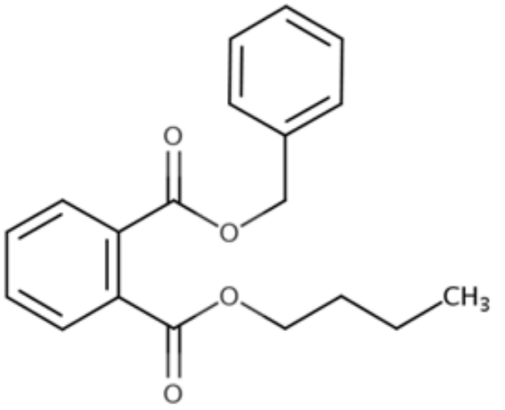
United States
Environmental Protection Agency

December 2025
Office of Chemical Safety and
Pollution Prevention

Data Quality Evaluation and Data Extraction Information for Dermal Absorption for Butyl benzyl phthalate (BBP) (1,2-Benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester)

Systematic Review Support Document for the Risk Evaluation

CASRN: 85-68-7



December 2025

This supplemental file contains information regarding the data evaluation results for data sources that met the PECO screening criteria for the *Risk Evaluation for Butyl benzyl phthalate (BBP)* 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 used 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'). Any updated steps in the systematic review process since the publication of the 2021 Draft Systematic Review Protocol are described in the *Systematic Review Protocol for Butyl Benzyl Phthalate (BBP)*.

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

Study Citation:	DuPont, (2006). Polyvinyl chloride film plasticized with butyl benzyl phthalate: In vitro dermal absorption rate testing.
Chemical:	Butyl benzyl phthalate
Exposure Type:	Other (e.g., metabolite, degradant, mixture/product)
HERO ID:	10617082
Unique ID:	BBP

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	Medium	The test substance was a polyvinyl film plasticized with unlabeled and 14C-BBP. All of the components of the film were reported. The position of the radiolabel was not reported. The physical properties of the films were tested at Haskell laboratories.
	Metric 2:	Test substance source	High	The source of the films was reported (Haskell Laboratories), and a certificate of analysis was provided.
	Metric 3:	Test substance purity	High	A certificate of analysis for the technical and radiolabeled BBP was provided. The radiochemical purity of 14C BBP in the PVC film was verified and was >98% and the specific activity was reported.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	No appropriate reference compound was used or reported, and the study did not provide evidence for an established history of test performance in the performing laboratory.
	Metric 5:	Assay procedures	Medium	BBP film (BBP concentration 301.4 mg/g film; 9mm diameter, ~0.64 cm2) was laid onto human cadaver skin pre-moistened with 10 uL/cm2 saline and weighted with glass beads. Exposure was conducted under occlusion in a static diffusion cell for 8 hours. The temperature was held at 32 degrees C. Humidity was not specified. The receptor fluid was saline fortified with 6% polyethyoxyoleate and was collected (50uL aliquots) at 0.5, 1, 4, and 8 hours post-application. An equivalent volume was replaced at each collection. At the end of the exposure period, the film was removed and the skin was washed with a 2% Ivory soap solution and then rinsed with water. After a post-exposure integrity assessment, the skin was tape stripped (5 times) to remove the corneum stratum. Radioactivity of the receptor fluid collections, the solubilized film piece, the beads/wash/rinse, donor chamber rinse, and tape strip extracts, and the remaining digested skin were measured by liquid scintillation counting. The time and number of counts were reported and the limit of detection was taken as twice the background obtained from blank samples.
	Metric 6:	Standards for tests	Medium	The skin integrity was assessed by measuring electrical impedance. Membranes with an EI of $\geq$17 k´Ω were considered to be intact. Skin integrity was also assessed at the end of the experiment after skin washing and prior to tape stripping. Percent recovery was reported and was 96.6 $\pm$ 2.37%. Coefficients of variation were not reported by the study authors, but sufficient data are available for an independent calculation.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	High	Details of how the films were prepared were provided in the appendix along with storage recommendations. The test substance was reported to be stable under the conditions of the study.

