium	In this study, epidermal membrane samples were placed in a static glass diffusion cell; details of the setup were cited to Dugard et al. 1984, which is open access and was viewed for this review. The number of donors or samples was not reported in the methods. After permeability testing using tritiated water (day 1), receptor chambers were filled with 4.5 mL of 50% v/v aqueous ethanol. The authors did not provide justification for the receptor fluid used, but aqueous ethanol is considered to be appropriate (OECD 156). A 0.5mL volume of DBP was applied neat to the donor compartment; the loading rate (mg/cm2) was not specified; however, the skin diameter was given (3 cm), and the area was calculated for this review to be 7.07 cm2. Diffusion cells were maintained at 30 ± 1°C. The system was left uncovered; humidity was not reported. Samples of receptor fluid (0.5mL) were “taken frequently” (number and frequency not specified) and replaced with equal volumes of fresh receptor fluid. The receptor fluid was analyzed using GC, although limited details regarding DBP detection were provided. At the end of the experiment, the skin was washed (washing method not specified), and a second permeability test was conducted. This allowed the determination of a damage ratio.
	Metric 6:	Standards for tests	Medium	The skin integrity was determined using tritiated water. Integrity was determined before the application of the test substance. Membranes with permeability constants >1.5 x 10^-3 (human), and >2.5 x 10^-2 (rat) were rejected. Another tritiated water permeability test was conducted at the end of the study and a damage ratio was calculated. Rat skin showed large changes in permeability between the start and end of the study. The authors stated that contact with the test substance resulted in “irreversibly alteration of the membrane.” The damage ratio was 4.0 .Percent recovery was not reported, but this is not expected for an infinite exposure study. Coefficients of variation for Kp and steady-state flux could be calculated using the data provided. CV values were >25% and an adjustment should be applied.
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Study Citation:	Scott, R. C., Dugard, P. H., Ramsey, J. D., Rhodes, C. (1987). In vitro absorption of some o-phthalate diesters through human and rat skin. Environmental Health Perspectives 74(0):223-227.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	674473			
Unique ID:	DBP-Rat skin			
Domain	Metric	Rating	Comments	
Domain 3: Exposure Characterization				
Metric 7:	Preparation and storage of test substance (chemical)	Medium	Storage of test substance was not adequately reported; however, this is not likely to substantially impact results. The substance is non-volatile. The test substance was used neat; therefore, a discussion of preparation was not necessary.	
Metric 8:	Consistency of exposure administration	Medium	Epidermal membranes 3cm in diameter were used (7.07 cm2). The thickness of the heat-isolated epidermis is not typically reported. The application volume was reported as approximately 0.5mL; given the application is an infinite dose slight deviation in volume are unlikely to substantially impact results. The available information suggests consistency of application across replicates.	
Metric 9:	Reporting of concentrations	Medium	The test substance was studied neat. The dose (mg/cm2) was not reported, only a volume of 0.5mL. It is possible the density of DBP could be used to calculate an approximate dose (mg). Based on the application area (7.07 cm2, based on a given diameter of 3 cm), the loading rate was 70 uL/cm2.	
Metric 10:	Exposure frequency	High	Rat epidermis studies were continued for 8 hours which is appropriate. The authors noted a lag time of 0.4 hours.	
Metric 11:	Number of exposure groups and concentration spacing	Low	The study only tested a single dose (neat).	
Domain 4: Test Model				
Metric 12:	Test model (skin)	Low	The dorsal skin from Wistar rats (number, sex, and age not reported) was removed and placed in 2M NaBr for up to 24 hours. The epidermis was then peeled from the dermis and stored at 4 degrees C; it was used within 7 days of preparation. The integrity of the skin was evaluated by measuring the permeability of tritiated water at both the beginning and end of the experiment. Split-thickness skin is preferred because the use of epidermal membranes may overestimate human in vivo skin absorption (OECD 156).	
Metric 13:	Number/Replicates per group	Medium	The number of replicates at the start of the study was not reported; absorption data were obtained from an n = 8- 9, which was sufficient.	
Domain 5: Outcome Assessment				
Metric 14:	Outcome assessment methodology	Medium	The study used approximately 70 uL/cm2 (calculated for this review, based on skin diameter and volume applied). This is less than the 100 uL/cm2 recommended for infinite dose scenarios. Steady-state absorption rates were calculated from linear portions of the curve. The study cited Dugard et al. (1984) for details on calculating permeability constants.	
Metric 15:	Consistency of outcome assessment	Medium	Details regarding the execution of the study protocol were mostly reported. The duration of exposure and the same receptor fluid composition were used across replicates. The same volume of receptor fluid was removed at each collection, although the frequency of collections was not specified (see metric 16).	
Metric 16:	Sampling adequacy and sensitivity	Low	Details regarding sampling were insufficiently reported. Samples of receptor fluid (0.5mL) were “taken frequently” (number and frequency not specified).	
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Study Citation:	Scott, R. C., Dugard, P. H., Ramsey, J. D., Rhodes, C. (1987). In vitro absorption of some o-phthalate diesters through human and rat skin. Environmental Health Perspectives 74(0):223-227.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	674473			
Unique ID:	DBP-Rat skin			
Domain	Metric	Rating	Comments	
Domain 6: Confounding/Variable Control				
	Metric 17: Confounding variables in test design and procedures	Low	The study did not report the thickness of the skin studied; therefore, it is unclear how much variation existed between the samples. Skin integrity was evaluated prior to the start of the study using tritiated water. Rat membranes with values greater than 2.5 x 10-3 were excluded which is acceptable. Actual measurements were not reported. Integrity was also measured at the end of the study. The authors described Large changes in permeability during the experiment as "irreversible alterations of the membrane" following contact with the test substance. It is unclear how this impacted the study results. The number of animals and skin samples per animal was not reported.	
	Metric 18: Confounding variables in outcomes unrelated to exposure	Medium	Solubility in the receptor fluid was not demonstrated, although solubility in water was reported. OECD guidelines recommend that with very lipophilic substances, such as DEHP, that BSA should be added to the receptor fluid to overcome solubility restrictions. This study used 50% v/v aqueous ethanol.	
Domain 7: Data Presentation and Analysis				
	Metric 19: Data analysis	High	Methods for calculating the permeability constants were cited to Dugard et al. (1984; available open access). The coefficients of variation, calculated for this review, were 3% for both Kp and the steady-state absorption rate.	
	Metric 20: Data interpretation	High	Data were properly interpreted. Permeability (Kp) was calculated using infinite concentration. Recovery was not reported, but this is not an important endpoint for infinite exposures.	
	Metric 21: Reporting of data	Medium	Calculated absorption rate and permeability constant are reported. The study does not graphically show the permeation curves.	
Overall Quality Determination		Medium		

Study Citation:	Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	3859042			
Unique ID:	DBP - full-thickness (rat)			
Domain	Metric	Rating	Comments	
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as dibutyl phthalate (DBP) A CASRN and structure were provided. The test substance was not radiolabeled.