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HERO ID: 10617082
Unique ID: BBP

Domain	Metric		Rating	Comments
	Metric 8:	Consistency of exposure administration	Medium	Details of exposure administration were reported. A consistent film thickness and diameter (9mm diameter, ~0.64 cm2) was used. Human skin samples were all from Caucasian females and from the same anatomical site (abdomen). The dermatomed thickness was measured to be between 248 to 470 microns.
	Metric 9:	Reporting of concentrations	High	The concentration of BBP in each film was 5,958 ug as determined using LSC.
	Metric 10:	Exposure frequency	Low	The study used an 8-hour exposure. No discussion or justification was provided for the chosen duration, but it may represent a typical 8-hour workday. The total absorbable dose was <0.01% at this exposure duration. It is unclear if a longer exposure period would have been more appropriate.
	Metric 11:	Number of exposure groups and concentration spacing	Low	The study exposed skin to a single concentration of BBP embedded as a plasticizer in a PVC film. A discussion was not provided explaining the rationale or relevance for conditions of use for using the PVC film, or for the concentration of BBP within the film.
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The study used previously frozen abdominal skin from Caucasian human females. The full thickness skin was dermatomed to approximately 450 microns, although the measured thicknesses ranged from 248 to 470 microns. The skin samples were stored refrigerated until use. The integrity of the skin was assessed my measuring electrical impedance both at the start of the study and at the end of the exposure period.
	Metric 13:	Number/Replicates per group	Medium	The study tested 6 replicates total (2 replicates each from 3 donors).
Domain 5: Outcome Assessment				
	Metric 14:	Outcome assessment methodology	Medium	It is difficult to assign this study as an infinite or finite exposure scenario because the bioavailability of the test substance is not known. Experiments were not conducted that tested the ability of BBP to migrate from the PVC film under any experimental conditions over 8 hours. Based on the results of the study, 96.2% of the test substance remained in the PVC film. Information from this study may be useful if the films represented material workers are exposed to during normal conditions of use, but no details or discussions were provided. However, the outcome assessment methods were appropriate and sensitive to the outcomes of interest. Total recovery was the sum in the solubilized film, receptor fluid, the amount in beads/wash/rinse, donor chamber rinse, the amount in tape strips, and remaining in digested skin.
	Metric 15:	Consistency of outcome assessment	High	Details of the outcome assessment were mostly reported and the same protocol was used across replicates. There is no indication of inconsistent methods across replicates.
	Metric 16:	Sampling adequacy and sensitivity	High	Details regarding sampling were reported. The study included an adequate number of replicates per group (n =6), and there was adequate sampling of receptor fluid (0.5, 1, 4, and 8 hours post-application). Scintillation counts were reported.
Domain 6: Confounding/Variable Control				

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HERO ID: 10617082
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Domain	Metric		Rating	Comments
	Metric 17:	Confounding variables in test design and procedures	Medium	There were no differences among study group parameters. Results of the skin integrity tests were acceptable for all samples prior to the start of the study. The end of exposure test did identify one sample that fell below 17 k-ohms. The sample was not excluded. No data were excluded as outliers.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates or groups in test model unrelated to exposure. Solubility of BBP in the receptor fluid was reported to be ~2800 ug/mL.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Absorption estimates in receptor fluid were presented across time. Statistical methods were described. Approximately half of the CV values, calculated for this review) were >25% or >50%; however, sufficient data are provided to allow for calculations using the 95th percent upper CI.
	Metric 20:	Data interpretation	High	Recovery of the applied test substance was adequate (96.6 ± 2.37%). Most of the absorption measurements were below the level of detection and the total absorbable dose was <0.01% (0.57ug equivalents of BBP). There are no concerns about the data interpretation.
	Metric 21:	Reporting of data	High	Results for all outcomes were adequately reported. Data for receptor fluid collections were shown for each replicate. Other results were reported as means ± SD, or as % absorption.

Overall Quality Determination Medium

Study Citation: DuPont, (2006). [Sanitized] Butyl benzyl phthalate: In vitro dermal absorption rate testing.
Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 10709437
Unique ID: ex vivo human skin

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	Test substances were identified as non-radiolabeled commercial-grade Santicizer 160 BBP and radiolabeled BBP [14C], CAS number: 85-68-7. The structure was reported for the radiolabeled substance noting the location of the radiolabel within the structure.
	Metric 2:	Test substance source	High	The non-radiolabeled, BBP was sourced from the sponsor (DuPont Haskell Laboratory); the radiolabeled 1,2-dichloroethane was sourced from American Radiolabeled Chemical, Inc. The study included certificates of analyses that included lot/batch numbers and purity.
	Metric 3:	Test substance purity	High	The purities of the stock non-radiolabeled test substance (98.3%) and radiochemical purity of the labeled substance (98.59%) were reported in the certificates of analysis. Impurities were not reported by name, but chromatograms were provided. The radiochemical purity of the mixed test substance (non-labeled and labeled combined) was determined by study authors using HPLC and found to be 99.74%.
Domain 2: Test Design				
	Metric 4:	Reference compounds	Low	The study authors did use a reference compound (such as testosterone) and the study did not provide evidence for an established history of test performance in the performing laboratory.
	Metric 5:	Assay procedures	Medium	This study was conducted according to OECD TG 428, and OECD 28, The assay procedures specified in the report were described in detail, although some information was missing. The static diffusion set-up is sufficiently reported including a schematic drawing. Human abdominal skin samples from 3 donors were obtained frozen; details on donors were not provided (age, sex). The skin was thawed and dermatomed; thickness ranged from 468-487 um. This is slightly larger than OECD 428 guidelines of 200-400 um. The skin was allowed to equilibrate for 30 minutes in the chamber before the study began. Skin was exposed to the test substance under occluded conditions (Parafilm) for 8 hours. An infinite dose of BBP (neat) was applied to human skin (6 replicates; 2 replicates from each donor). Dose volume (100 uL/cm2) was applied to 0.64 cm2 surface area. The receptor solution (0.9% saline fortified with 6% polyethoxyoleate 20 oleyl ether) was appropriate for this lipophilic chemical. The solubility of BBP was tested in the receptor fluid prior to the study and it was determined that dissolution of BBP was not rate-limiting. The receptor fluid was maintained at 32 degrees C using a recirculating water bath system; humidity was not reported. It was not specified whether the receptor fluid was continuously stirred as per OECD 428 guidelines. Receptor fluid samples (50uL) were collected at 0.5, 1, 2, 4, and 8 hours post-application and analyzed for radioactivity. After 8 hours the skin was washed with 2% Ivory Soap solution and rinsed with deionized water. Skin was tape-stripped using Leukotape; the number of times not reported. Skin washes/rinses and tape stripes were analyzed for radioactivity. Radioactivity was measured using a liquid scintillation counter. The limit of detection “was taken as twice the background disintegration rate obtained from analysis of appropriate blank samples.”

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Domain	Metric		Rating	Comments
	Metric 6:	Standards for tests	Medium	The integrity of the skin was determined by measurement of electrical impedance prior to and after to test substance application. Membranes with an EI of $\geq$ 17 k´Ω were considered acceptable. These readings were reported and appropriate. The total recovered test substance was 96.4%. Coefficients of variation were not reported by the study authors, but sufficient data are available for an independent calculation.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Medium	Preparation of test substance was partially reported. The non-radiolabeled test substance was spiked with radiolabeled test substance (volumes not reported). The activity and homogeneity of the diluted doses were assessed. The study does not report findings of homogeneity. Storage conditions of stock radiolabeled and non-radiolabeled BBP were not reported, but the study reports "test substance appeared to be stable under the conditions of the study; no evidence of instability was observed".
	Metric 8:	Consistency of exposure administration	Medium	The application rate (100 uL/cm2) was delivered consistently across study groups to exposed skin. The skin surface area of 0.64 cm2 was consistent across groups. The skin thickness was reported as a range (468-487 uM). This small variation is unlikely to substantially impact results.
	Metric 9:	Reporting of concentrations	High	The application rate is reported 100 uL/cm2 or 64 uL (100 uL/cm2 x 0.64 cm2). The density of BBP is 1120 mg/ml. Given the above information the dose can be calculated as 0.1 ml/cm2 x 1120 mg/ml = 112 mg/cm2.
	Metric 10:	Exposure frequency	Low	The test substance was in contact with the skin for 8 hours prior to washing. Receptor fluid samples were not collected post-washing. OECD guidelines recommend collecting samples post-washing (up to 24 hours total) to account for retained dose in the skin. The total absorbed into the skin was low (0.2%), it is unclear if a longer collection time or exposure period would have substantially impacted results.
	Metric 11:	Number of exposure groups and concentration spacing	Low	Only one dose group was studied (neat).
Domain 4: Test Model				
	Metric 12:	Test model (skin)	High	The test model and descriptive information were reported. Female Caucasian abdominal skin from 3 cadavers were studied. The age of the donors and timing from death to harvest were not reported. The samples were stored frozen at -20 degrees C. Prior to use, the skin samples were thawed and dermatomed using a Padgett Electro Dermatome. The thickness ranged from 468 to 487 uM. These methods were in agreement with OECD guidelines which state split thickness (dermatomed) skin is preferred. The thickness is slightly greater than OECD recommendation (200-400um). Membrane integrity was determined by measuring electrical impedance prior to/and upon completion of the experiment.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates was appropriate as per OECD 428. Guidelines recommend a minimum of 4 replicated per test preparation. This study examined 6 replicates/dose.
Domain 5: Outcome Assessment				