	Metric 2:	Test substance source	High	The test substance was purchased from Wako Pure Chemical Industries, Ltd. Certificates of analysis are available on the supplier website for the current listings of this chemical. The performing laboratory did not analytically verify the test substance.
	Metric 3:	Test substance purity	Medium	The purity was not reported in the study. The product currently listed on the website of the supplier has a purity of >98%. Other chemicals used in the study were of special or HPLC grade. It is assumed the purity is high, but due to the lack of listing in the main study report, there is some uncertainty.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No reference compound was used and no history of test performance in the laboratory was reported.
	Metric 5:	Assay procedures	Medium	The assay procedures were clearly described, with only a few missing details. Skin samples (presumably n = 4/group) were mounted on static diffusion cells yielding a surface area of 0.95 cm2. It was not specified whether the chambers were open or closed, but the test substance has low volatility. The donor and receiver chambers were held at 32 degrees C; humidity was not reported. Prior to exposure, skin was hydrated with PBS. At the time of exposure, the receptor chamber was filled with 2.5 mL of fresh PBS, and the donor chamber was filled with 2.5 mL of PBS containing 0.718mM DBP. All of the solutions were stirred with a magnetic stir bar. In some cases 0.53mM DFP (an esterase inhibitor) was added to the receptor fluid for metabolism tests. Receptor fluid samples were taken periodically (~ every 1 [stripped skin] or 2 [full-thickness skin] hours based on provided figures), and replenished with an equal volume of PBS. The collected fractions were held at 4 degrees C until analysis. At the end of exposure (6 or 12 hours, depending on the time to reach a steady state), the skin was washed 3 times with receptor fluid, and then homogenized for analysis via HPLC. The lower limits of quantitation were reported.
	Metric 6:	Standards for tests	Low	This study did not conduct the typical standard tests to determine the validity, reliability, or quality of the experiments. Skin integrity was not tested prior to use. Percent recovery was not determined; however, recovery determination is not relevant for infinite dose applications determining a Kp. Coefficients of variation across replicates can be determined for most endpoints (see Metric 19 for further details). There is no text indicating the test met pre-established criteria.
Domain 3: Exposure Characterization				
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Study Citation: Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17. Chemical: Dibutyl Phthalate Exposure Type: Parent compound HERO ID: 3859042 Unique ID: DBP - full-thickness (rat)				
Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Limited details of the test substance preparation were provided. The test substance (0.718 mM) was diluted in PBS. No details on stability, or mixing to assure homogeneity, mixing temperature, stirring methods, or storage conditions were reported. The solubility of the test substance in PBS was not specified. DBP is lipophilic, so it is unclear if PBS was an appropriate vehicle. Other lipophilic chemicals tested in the same study used DMSO-PBS as a vehicle.
	Metric 8:	Consistency of exposure administration	Low	The study included a single exposure group with presumably 4 replicates for each skin type (full-thickness and stripped skin). The consistency of skin thicknesses, or sources of skin samples between replicates (two sources were reported), is not known. Tests were conducted using a consistent test solution volume of 2.5 mL, and a skin surface area of 0.95 cm ² . The missing information could have a significant impact on the results.
	Metric 9:	Reporting of concentrations	Medium	A nominal 0.718 mM concentration was added to the donor chamber. The volume applied and skin surface area was reported. It is unclear whether the test concentration was analytically verified. The selected concentration was not justified by the study authors.
	Metric 10:	Exposure frequency	High	The duration of exposure was dependent on when permeation reached a steady state. For stripped skin, the exposure duration was 6 hours and for full-thickness skin was 12 hours. The durations were in line with OECD guidelines.
	Metric 11:	Number of exposure groups and concentration spacing	Low	The study used a single exposure concentration; however, the purpose of the study was to compare data from multiple skin types (full-thickness and stripped), chemicals, and species (rat and human), and also to assess metabolic parameters. It is not clear that testing multiple concentrations was in line with the goals of the study, although OECD guidelines recommend at least three exposure groups.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	Abdominal skin was excised from 8-10 week-old male hairless rats (WBN/IIa-Ht) obtained from either the Life Science Research Center in Josai University or Ishikawa Experimental Animals Laboratories (Fukaya, Saitama). It is unclear how many donors were used, and if samples from animals from the different sites were randomly distributed. The skin samples were not stored. Skin integrity was not assessed and thickness was not reported. The samples were used either as full-thickness with the fat trimmed off or as stripped skin. According to OECD guidelines, full-thickness skin should not be used to calculate flux, which was the main endpoint in this study. However, the Kp results were essentially the same comparing full-thickness to stripped skin, and also across species (rat and human), so seemed appropriate in the current study.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates per group was not specified in the methods, but the data points represented an n of 4 for receptor fluid measurements. The data table reporting Kp reports and n of 3-5. A sample size of 4 is the minimum sample size required, as specified in OECD 428.
Domain 5: Outcome Assessment				
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Study Citation: Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17. Chemical: Dibutyl Phthalate Exposure Type: Parent compound HERO ID: 3859042 Unique ID: DBP - full-thickness (rat)				
Domain		Metric	Rating	Comments
	Metric 14:	Outcome assessment methodology	High	Use of a guideline was not specified. The study was focused on determining Kp and flux, which should be obtained using an infinite dose scenario. A volume of 2.5 mL was applied to the donor chamber (area 0.95 cm ²), so the applied volume was ~ 2.6 mL/cm ² which is appropriate for infinite exposure of a liquid, regardless of concentration. A molar concentration of 0.718 mM was reported. Based on a molecular weight of 278.34, and the 2.5 mL volume, approximately 0.5 mg of the test substance was added to the donor chamber (equivalent to ~0.52 mg/cm ²).
	Metric 15:	Consistency of outcome assessment	Medium	Based on the data available, there is no indication of inconsistencies across replicates in the outcome assessment protocols. The same vehicle and receptor fluids were used for each replicate, and the duration of exposure by skin type was consistent. Some information was not specified, for example, how soon after the collection of receptor fluids concentrations was analyzed, but this is not expected to have a significant impact on the study results.
	Metric 16:	Sampling adequacy and sensitivity	High	The sample size was reported for all of the outcomes. An adequate number of receptor fluid aliquots were taken to allow an accurate graphical representation of the content of the test article in the receptor fluid vs. time.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	The study included only a single group. Skin was excised from animals from two different sources. It is unclear if the same source was used within a single group. Skin thicknesses were not reported and integrity/quality was not assessed making it difficult to determine whether there were any confounding differences across replicates. The missing details could have a substantial impact on the study results.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Low	The study did not indicate whether the test substance was soluble in the receptor fluid (PBS). Given that DBP is lipophilic, solubility in PBS may have been an issue. This could have an impact on the study results. The study noted significant metabolism to BP and therefore permeation of both DBP and BP were assessed.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The data analysis methods were clearly reported. Because metabolism in the skin was an issue, an alternative Kp (the steady-state flux of the metabolite divided by the concentration of the parent test substance) was used in place of a true Kp. In addition to skin permeation, metabolic rates were also determined. The coefficients of variation (CoV) across replicates were acceptable (SD <25%) for some, but not all tests. The CoV was <25% for the Kp determination for full thickness (19%) skin, but not for stripped skin (32%). However, the CoVs for measurements in receptor fluid were >25% for most collection points in the full-thickness test but were <25% for the split-thickness test, except for the final collection at 6 hours. The CoVs for measurements in the skin were <25% in both skin types.