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Domain	Metric		Rating	Comments
	Metric 14:	Outcome assessment methodology	Medium	The outcome assessment methodology slightly deviated from OECD guidelines. The study assessed absorption of the test substance over an 8-hour time period. An infinite application dose (100uL/cm2) was used instead of a finite dose (which is usually used for absorption measurements). However, since the absorption was so low for the test substance the use of an infinite dose was unlikely to substantially impact the results. Receptor samples were only collected for the 8 hours the test substance was on the skin. OECD guidelines specify that samples should be collected after the test substance is washed off (up to 24 hours). Measurement techniques were appropriate.
	Metric 15:	Consistency of outcome assessment	High	Details of outcome assessment protocol were reported and outcomes were assessed consistently across study replicates. The same duration of exposure, receptor fluid used, and sampling period were consistent across replicates.
	Metric 16:	Sampling adequacy and sensitivity	High	The study reported adequate sampling for the outcomes of interest; measurement sensitivity was sufficient. The sampling intervals were adequate. Methods for determination of radioactivity are reported. Samples were counted for 10 minutes or until 160,000 disintegrations were accumulated. The limit of detection was taken as twice the background obtained from appropriate blank samples. The cumulative amount of test substance that penetrated into the receptor chamber was shown at each timepoint.
Domain 6: Confounding/Variable Control				
	Metric 17:	Confounding variables in test design and procedures	Medium	The study used a single batch of non-radiolabeled and radio-labeled test substances. Human abdominal skin was obtained from 3 female cadavers, the ages were not reported and could potentially confound results. The split-thickness was reported as a range (468-487 um). This variation in thickness is small and the authors stated that it did not affect the results of the study. Skin integrity was confirmed by electrical impedance both pre and post-exposure. All samples were acceptable with EI $\geq$ 17 k´Ω.
	Metric 18:	Confounding variables in outcomes unrelated to exposure	High	There were no reported differences among the study replicates that were unrelated to exposure; the test substance was demonstrated to be soluble in the receptor fluid.
Domain 7: Data Presentation and Analysis				
	Metric 19:	Data analysis	Low	Absorption estimates were based on appropriate measurements. For half of the scenarios, the CVs were either $>$ 25% and $<$ 50% or $>$50%; however, the data are available for EPA to calculate an alternate (upper end) value to account for variability in the results.
	Metric 20:	Data interpretation	High	Absorption estimates were calculated appropriately and included dislodegeable doses skin washes, tape stripping, skin, donor chamber, and receptor fluid. Recovery of applied test substance was adequate 96.4%.
	Metric 21:	Reporting of data	High	Data for all relevant endpoints were reported quantitatively as means $\pm$ SD. Individual replicate data were provided.

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:	Butyl benzyl phthalate
Exposure Type:	Parent compound
HERO ID:	3859042
Unique ID:	BBP - full-thickness (rat) - BnP metabolite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as benzyl butyl phthalate (BnBP) 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 >95%. 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 = 4-5/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 exposure time, the receptor chamber was filled with 2.5 mL of fresh PBS + 10% DMSO, and the donor chamber was filled with 2.5 mL of PBS + 10% DMSO containing 0.4 mM 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, with at least 12 collections based on provided figures, and replenished with an equal volume of the receptor fluid. The collected fractions were held at 4 degrees C until analysis. At the end of exposure (24 hours), 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. Based on graphical presentations, the variation across replicates was >25% in most cases (see Metric 19). There is no text indicating the test met pre-established criteria.
Domain 3: Exposure Characterization				

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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - full-thickness (rat) - BnP metabolite

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 (0.4 mM) was diluted in PBS +10% DMSO. 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 the receptor fluid was not specified. BBP is lipophilic and it is assumed DMSO was added to increase solubility.
	Metric 8:	Consistency of exposure administration	Low	The study included a single exposure group. The number of replicates was not explicitly reported but was between 4 and 5 (based on sample sizes). 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 cm2. The missing information could have a significant impact on the results.
	Metric 9:	Reporting of concentrations	Medium	A nominal 0.4 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 full-thickness skin, the duration was 24 hours. The durations was 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/Ila-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 for the BnP metabolite were essentially the same comparing full-thickness to stripped skin, and also across species (rat and human), so the full-thickness skin 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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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 cm2), so the applied volume was ~ 2.6 mL/cm2 which is appropriate for infinite exposure to a liquid, regardless of concentration. A molar concentration of 0.4 mM was reported. Based on a molecular weight of 312.4, and the 2.5 mL volume, approximately 0.312 mg of the test substance was added to the donor chamber with a 0.95 cm2 surface area (equivalent to ~0.328 mg/cm2).
	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	There was insufficient information to determine whether there were confounding variables between replicates that were unrelated to exposure. The study did not indicate whether the test substance was soluble in the receptor fluid (PBS + 10% DMSO) although DMSO is expected to enhance the solubility of lipophilic substances. The study noted significant metabolism occurred and concentrations of two metabolites were assessed. This could cause additional variation across replicates.
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 metabolites 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 coefficient of variation across replicates was not acceptable (>25%) for several endpoints. The SDs relative to the mean were >25% for the concentrations of the BP metabolite in receptor fluid at each time point. It is unclear what impact this had on the Kp determinations. Using data extraction software, the mean concentration of the parent molecule in the skin samples (with or without DFP treatment) also had relative SDs >25% for measurements of the parent compound.