	Metric 20:	Data interpretation	High	Infinite exposure conditions were used to derive Kp and flux. This study did not determine % recovery; however, for infinite dose applications in which Kp or flux are determined, recovery is not relevant (OECD TG 28).

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Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	3859042			
Unique ID:	DBP - full-thickness (rat)			
Domain	Metric	Rating	Comments	
	Metric 21: Reporting of data	High	Data for all outcomes were adequately reported and presented in tables or figures as means \pm SD	

Overall Quality Determination	Medium
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Study Citation:	Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	3859042			
Unique ID:	DBP - stripped skin (rat)			
Domain	Metric	Rating	Comments	
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as dibutyl phthalate (DBP) A CASRN and structure were provided. The test substance was not radiolabeled.
	Metric 2:	Test substance source	High	The test substance was purchased from Wako Pure Chemical Industries, Ltd. Certificates of analysis are available on the supplier website for the current listings of this chemical. The performing laboratory did not analytically verify the test substance.
	Metric 3:	Test substance purity	Medium	The purity was not reported in the study. The product currently listed on the website of the supplier has a purity of >98%. Other chemicals used in the study were of special or HPLC grade. It is assumed the purity is high, but due to the lack of listing in the main study report, there is some uncertainty.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No reference compound was used and no history of test performance in the laboratory was reported.
	Metric 5:	Assay procedures	Medium	The assay procedures were clearly described, with only a few missing details. Skin samples (presumably n = 4/group) were mounted on static diffusion cells yielding a surface area of 0.95 cm2. It was not specified whether the chambers were open or closed, but the test substance has low volatility. The donor and receiver chambers were held at 32 degrees C; humidity was not reported. Prior to exposure, skin was hydrated with PBS. At the time of exposure, the receptor chamber was filled with 2.5 mL of fresh PBS, and the donor chamber was filled with 2.5 mL of PBS containing 0.718mM DBP. All of the solutions were stirred with a magnetic stir bar. In some cases 0.53mM DFP (an esterase inhibitor) was added to the receptor fluid for metabolism tests. Receptor fluid samples were taken periodically (~ every 1 [stripped skin] or 2 [full-thickness skin] hours based on provided figures), and replenished with an equal volume of PBS. The collected fractions were held at 4 degrees C until analysis. At the end of exposure (6 or 12 hours, depending on the time to reach a steady state), the skin was washed 3 times with receptor fluid, and then homogenized for analysis via HPLC. The lower limits of quantitation were reported.
	Metric 6:	Standards for tests	Low	This study did not conduct the typical standard tests to determine the validity, reliability, or quality of the experiments. Skin integrity was not tested prior to use. Percent recovery was not determined; however, recovery determination is not relevant for infinite dose applications determining a Kp. Coefficients of variation across replicates can be determined for most endpoints (see Metric 19 for further details). There is no text indicating the test met pre-established criteria.
Domain 3: Exposure Characterization				
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Study Citation: Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17. Chemical: Dibutyl Phthalate Exposure Type: Parent compound HERO ID: 3859042 Unique ID: DBP - stripped skin (rat)				
Domain	Metric		Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Limited details of the test substance preparation were provided. The test substance (0.718 mM) was diluted in PBS. No details on stability, or mixing to assure homogeneity, mixing temperature, stirring methods, or storage conditions were reported. The solubility of the test substance in PBS was not specified. DBP is lipophilic, so it is unclear if PBS was an appropriate vehicle. Other lipophilic chemicals tested in the same study used DMSO-PBS as a vehicle.
	Metric 8:	Consistency of exposure administration	Low	The study included a single exposure group with presumably 4 replicates for each skin type (full-thickness and stripped skin). The consistency of skin thicknesses, or sources of skin samples between replicates (two sources were reported), is not known. Tests were conducted using a consistent test solution volume of 2.5 mL, and a skin surface area of 0.95 cm ² . The missing information could have a significant impact on the results.
	Metric 9:	Reporting of concentrations	Medium	A nominal 0.718 mM concentration was added to the donor chamber. The volume applied and skin surface area was reported. It is unclear whether the test concentration was analytically verified. The selected concentration was not justified by the study authors.
	Metric 10:	Exposure frequency	High	The duration of exposure was dependent on when permeation reached a steady state. For stripped skin, the exposure duration was 6 hours and for full-thickness skin was 12 hours. The durations were in line with OECD guidelines.
	Metric 11:	Number of exposure groups and concentration spacing	Low	The study used a single exposure concentration; however, the purpose of the study was to compare data from multiple skin types (full-thickness and stripped), chemicals, and species (rat and human), and also to assess metabolic parameters. It is not clear that testing multiple concentrations was in line with the goals of the study, although OECD guidelines recommend at least three exposure groups.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	Abdominal skin was excised from 8-10 week-old male hairless rats (WBN/IIa-Ht) obtained from either the Life Science Research Center in Josai University or Ishikawa Experimental Animals Laboratories (Fukaya, Saitama). It is unclear how many donors were used, and if samples from animals from the different sites were randomly distributed. The skin samples were not stored. Skin integrity was not assessed and thickness was not reported. The samples were used either as full-thickness with the fat trimmed off or as stripped skin. According to OECD guidelines, full-thickness skin should not be used to calculate flux, which was the main endpoint in this study. However, the Kp results were essentially the same comparing full-thickness to stripped skin, and also across species (rat and human), so seemed appropriate in the current study.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates per group was not specified in the methods, but the data points represented an n of 4 for receptor fluid measurements. The data table reporting Kp reports and n of 3-5. A sample size of 4 is the minimum sample size required, as specified in OECD 428.
Domain 5: Outcome Assessment				
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Study Citation: Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17. Chemical: Dibutyl Phthalate Exposure Type: Parent compound HERO ID: 3859042 Unique ID: DBP - stripped skin (rat)				
Domain		Metric	Rating	Comments
	Metric 14:	Outcome assessment methodology	High	Use of a guideline was not specified. The study was focused on determining Kp and flux, which should be obtained using an infinite dose scenario. A volume of 2.5 mL was applied to the donor chamber (area 0.95 cm ²), so the applied volume was ~ 2.6 mL/cm ² which is appropriate for infinite exposure of a liquid, regardless of concentration. A molar concentration of 0.718 mM was reported. Based on a molecular weight of 278.34, and the 2.5 mL volume, approximately 0.5 mg of the test substance was added to the donor chamber (equivalent to ~0.52 mg/cm ²).
	Metric 15:	Consistency of outcome assessment	Medium	Based on the data available, there is no indication of inconsistencies across replicates in the outcome assessment protocols. The same vehicle and receptor fluids were used for each replicate, and the duration of exposure by skin type was consistent. Some information was not specified, for example, how soon after the collection of receptor fluids concentrations was analyzed, but this is not expected to have a significant impact on the study results.
	Metric 16:	Sampling adequacy and sensitivity	High	The sample size was reported for all of the outcomes. An adequate number of receptor fluid aliquots were taken to allow an accurate graphical representation of the content of the test article in the receptor fluid vs. time.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Low	The study included only a single group. Skin was excised from animals from two different sources. It is unclear if the same source was used within a single group. Skin thicknesses were not reported and integrity/quality was not assessed making it difficult to determine whether there were any confounding differences across replicates. The missing details could have a substantial impact on the study results.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Low	The study did not indicate whether the test substance was soluble in the receptor fluid (PBS). Given that DBP is lipophilic, solubility in PBS may have been an issue. This could have an impact on the study results. The study noted significant metabolism to BP and therefore permeation of both DBP and BP were assessed.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	The data analysis methods were clearly reported. Because metabolism in the skin was an issue, an alternative Kp (the steady-state flux of the metabolite divided by the concentration of the parent test substance) was used in place of a true Kp. In addition to skin permeation, metabolic rates were also determined. The coefficients of variation (CoV) across replicates were acceptable (SD <25%) for some, but not all tests. The CoV was <25% for the Kp determination for full thickness (19%) skin, but not for stripped skin (32%). However, the CoVs for measurements in receptor fluid were >25% for most collection points in the full-thickness test but were <25% for the split-thickness test, except for the final collection at 6 hours. The CoVs for measurements in the skin were <25% in both skin types.
	Metric 20:	Data interpretation	High	Infinite exposure conditions were used to derive Kp and flux. This study did not determine % recovery; however, for infinite dose applications in which Kp or flux are determined, recovery is not relevant (OECD TG 28).

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Study Citation:	Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	3859042			
Unique ID:	DBP - stripped skin (rat)			
Domain	Metric		Rating	Comments
	Metric 21:	Reporting of data	High	Data for all outcomes were adequately reported and presented in tables or figures as means \pm SD
Overall Quality Determination			Medium	

Study Citation:	Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	3859042			
Unique ID:	DBP - Full thickness (human)			
Domain	Metric	Rating	Comments	
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as dibutyl phthalate (DBP) A CASRN and structure were provided. The test substance was not radiolabeled.
	Metric 2:	Test substance source	High	The test substance was purchased from Wako Pure Chemical Industries, Ltd. Certificates of analysis are available on the supplier website for the current listings of this chemical. The performing laboratory did not analytically verify the test substance.
	Metric 3:	Test substance purity	Medium	The purity was not reported in the study. The product currently listed on the website of the supplier has a purity of >98%. Other chemicals used in the study were of special or HPLC grade. It is assumed the purity is high, but due to the lack of listing in the main study report, there is some uncertainty.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No reference compound was used and no history of test performance in the laboratory was reported.
	Metric 5:	Assay procedures	Medium	The assay procedures were clearly described, with only a few missing details. Skin samples (presumably n = 4/group) were mounted on static diffusion cells yielding a surface area of 0.95 cm2. It was not specified whether the chambers were open or closed, but the test substance has low volatility. The donor and receiver chambers were held at 32 degrees C; humidity was not reported. Prior to exposure, the skin was hydrated with PBS. At the time of exposure, the receptor chamber was filled with 2.5 mL of fresh PBS, and the donor chamber was filled with 2.5 mL of PBS containing 0.718mM DBP. All of the solutions were stirred with a magnetic stir bar. In some cases, 0.53mM DFP (an esterase inhibitor) was added to the receptor fluid for metabolism tests. Receptor fluid samples were taken periodically (~ every 1 [stripped skin] or 2 [full-thickness skin] hours based on provided figures) and replenished with an equal volume of PBS. The collected fractions were held at 4 degrees C until analysis. At the end of exposure (6 or 12 hours, depending on the time to reach a steady state), the skin was washed 3 times with receptor fluid and then homogenized for analysis via HPLC. The lower limits of quantitation were reported.
	Metric 6:	Standards for tests	Low	This study did not conduct the typical standard tests to determine the validity, reliability, or quality of the experiments. Skin integrity was not tested prior to use. Percent recovery was not determined; however, recovery determination is not relevant for infinite dose applications determining a Kp. Coefficients of variation across replicates can be determined for Kp (see Metric 19 for further details). There is no text indicating the test met pre-established criteria.
Domain 3: Exposure Characterization				
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Study Citation:	Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	3859042			
Unique ID:	DBP - Full thickness (human)			
Domain	Metric	Rating	Comments	
	Metric 7: Preparation and storage of test substance (chemical)	Low	Limited details of the test substance preparation were provided. The test substance (0.718 mM) was diluted in PBS. No details on stability, or mixing to assure homogeneity, mixing temperature, stirring methods, or storage conditions were reported. The solubility of the test substance in PBS was not specified. DBP is lipophilic, so it is unclear if PBS was an appropriate vehicle. Other lipophilic chemicals tested in the same study used DMSO-PBS as a vehicle.	
	Metric 8: Consistency of exposure administration	Medium	Details of exposure administration were reported and were consistent across groups. The study included a single exposure group with presumably 4 replicates for each skin type (full-thickness and stripped skin). The skin thicknesses were 500 and 550 um from each donor, respectively Tests were conducted using a consistent test solution volume of 2.5 mL, and a skin surface area of 0.95 cm2.	
	Metric 9: Reporting of concentrations	Medium	A nominal 0.718 mM concentration was added to the donor chamber. The volume applied and skin surface area was reported. It is unclear whether the test concentration was analytically verified. The selected concentration was not justified by the study authors.	
	Metric 10: Exposure frequency	Low	The duration of exposure was dependent on when permeation reached a steady state. Because the data for human skin exposed to DBP were not quantitatively reported, the exact durations are not known. For the studies in rat skin, exposure durations were 6 hours for stripped skin and 12 hours for full-thickness skin. It is unclear if the same durations were used for the human skin samples.	
	Metric 11: Number of exposure groups and concentration spacing	Low	The study used a single exposure concentration; however, the purpose of the study was to compare data from multiple skin types (full-thickness and stripped), chemicals, and species (rat and human), and also to assess metabolic parameters. It is not clear that testing multiple concentrations was in line with the goals of the study, although OECD guidelines recommend at least three exposure groups.	
Domain 4: Test Model				
	Metric 12: Test model (skin)	Low	Frozen abdominal skin (4 pieces total) from two Caucasian females aged 51 and 55 yrs old, was purchased from Biopredic International. The skin was stored at -50 degrees C and thawed just prior to the experiments. The samples were used either as full-thickness with the fat trimmed off or as stripped skin. Stripped samples were tape-stripped 20 times to remove the stratum corneum. Thicknesses, presumably of the full-thickness samples were 500 and 550 um, from each donor, respectively. The thickness of the stripped skin samples was not reported. Skin integrity was not assessed. According to OECD guidelines, full-thickness skin should not be used to calculate flux, which was the main endpoint in this study. However, the Kp results were essentially the same comparing full-thickness to stripped skin, and also across species (rat and human), so seemed appropriate in the current study. The missing details are likely to have a substantial impact on the results.	