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Domain	Metric		Rating	Comments
	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).
	Metric 21:	Reporting of data	High	Data for all outcomes specified in the methods were adequately reported and presented in tables or figures as means ± SD

Overall Quality Determination Medium

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Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as benzyl butyl phthalate (BnBP) 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 >95%. 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 = 4-5/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 exposure time, the receptor chamber was filled with 2.5 mL of fresh PBS + 10% DMSO, and the donor chamber was filled with 2.5 mL of PBS + 10% DMSO containing 0.4 mM 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, with at least 12 collections based on provided figures, and replenished with an equal volume of the receptor fluid. The collected fractions were held at 4 degrees C until analysis. At the end of exposure (24 hours), 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. Based on graphical presentations, the variation across replicates was >25% in most cases (see Metric 19). There is no text indicating the test met pre-established criteria.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Limited details of the test substance preparation were provided. The test substance (0.4 mM) was diluted in PBS +10% DMSO. 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 the receptor fluid was not specified. BBP is lipophilic and it is assumed DMSO was added to increase solubility.

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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - full-thickness (rat) - BP metabolite

Domain	Metric		Rating	Comments
	Metric 8:	Consistency of exposure administration	Low	The study included a single exposure group. The number of replicates was not explicitly reported but was between 4 and 5 (based on sample sizes). 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 cm2. The missing information could have a significant impact on the results.
	Metric 9:	Reporting of concentrations	Medium	A nominal 0.4 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 full-thickness skin, the duration was 24 hours. The durations was 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/Ila-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 for the BnP metabolite were essentially the same comparing full-thickness to stripped skin, and also across species (rat and human), so the full-thickness skin 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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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - full-thickness (rat) - BP metabolite

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 cm2), so the applied volume was ~ 2.6 mL/cm2 which is appropriate for infinite exposure to a liquid, regardless of concentration. A molar concentration of 0.4 mM was reported. Based on a molecular weight of 312.4, and the 2.5 mL volume, approximately 0.312 mg of the test substance was added to the donor chamber with a 0.95 cm2 surface area (equivalent to ~0.328 mg/cm2).
	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	There was insufficient information to determine whether there were confounding variables between replicates that were unrelated to exposure. The study did not indicate whether the test substance was soluble in the receptor fluid (PBS + 10% DMSO) although DMSO is expected to enhance the solubility of lipophilic substances. The study noted significant metabolism occurred and concentrations of two metabolites were assessed. This could cause additional variation across replicates.
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 metabolites 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 coefficient of variation across replicates was not acceptable (>25%) for several endpoints. The SDs relative to the mean were >25% for the concentrations of the BP metabolite in receptor fluid at each time point. It is unclear what impact this had on the Kp determinations. Using data extraction software, the mean concentration of the parent molecule in the skin samples (with or without DFP treatment) also had relative SDs >25% for measurements of the parent compound.

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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - full-thickness (rat) - BP metabolite

Domain	Metric		Rating	Comments
	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).
	Metric 21:	Reporting of data	High	Data for all outcomes specified in the methods were adequately reported and presented in tables or figures as means ± SD

Overall Quality Determination Medium

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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - Stripped (rat) - BnP metabolite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as benzyl butyl phthalate (BnBP) 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 >95%. 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 = 4-5/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 exposure time, the receptor chamber was filled with 2.5 mL of fresh PBS + 10% DMSO, and the donor chamber was filled with 2.5 mL of PBS + 10% DMSO containing 0.4 mM 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 and replenished with an equal volume of the receptor fluid. The collected fractions were held at 4 degrees C until analysis. At the end of exposure (24 hours), 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				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Limited details of the test substance preparation were provided. The test substance (0.4 mM) was diluted in PBS +10% DMSO. 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 the receptor fluid was not specified. BBP is lipophilic and it is assumed DMSO was added to increase solubility.

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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - Stripped (rat) - BnP metabolite

Domain	Metric		Rating	Comments
	Metric 8:	Consistency of exposure administration	Low	The study included a single exposure group. The number of replicates was not explicitly reported but was between 4 and 5 (based on sample sizes). 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 cm2. The missing information could have a significant impact on the results.
	Metric 9:	Reporting of concentrations	Medium	A nominal 0.4 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	Uninformative	The duration of exposure was dependent on when permeation reached a steady state. The duration was not reported for the tests on stripped skin.
	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/Ila-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.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates per group was not specified in the methods. The data table reporting Kps indicates a n of 3-5. A sample size of 4 is the minimum sample size required, as specified in OECD 428.
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 cm2), so the applied volume was ~ 2.6 mL/cm2 which is appropriate for infinite exposure to a liquid, regardless of concentration. A molar concentration of 0.4 mM was reported. Based on a molecular weight of 312.4, and the 2.5 mL volume, approximately 0.312 mg of the test substance was added to the donor chamber with a 0.95 cm2 surface area (equivalent to ~0.328 mg/cm2).