	Metric 13: Number/Replicates per group	Medium	The number of replicates per group was not specified in the methods, but the data points represented an n of 4 for receptor fluid measurements. The data table reporting Kp reports and n of 3-5. A sample size of 4 is the minimum sample size required, as specified in OECD 428.	

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Study Citation:	Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17.		
Chemical:	Dibutyl Phthalate		
Exposure Type:	Parent compound		
HERO ID:	3859042		
Unique ID:	DBP - Full thickness (human)		
Domain	Metric	Rating	Comments
Domain 5: Outcome Assessment			
Metric 14:	Outcome assessment methodology	High	Use of a guideline was not specified. The study was focused on determining Kp and flux, which should be obtained using an infinite dose scenario. A volume of 2.5 mL was applied to the donor chamber (area 0.95 cm ²), so the applied volume was ~ 2.6 mL/cm ² which is appropriate for infinite exposure of a liquid, regardless of concentration. A molar concentration of 0.718 mM was reported. Based on a molecular weight of 278.34, and the 2.5 mL volume, approximately 0.5 mg of the test substance was added to the donor chamber (equivalent to ~0.52 mg/cm ²).
Metric 15:	Consistency of outcome assessment	Medium	Based on the data available, there is no indication of inconsistencies across replicates in the outcome assessment protocols. The same vehicle and receptor fluids were used for each replicate, and the duration of exposure by skin type was consistent. Some information was not specified, for example, how soon after the collection of receptor fluids concentrations was analyzed, but this is not expected to have a significant impact on the study results.
Metric 16:	Sampling adequacy and sensitivity	Low	The sample size was reported for only some outcomes. The sample sizes for receptor fluid collections and for measurements of the test material in the skin were not reported. A graphical representation of the content of the test article in the receptor fluid vs. time was not provided. The Kp values were derived from a mean of 3-5 experiments.
Domain 6: Confounding/Variable Control			
Metric 17:	Confounding variables in test design and procedures	Low	The study included only a single group. Skin integrity/quality was not assessed making it difficult to determine whether there were any confounding differences across replicates. Skin thicknesses were reported for full-thickness samples only. The missing details could have a substantial impact on the study results.
Metric 18:	Confounding variables in outcomes unrelated to exposure	Low	The study did not indicate whether the test substance was soluble in the receptor fluid (PBS). Given that DBP is lipophilic, solubility in PBS may have been an issue. This could have an impact on the study results. The study noted significant metabolism to BP and therefore permeation of both DBP and BP were assessed.
Domain 7: Data Presentation and Analysis			
Metric 19:	Data analysis	Low	The data analysis methods were clearly reported. Because metabolism in the skin was an issue, an alternative Kp (the steady-state flux of the metabolite divided by the concentration of the parent test substance) was used in place of a true Kp. In addition to skin permeation, metabolic rates were also determined. Although the methods are described, it cannot be determined if the analysis was appropriate (e.g., whether there were statistical outliers), because the data were not provided for independent review. The CoV was <25% for the Kp determination for full thickness (6%) and stripped skin (15%).
Metric 20:	Data interpretation	High	Infinite exposure conditions were used to derive Kp and flux. This study did not determine % recovery; however, for infinite dose applications in which Kp or flux are determined, recovery is not relevant (OECD TG 28).
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Study Citation:	Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	3859042			
Unique ID:	DBP - Full thickness (human)			
Domain	Metric		Rating	Comments
	Metric 21:	Reporting of data	Low	Data for some outcomes specified in the methods (Kp values) were adequately reported and presented in tables or figures as means \pm SD. Measurements of the test substance in the receptor fluid and in the skin were not reported.
Overall Quality Determination			Low	

Study Citation:	Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	3859042			
Unique ID:	DBP - stripped (human)			
Domain	Metric	Rating	Comments	
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as dibutyl phthalate (DBP) A CASRN and structure were provided. The test substance was not radiolabeled.
	Metric 2:	Test substance source	High	The test substance was purchased from Wako Pure Chemical Industries, Ltd. Certificates of analysis are available on the supplier website for the current listings of this chemical. The performing laboratory did not analytically verify the test substance.
	Metric 3:	Test substance purity	Medium	The purity was not reported in the study. The product currently listed on the website of the supplier has a purity of >98%. Other chemicals used in the study were of special or HPLC grade. It is assumed the purity is high, but due to the lack of listing in the main study report, there is some uncertainty.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No reference compound was used and no history of test performance in the laboratory was reported.
	Metric 5:	Assay procedures	Medium	The assay procedures were clearly described, with only a few missing details. Skin samples (presumably n = 4/group) were mounted on static diffusion cells yielding a surface area of 0.95 cm2. It was not specified whether the chambers were open or closed, but the test substance has low volatility. The donor and receiver chambers were held at 32 degrees C; humidity was not reported. Prior to exposure, the skin was hydrated with PBS. At the time of exposure, the receptor chamber was filled with 2.5 mL of fresh PBS, and the donor chamber was filled with 2.5 mL of PBS containing 0.718mM DBP. All of the solutions were stirred with a magnetic stir bar. In some cases, 0.53mM DFP (an esterase inhibitor) was added to the receptor fluid for metabolism tests. Receptor fluid samples were taken periodically (~ every 1 [stripped skin] or 2 [full-thickness skin] hours based on provided figures) and replenished with an equal volume of PBS. The collected fractions were held at 4 degrees C until analysis. At the end of exposure (6 or 12 hours, depending on the time to reach a steady state), the skin was washed 3 times with receptor fluid and then homogenized for analysis via HPLC. The lower limits of quantitation were reported.
	Metric 6:	Standards for tests	Low	This study did not conduct the typical standard tests to determine the validity, reliability, or quality of the experiments. Skin integrity was not tested prior to use. Percent recovery was not determined; however, recovery determination is not relevant for infinite dose applications determining a Kp. Coefficients of variation across replicates can be determined for Kp (see Metric 19 for further details). There is no text indicating the test met pre-established criteria.
Domain 3: Exposure Characterization				
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Study Citation: Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17. Chemical: Dibutyl Phthalate Exposure Type: Parent compound HERO ID: 3859042 Unique ID: DBP - stripped (human)				
Domain		Metric	Rating	Comments
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Limited details of the test substance preparation were provided. The test substance (0.718 mM) was diluted in PBS. No details on stability, or mixing to assure homogeneity, mixing temperature, stirring methods, or storage conditions were reported. The solubility of the test substance in PBS was not specified. DBP is lipophilic, so it is unclear if PBS was an appropriate vehicle. Other lipophilic chemicals tested in the same study used DMSO-PBS as a vehicle.
	Metric 8:	Consistency of exposure administration	Medium	Details of exposure administration were reported and were consistent across groups. The study included a single exposure group with presumably 4 replicates for each skin type (full-thickness and stripped skin). The skin thicknesses were 500 and 550 um from each donor, respectively. Tests were conducted using a consistent test solution volume of 2.5 mL, and a skin surface area of 0.95 cm ² .
	Metric 9:	Reporting of concentrations	Medium	A nominal 0.718 mM concentration was added to the donor chamber. The volume applied and skin surface area was reported. It is unclear whether the test concentration was analytically verified. The selected concentration was not justified by the study authors.
	Metric 10:	Exposure frequency	Low	The duration of exposure was dependent on when permeation reached a steady state. Because the data for human skin exposed to DBP were not quantitatively reported, the exact durations are not known. For the studies in rat skin, exposure durations were 6 hours for stripped skin and 12 hours for full-thickness skin. It is unclear if the same durations were used for the human skin samples.
	Metric 11:	Number of exposure groups and concentration spacing	Low	The study used a single exposure concentration; however, the purpose of the study was to compare data from multiple skin types (full-thickness and stripped), chemicals, and species (rat and human), and also to assess metabolic parameters. It is not clear that testing multiple concentrations was in line with the goals of the study, although OECD guidelines recommend at least three exposure groups.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	Low	Frozen abdominal skin (4 pieces total) from two Caucasian females aged 51 and 55 yrs old, was purchased from Biopredic International. The skin was stored at -50 degrees C and thawed just prior to the experiments. The samples were used either as full-thickness with the fat trimmed off or as stripped skin. Stripped samples were tape-stripped 20 times to remove the stratum corneum. Thicknesses, presumably of the full-thickness samples were 500 and 550 um, from each donor, respectively. The thickness of the stripped skin samples was not reported. Skin integrity was not assessed. According to OECD guidelines, full-thickness skin should not be used to calculate flux, which was the main endpoint in this study. However, the Kp results were essentially the same comparing full-thickness to stripped skin, and also across species (rat and human), so seemed appropriate in the current study. The missing details are likely to have a substantial impact on the results.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates per group was not specified in the methods, but the data points represented an n of 4 for receptor fluid measurements. The data table reporting Kp reports and n of 3-5. A sample size of 4 is the minimum sample size required, as specified in OECD 428.

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Study Citation:	Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17.		
Chemical:	Dibutyl Phthalate		
Exposure Type:	Parent compound		
HERO ID:	3859042		
Unique ID:	DBP - stripped (human)		
Domain	Metric	Rating	Comments
Domain 5: Outcome Assessment			
Metric 14:	Outcome assessment methodology	High	Use of a guideline was not specified. The study was focused on determining Kp and flux, which should be obtained using an infinite dose scenario. A volume of 2.5 mL was applied to the donor chamber (area 0.95 cm ²), so the applied volume was ~ 2.6 mL/cm ² which is appropriate for infinite exposure of a liquid, regardless of concentration. A molar concentration of 0.718 mM was reported. Based on a molecular weight of 278.34, and the 2.5 mL volume, approximately 0.5 mg of the test substance was added to the donor chamber (equivalent to ~0.52 mg/cm ²).
Metric 15:	Consistency of outcome assessment	Medium	Based on the data available, there is no indication of inconsistencies across replicates in the outcome assessment protocols. The same vehicle and receptor fluids were used for each replicate, and the duration of exposure by skin type was consistent. Some information was not specified, for example, how soon after the collection of receptor fluids concentrations was analyzed, but this is not expected to have a significant impact on the study results.
Metric 16:	Sampling adequacy and sensitivity	Low	The sample size was reported for only some outcomes. The sample sizes for receptor fluid collections and for measurements of the test material in the skin were not reported. A graphical representation of the content of the test article in the receptor fluid vs. time was not provided. The Kp values were derived from a mean of 3-5 experiments.
Domain 6: Confounding/Variable Control			
Metric 17:	Confounding variables in test design and procedures	Low	The study included only a single group. Skin integrity/quality was not assessed making it difficult to determine whether there were any confounding differences across replicates. Skin thicknesses were reported for full-thickness samples only. The missing details could have a substantial impact on the study results.
Metric 18:	Confounding variables in outcomes unrelated to exposure	Low	The study did not indicate whether the test substance was soluble in the receptor fluid (PBS). Given that DBP is lipophilic, solubility in PBS may have been an issue. This could have an impact on the study results. The study noted significant metabolism to BP and therefore permeation of both DBP and BP were assessed.
Domain 7: Data Presentation and Analysis			
Metric 19:	Data analysis	Low	The data analysis methods were clearly reported. Because metabolism in the skin was an issue, an alternative Kp (the steady-state flux of the metabolite divided by the concentration of the parent test substance) was used in place of a true Kp. In addition to skin permeation, metabolic rates were also determined. Although the methods are described, it cannot be determined if the analysis was appropriate (e.g., whether there were statistical outliers), because the data were not provided for independent review. The CoV was <25% for the Kp determination for full thickness (6%) and stripped skin (15%).
Metric 20:	Data interpretation	High	Infinite exposure conditions were used to derive Kp and flux. This study did not determine % recovery; however, for infinite dose applications in which Kp or flux are determined, recovery is not relevant (OECD TG 28).
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Study Citation:	Sugino, M., Hatanaka, T., Todo, H., Mashimo, Y., Suzuki, T., Kobayashi, M., Hosoya, O., Jinno, H., Juni, K., Sugibayashi, K. (2017). Safety evaluation of dermal exposure to phthalates: Metabolism-dependent percutaneous absorption. Toxicology and Applied Pharmacology 328(Elsevier):10-17.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	3859042			
Unique ID:	DBP - stripped (human)			
Domain	Metric	Rating	Comments	
	Metric 21: Reporting of data	Low	Data for some outcomes specified in the methods (Kp values) were adequately reported and presented in tables or figures as means ± SD. Measurements of the test substance in the receptor fluid and in the skin were not reported.	
Overall Quality Determination		Low		

Study Citation:	Doan, K., Bronaugh, R. L., Yourick, J. J. (2010). In vivo and in vitro skin absorption of lipophilic compounds, dibutyl phthalate, farnesol and geraniol in the hairless guinea pig. Food and Chemical Toxicology 48(1):18-23.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	1323147			
Unique ID:	in vivo DBP			
Domain	Metric	Rating	Comments	
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was identified as DBP and 14C DBP (CASRN 84-74-2). The position of the radiolabel was not specified. No structure was provided.
	Metric 2:	Test substance source	High	Radiolabeled DBP was purchased from Sigma. This product can no longer be located on the supplier website and the performing laboratory did not analytically verify the test substance identity. Unlabeled DBP was purchased from Acros Organics; the catalogue, or lot/batch number were not reported. A single DBP product currently on the supplier's website has a certificate of analysis; however, because this study is over ten years old, the information currently on the supplier's website may not be applicable to the test material used in this study.
	Metric 3:	Test substance purity	Medium	The radiochemical purity was >97%. Impurities were not reported. The purity of the unlabeled test substance was not reported. The purity of DBP currently listed on the suppliers website is >99%.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Low	The method of animal allocation into study groups was not specified.
	Metric 5:	Standards for Tests	Medium	The percent recovery was 92.9%, which is acceptable according to OECD TG 427. The CVs for all measurements were <25%.