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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - Stripped (rat) - BnP metabolite

Domain	Metric		Rating	Comments
	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 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.
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	There was insufficient information to determine whether there were confounding variables between replicates that were unrelated to exposure. The study did not indicate whether the test substance was soluble in the receptor fluid (PBS + 10% DMSO) although DMSO is expected to enhance the solubility of lipophilic substances. The study noted significant metabolism occurred and concentrations of two metabolites were assessed. This could cause additional variation across replicates.
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 metabolites 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 coefficient of variation across replicates could not be determined for several endpoints, including measurements in receptor fluid and in the skin. The data were not provided to conduct an independent analysis. The CoV for Kp was appropriate <25%.
	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).
	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 Uninformative

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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - stripped (rat) - BP metabolite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as benzyl butyl phthalate (BnBP) 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 >95%. 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 = 4-5/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 exposure time, the receptor chamber was filled with 2.5 mL of fresh PBS + 10% DMSO, and the donor chamber was filled with 2.5 mL of PBS + 10% DMSO containing 0.4 mM 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 and replenished with an equal volume of the receptor fluid. The collected fractions were held at 4 degrees C until analysis. At the end of exposure (24 hours), 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				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Limited details of the test substance preparation were provided. The test substance (0.4 mM) was diluted in PBS +10% DMSO. 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 the receptor fluid was not specified. BBP is lipophilic and it is assumed DMSO was added to increase solubility.

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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - stripped (rat) - BP metabolite

Domain	Metric		Rating	Comments
	Metric 8:	Consistency of exposure administration	Low	The study included a single exposure group. The number of replicates was not explicitly reported but was between 4 and 5 (based on sample sizes). 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 cm2. The missing information could have a significant impact on the results.
	Metric 9:	Reporting of concentrations	Medium	A nominal 0.4 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	Uninformative	The duration of exposure was dependent on when permeation reached a steady state. The duration was not reported for the tests on stripped skin.
	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/Ila-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.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates per group was not specified in the methods. The data table reporting Kps indicates a n of 3-5. A sample size of 4 is the minimum sample size required, as specified in OECD 428.
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 cm2), so the applied volume was ~ 2.6 mL/cm2 which is appropriate for infinite exposure to a liquid, regardless of concentration. A molar concentration of 0.4 mM was reported. Based on a molecular weight of 312.4, and the 2.5 mL volume, approximately 0.312 mg of the test substance was added to the donor chamber with a 0.95 cm2 surface area (equivalent to ~0.328 mg/cm2).

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Domain	Metric		Rating	Comments
	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 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.
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	There was insufficient information to determine whether there were confounding variables between replicates that were unrelated to exposure. The study did not indicate whether the test substance was soluble in the receptor fluid (PBS + 10% DMSO) although DMSO is expected to enhance the solubility of lipophilic substances. The study noted significant metabolism occurred and concentrations of two metabolites were assessed. This could cause additional variation across replicates.
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 metabolites 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 coefficient of variation across replicates could not be determined for several endpoints, including measurements in receptor fluid and in the skin. The data were not provided to conduct an independent analysis. The CoV for Kp was appropriate <25%.
	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).
	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 Uninformative

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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - full-thickness (human) - BnP metabolite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as benzyl butyl phthalate (BnBP) 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 >95%. 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 = 4-5/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 exposure time, the receptor chamber was filled with 2.5 mL of fresh PBS + 10% DMSO, and the donor chamber was filled with 2.5 mL of PBS + 10% DMSO containing 0.4 mM 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 and replenished with an equal volume of the receptor fluid. The collected fractions were held at 4 degrees C until analysis. At the end of exposure (24 hours), 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. Reported results allow for the determination of the relative standard deviation, see metric 19 for further details.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Limited details of the test substance preparation were provided. The test substance (0.4 mM) was diluted in PBS +10% DMSO. 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 the receptor fluid was not specified. BBP is lipophilic and it is assumed DMSO was added to increase solubility.