Domain 3: Exposure Characterization				
	Metric 6:	Preparation and storage of test substance (chemical)	Medium	The dosing solution was prepared by spiking an oil-in-water emulsion (consisting of 3% polyglyceryl distearate; 3% cetyl stearyl alcohol; 10% light mineral oil; 5% propylene glycol; 0.5% propyl-p-hydroxybenzoate; 0.5% methyl-p-hydroxybenzoate and 78% water) containing 7% cold DBP with the radiolabeled DBP. No details on the frequency of preparation, storage conditions, or statements of homogeneity were provided. Due to the short time of the test (a single administration), these missing details are unlikely to influence the interpretation of the study results.
	Metric 7:	Consistency of exposure administration	High	Details of exposure administration were reported and exposures appeared to be consistent across replicates. Approximately 0.5 uCi of radiolabeled DBP was applied per cm2. The emulsion described in Metric 6 was applied at a dose of 1 mg/cm2. The skin area was reported to be 9 cm2 (3 x 3 cm) on the mid-scapular region of the guinea pig's back. It is unclear if this represents 10% of the animal body surface.
	Metric 8:	Reporting of concentrations	Medium	The study applied a single administered a dosage of 1 mg/cm2 onto a 9 cm2 area of skin (9 mg/animal). The body weights of the guinea pigs were not reported, so default weights would be required to estimate doses in mg/kg. The age of animals was also not specified which introduces uncertainty in the default weights selected. Prior to application, aliquots of the dosing emulsion were assayed in triplicate using scintillation counting to verify the applied dose.
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Study Citation:	Doan, K., Bronaugh, R. L., Yourick, J. J. (2010). In vivo and in vitro skin absorption of lipophilic compounds, dibutyl phthalate, farnesol and geraniol in the hairless guinea pig. Food and Chemical Toxicology 48(1):18-23.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	1323147			
Unique ID:	in vivo DBP			
Domain	Metric	Rating	Comments	
	Metric 9:	Exposure duration	High	The test material remained on the skin for 24 hours. This duration was selected by the authors to replicate a typical cosmetic application. Collections did not continue beyond 24 hours.
	Metric 10:	Number of exposure groups and concentration spacing	Medium	Only one dose was tested; however, the concentration selected was justified by the authors as one typically found in cosmetic products.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	The test animal species, strain, sex, and source we reported. Age and starting body weights were not provided. The use of guinea pigs was justified by the authors.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	High	Animal husbandry conditions (cage type, # of animals per cage, bedding, food and water availability, room temperature, humidity, air changes per hour and light cycle) were reported, adequate, and consistent across replicates.
	Metric 13:	Number of animals per group	Low	The study included three replicates. This is less than the OECD (427) recommendation of at least 4 animals per group.
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	Hairless guinea pigs (n =3) were administered a single dermal application of the test emulsion equivalent to 1 mg/cm2, or 9 mg total. The test area was semi-occluded. Immediately after application, a carbon filter was used to capture volatile test material for 1 hr. Animals were then placed individually into metabolism cages. Urine and feces were collected over 24 hours. At the end of the exposure period, blood was collected. The treatment site was washed with 1% /v liquid detergent (Palmolive original) and water. The washes and rinses were collected. Radioactivity from the collections noted and from the skin at the treatment site, ovaries, liver, and kidneys and carcass were measured by liquid scintillation counting. The study did not measure or collect 14 C-carbon dioxide. The collected skin from the application site was not fractionated. The study reported total absorption as a percent of the applied dose.
	Metric 15:	Consistency of outcome assessment	Medium	The outcome assessment protocol was mostly reported and consistent across the three replicates. The handling of samples following collection and the time elapsed before scintillation counting was not specified.
	Metric 16:	Sampling adequacy and sensitivity	Low	Limited details of scintillation counts were provided. The number of scintillation counts per sample and limits of quantitation were not reported. The background level was not specified.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study did not report all information to determine confounding. The skin area was consistent across replicates. Although not explicitly stated, it is presumed that the same lot number of the chemical was used for the test. Animal body weights were not reported, so it is unclear whether the % of the body surface area was consistent. Details of the exposed skin (e.g., level of hair removal) were not discussed.
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Study Citation:	Doan, K., Bronaugh, R. L., Yourick, J. J. (2010). In vivo and in vitro skin absorption of lipophilic compounds, dibutyl phthalate, farnesol and geraniol in the hairless guinea pig. Food and Chemical Toxicology 48(1):18-23.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	1323147			
Unique ID:	in vivo DBP			
Domain	Metric		Rating	Comments
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	All animals were held for three days and screened for evidence of disease. No issues with animal attrition or health outcomes unrelated to exposure were reported.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	High	No statistical methods or calculations were reported. The CV values for urine, total systemic absorption (urine, organs, carcass), skin, total penetration (total systemic absorption + skin absorption + recovery of materials in the skin around the dosing site), carbon filter, and total recovery were all <25%. No outliers were discussed.
	Metric 20:	Data interpretation	Medium	Recovery was sufficient (92.9%), although the data table did not include measurements in feces. The skin was not tape stripped, so measurements were from total skin.
	Metric 21:	Reporting of Data	Medium	Data for the organs and carcass were not reported separately, but were estimated to represent <2% of the applied dose. Measurements in feces were not reported. All other data were adequately reported as means \pm SEM
Overall Quality Determination			Medium	

Study Citation:	Elsisi, A. E., Carter, D. E., Sipes, I. G. (1989). Dermal absorption of phthalate diesters in rats. Fundamental and Applied Toxicology 12(1):70-77.			
Chemical:	Dibutyl Phthalate			
Exposure Type:	Parent compound			
HERO ID:	675074			
Unique ID:	DBP absorption in rat			
Domain		Metric	Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was clearly identified. Radiolabeled chemicals were synthesized by the study authors using 14C-radiolabeled phthalic acid (uniformly labeled on the ring).
	Metric 2:	Test substance source	High	The source of the test substance was reported. The lot/ batch number were not reported.
	Metric 3:	Test substance purity	High	The test substance was >96% pure.
Domain 2: Test Design				
	Metric 4:	Randomized allocation of animals	Low	The study did not report how animals were allocated into groups.
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Domain	Metric		Rating	Comments
	Metric 5:	Standards for Tests	Low	OECD 427 guidelines recommend clipping the skin approximately 24 hours prior to dosing. The area should then be gently wiped with acetone to remove sebum. The application area should be at least 10 cm ² for rats weighing 20-250 grams. This study did not adhere to these guidelines. The skin clipped one hour before compound application and was not wiped with acetone. The skin surface area used for application of test substance was 1.3 cm ² . These deficiencies are not considered critical deficiencies. Absorption could be enhanced if skin is recently abraded; however, study authors stated that "animals which had any visual signs of abrasions were eliminated from the study". Impact is expected to be negligible to slight overestimation of absorption. Actual application area is 13% of guideline recommended area of application. The application rate per surface area of 5-8 mg/cm ² likely represents an infinite (instead of finite) dose, which is also supported by the fact that 80% of DIDP remained unabsorbed at the end of 7-d exposure. Similar saturation of absorption would be expected over a larger surface area with the same loading rate. Impact is expected to be negligible. The study did not follow OECD 427 guidelines for determining amount of test substance that remained on the surface of the skin compared to the amount absorbed into the skin (stratum corneum). The test substance remained on the skin surface for 7 days. Feces and urine were collected and analyzed every 24 hours. At the end of the 7 days, the skin, at the application site, was collected and analyzed, however the study authors did not wash the remaining test solution off before analyzing the skin. This could slightly underestimate actual dermal absorption because the potentially absorbable dose (in stratum corneum) is excluded as unabsorbed. Given the fact that the exposure was 7 days, it is reasonable to conclude that the any amount in the skin at 7 days is negligible and/or not absorbable. Impact is expected to be negligible to slight underestimation of absorption. The study also did not collect blood samples at the time of sacrifice. The study also did not collect blood samples at the time of sacrifice. Recovery was within 10% of 100% (93-105%) for DBP, DEHP and DIBP. Recovery was 82% for DIDP and 86% for BBP. It is unlikely that the material unaccounted for was in any unanalyzed tissues (e.g., carcass), given that the %dose in the adipose tissue+muscle+skin accounted for 0.5-4.9% dose across the phthalates, and the "other tissues" were <0.5% and represented the sum of the % dose found in brain, lungs, liver, spleen, small intestine, kidneys, testes, spinal cord, and blood. It is possible the unaccounted test substance was lost to evaporation, given the fact that the study had a 7-day duration with partial occlusion.
Domain 3: Exposure Characterization	Metric 6:	Preparation and storage of test substance (chemical)	Medium	The test substance was dissolved in absolute alcohol (no other details are provided). It is unclear if the dissolved test substance was used immediately or may have been stored for days/weeks. The radioactivity in the dosing solution was measured after preparation and before application to the skin, therefore the lack of reporting storage conditions is not expected to substantially impact results.
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	Metric 7:	Consistency of exposure administration	Low	The skin surface used for application of test substance was consistent (1.3 cm diameter which is equivalent to an area of 1.69 cm2). This is substantially smaller than the OECD recommended surface of 10 cm2. The volume applied was not reported. Animals were exposed to a dose range of 5-8 mg/cm2 . Inconsistencies in exposure administration may have contributed to variation in the study results. The study also states the ethanol was allowed to evaporate before the skin was covered. It is not clear whether any evaporation of the test substance also occurred during this step.
	Metric 8:	Reporting of concentrations	Medium	The applied dose was reported in the abstract as 157 umol/kg. Later, the study indicated that the applied dose ranged from 30-40 mg/kg. The specific activity of the dosing solutions was determined before application to the skin using liquid scintillation counting.
	Metric 9:	Exposure duration	Low	The duration (7 days) was longer than OECD guidelines of 6-24 hours based on expected human exposure duration. The study did collect urine and feces daily to measure extracts.
	Metric 10:	Number of exposure groups and concentration spacing	Medium	Only one dose group was studied. The chosen concentration was justified as being approximately 0.01 times the reported oral or intraperitoneal LD50.
Domain 4: Test Model				
	Metric 11:	Test animal characteristics	Medium	Male Fisher 344 rats with weight ranging from 180-220 grams were used for this study. The age of the animals was not reported. The animals were obtained from the Division of Animal Resources of the University of Arizona Health Sciences Center.
	Metric 12:	Adequacy and consistency of animal husbandry conditions	Low	Husbandry conditions were not adequately reported. Temperature and humidity of the animal facility were not reported. Food and water were available ad lib and a 12-hour light/dark cycle was maintained.
	Metric 13:	Number of animals per group	Low	The number of animals per group was not specified in the study methods. Based on information in the data figures, three animals were tested. This is less than the OECD guideline recommendation of 4 animals.
Domain 5: Outcome Assessment				
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	Metric 14:	Outcome assessment methodology	Low	There were several deviations from OECD 427 guidelines. For finite dosing 1-5 mg/cm ² is recommended, this study reported an application rate of 5-8 mg/cm ² , which is at the upper end to slightly higher than recommendations, and may have approached an infinite exposure scenario. The study did not follow OECD 427 guidelines for determining amount of test substance that remained on the surface of the skin compared to the amount absorbed into the skin (stratum corneum); no skin washing or tape stripping was done and the test substance remained on the skin surface for 7 days. Since no penetration information was provided, it is unclear if the concentrations on the skin of the application site were considered to be absorbable. OECD 427 guidelines recommend clipping the skin approximately 24 hours prior to dosing. The area should then be gently wiped with acetone to remove sebum. In this study, the skin clipped one hour before compound application and was not wiped with acetone. These deficiencies are not considered critical deficiencies. Absorption could be enhanced if skin is recently abraded; however, study authors stated that "animals which had any visual signs of abrasions were eliminated from the study". Impact is expected to be negligible to slight overestimation of absorption. Concentrations in exhaled air were not measured. Urine and feces were collected every 24 hours over 7 days. At the end of the study duration, concentrations in adipose tissue, muscle, skin, application site, the plastic cap, and "other tissues" (brain, lung, liver, spleen, small intestine, kidney, testis, spinal cord, and blood) were measured. Occluded conditions are recommended for finite exposures. In this study, the application sight was covered by a circular plastic cap that was perforated with needle holes to allow aeration."
	Metric 15:	Consistency of outcome assessment	High	Outcomes were assessed consistently across animals.
	Metric 16:	Sampling adequacy and sensitivity	Medium	Measurement sensitivity (signal:noise ratio) and the number of scintillation counts was not reported. The sampling interval (24 hours) was appropriate.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study did not report all information to determine confounding, although minor differences are not expected to substantially impact results. Initial body weights were reported as a range (exact not reported). No gross changes in the appearance of the skin were seen.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	Medium	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition, health outcomes unrelated to exposure, or solubility that could influence the outcome assessment.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	CV values were >25% in at least half of the samples for DEHP, BBP, and DIBP, and in 2/6 reported measurements for DBP and DIDP, and all chemicals had at least one CV value >50%. However, sufficient information is provided to conduct alternate calculations. Absorption estimates were presented across a time series (urine and feces). Statistical methods were described.
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Exposure Type:	Parent compound			
HERO ID:	675074			
Unique ID:	DBP absorption in rat			
Domain	Metric		Rating	Comments
	Metric 20:	Data interpretation	Low	There are major uncertainties regarding the interpretation of data. The test substance was not wiped off of the skin prior to collection and analysis of the skin sample. It cannot be determined how much of the test substance was on the surface of the skin (not absorbed) and how much was in the stratum corneum or deeper layers. The study does provide data on excreted amounts in urine and feces, amount of test substance in other organs, and amount of test substance on the cap used for occlusion.
	Metric 21:	Reporting of Data	Medium	Data for some outcomes specified were presented in figures as bar graphs with unspecified measures of variance, or no measures of variance (time-series excretion profiles). The percent recovery in various samples was quantitatively reported as means \pm SD. The sample size was only reported in 2 figures. The study did not report if skin at the application site appeared irritated. Blood measurements were not reported separately; however, it was lumped in with "other tissues" which accounted for <0.5% of the applied dose.

Overall Quality Determination**Medium**