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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - full-thickness (human) - BnP metabolite

Domain	Metric		Rating	Comments
	Metric 8:	Consistency of exposure administration	Medium	The study included a single exposure group. The number of replicates was not explicitly reported. Human skin thicknesses were 500 and 550 um from donors 1 and 2, respectively; these are presumably the thicknesses of the full-thickness samples. Tests were conducted using a consistent test solution volume of 2.5 mL, and a skin surface area of 0.95 cm2. The missing information could have a significant impact on the results.
	Metric 9:	Reporting of concentrations	Medium	A nominal 0.4 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	Uninformative	The duration of exposure was dependent on when permeation reached a steady state. The durations were not reported for 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 per group, thickness 500 and 550 um) 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. No information on skin integrity was provided. According to OECD guidelines, full-thickness skin should not be used to calculate flux, which was the main endpoint in this study. Purported results were similar to those obtained using stripped skin, so the full-thickness skin may have been acceptable for this study.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates per group was not specified in the methods. The data table reporting Kps indicates a n of 3-5. A sample size of 4 is the minimum sample size required, as specified in OECD 428.
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 cm2), so the applied volume was ~ 2.6 mL/cm2 which is appropriate for infinite exposure to a liquid, regardless of concentration. A molar concentration of 0.4 mM was reported. Based on a molecular weight of 312.4, and the 2.5 mL volume, approximately 0.312 mg of the test substance was added to the donor chamber with a 0.95 cm2 surface area (equivalent to ~0.328 mg/cm2).
	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.

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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - full-thickness (human) - BnP metabolite

Domain	Metric		Rating	Comments
	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. The skin was excised from animals from two donors. Skin thicknesses between donors were within an acceptable range (500 to 550 um). 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	There was insufficient information to determine whether there were confounding variables between replicates that were unrelated to exposure. The study did not indicate whether the test substance was soluble in the receptor fluid (PBS + 10% DMSO) although DMSO is expected to enhance the solubility of lipophilic substances. The study noted significant metabolism occurred and concentrations of two metabolites were assessed. This could cause additional variation across replicates.
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 metabolites 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 coefficient of variation across replicates was acceptable for some, but not all endpoints. The relative standard deviations were <25% for the Kp determinations, but the coefficients of variation were >25% for most of the measurements of both metabolites in the receptor fluid.
	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).
	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 Uninformative

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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - full-thickness (human) - BP metabolite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as benzyl butyl phthalate (BnBP) 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 >95%. 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 = 4-5/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 exposure time, the receptor chamber was filled with 2.5 mL of fresh PBS + 10% DMSO, and the donor chamber was filled with 2.5 mL of PBS + 10% DMSO containing 0.4 mM 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 and replenished with an equal volume of the receptor fluid. The collected fractions were held at 4 degrees C until analysis. At the end of exposure (24 hours), 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. Reported results allow for the determination of the relative standard deviation, see metric 19 for further details.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and storage of test substance (chemical)	Low	Limited details of the test substance preparation were provided. The test substance (0.4 mM) was diluted in PBS +10% DMSO. 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 the receptor fluid was not specified. BBP is lipophilic and it is assumed DMSO was added to increase solubility.

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Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - full-thickness (human) - BP metabolite

Domain	Metric		Rating	Comments
	Metric 8:	Consistency of exposure administration	Medium	The study included a single exposure group. The number of replicates was not explicitly reported. Human skin thicknesses were 500 and 550 um from donors 1 and 2, respectively; these are presumably the thicknesses of the full-thickness samples. Tests were conducted using a consistent test solution volume of 2.5 mL, and a skin surface area of 0.95 cm2. The missing information could have a significant impact on the results.
	Metric 9:	Reporting of concentrations	Medium	A nominal 0.4 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	Uninformative	The duration of exposure was dependent on when permeation reached a steady state. The durations were not reported for 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 per group, thickness 500 and 550 um) 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. No information on skin integrity was provided. According to OECD guidelines, full-thickness skin should not be used to calculate flux, which was the main endpoint in this study. Purported results were similar to those obtained using stripped skin, so the full-thickness skin may have been acceptable for this study.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates per group was not specified in the methods. The data table reporting Kps indicates a n of 3-5. A sample size of 4 is the minimum sample size required, as specified in OECD 428.
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 cm2), so the applied volume was ~ 2.6 mL/cm2 which is appropriate for infinite exposure to a liquid, regardless of concentration. A molar concentration of 0.4 mM was reported. Based on a molecular weight of 312.4, and the 2.5 mL volume, approximately 0.312 mg of the test substance was added to the donor chamber with a 0.95 cm2 surface area (equivalent to ~0.328 mg/cm2).
	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.

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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - full-thickness (human) - BP metabolite

Domain	Metric		Rating	Comments
	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. The skin was excised from animals from two donors. Skin thicknesses between donors were within an acceptable range (500 to 550 um). 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	There was insufficient information to determine whether there were confounding variables between replicates that were unrelated to exposure. The study did not indicate whether the test substance was soluble in the receptor fluid (PBS + 10% DMSO) although DMSO is expected to enhance the solubility of lipophilic substances. The study noted significant metabolism occurred and concentrations of two metabolites were assessed. This could cause additional variation across replicates.
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 metabolites 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 coefficient of variation across replicates was acceptable for some, but not all endpoints. The relative standard deviations were <25% for the Kp determinations, but the coefficients of variation were >25% for most of the measurements of both metabolites in the receptor fluid.
	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).
	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 Uninformative

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Chemical:	Butyl benzyl phthalate
Exposure Type:	Parent compound
HERO ID:	3859042
Unique ID:	BBP - stripped (human) - BP metabolite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as benzyl butyl phthalate (BnBP) 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 >95%. 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 = 4-5/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 exposure time, the receptor chamber was filled with 2.5 mL of fresh PBS + 10% DMSO, and the donor chamber was filled with 2.5 mL of PBS + 10% DMSO containing 0.4 mM 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 and replenished with an equal volume of the receptor fluid. The collected fractions were held at 4 degrees C until analysis. At the end of exposure (24 hours), 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). The results for measurements of BBP in the receptor fluid and split-thickness skin samples were not quantitatively reported, and it is unclear whether coefficients of variation were assessed.
Domain 3: Exposure Characterization				

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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 (0.4 mM) was diluted in PBS +10% DMSO. 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 the receptor fluid was not specified. BBP is lipophilic and it is assumed DMSO was added to increase solubility.
	Metric 8:	Consistency of exposure administration	Low	Details of exposure administration were insufficiently reported. The study included a single exposure group. The number of replicates was not explicitly reported, but based on sampling, there were at least 3-5 replicates. Human skin thicknesses were not reported. Tests were conducted using a consistent test solution volume of 2.5 mL, and a skin surface area of 0.95 cm2. The missing information could have a significant impact on the results.
	Metric 9:	Reporting of concentrations	Medium	A nominal 0.4 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	Uninformative	The duration of exposure was dependent on when permeation reached a steady state. The durations were not reported for 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 (presumably 4 pieces total per group) 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 tape stripped 20 times to remove the stratum corneum. No information on thickness or skin integrity was provided.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates per group was not specified in the methods. The data table reporting Kps indicates a n of 3-5. A sample size of 4 is the minimum sample size required, as specified in OECD 428.
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 cm2), so the applied volume was ~ 2.6 mL/cm2 which is appropriate for infinite exposure to a liquid, regardless of concentration. A molar concentration of 0.4 mM was reported. Based on a molecular weight of 312.4, and the 2.5 mL volume, approximately 0.312 mg of the test substance was added to the donor chamber with a 0.95 cm2 surface area (equivalent to ~0.328 mg/cm2).

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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - stripped (human) - BP metabolite

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	Medium	Details regarding the outcome assessment protocol were limited. The same vehicle and receptor fluids were used for each replicate. Some information was not specified, including the duration of exposure, and 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. The skin was excised from animals from two donors. The skin was tape stripped, and the thickness was not reported. 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	There was insufficient information to determine whether there were confounding variables between replicates that were unrelated to exposure. The study did not indicate whether the test substance was soluble in the receptor fluid (PBS + 10% DMSO) although DMSO is expected to enhance the solubility of lipophilic substances. The study noted significant metabolism occurred and concentrations of two metabolites were assessed. This could cause additional variation across replicates.
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 metabolites 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 coefficient of variation across replicates could not be determined for several endpoints, including measurements in receptor fluid and in the skin. CoV for Kp was >25% for both metabolites.
	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).
	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 Uninformative

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Chemical:	Butyl benzyl phthalate
Exposure Type:	Parent compound
HERO ID:	3859042
Unique ID:	BBP - stripped (human) - BnP metabolite

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test substance identity	High	The test substance was identified as benzyl butyl phthalate (BnBP) 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 >95%. 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 = 4-5/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 exposure time, the receptor chamber was filled with 2.5 mL of fresh PBS + 10% DMSO, and the donor chamber was filled with 2.5 mL of PBS + 10% DMSO containing 0.4 mM 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 and replenished with an equal volume of the receptor fluid. The collected fractions were held at 4 degrees C until analysis. At the end of exposure (24 hours), the skin was washed 3 times with receptor fluid and then homogenized for analysis via HPLC. The lower limits of quantitation were reported.
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Domain 3: Exposure Characterization				

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Chemical: Butyl benzyl phthalate
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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 (0.4 mM) was diluted in PBS +10% DMSO. 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 the receptor fluid was not specified. BBP is lipophilic and it is assumed DMSO was added to increase solubility.
	Metric 8:	Consistency of exposure administration	Low	Details of exposure administration were insufficiently reported. The study included a single exposure group. The number of replicates was not explicitly reported, but based on sampling, there were at least 3-5 replicates. Human skin thicknesses were not reported. Tests were conducted using a consistent test solution volume of 2.5 mL, and a skin surface area of 0.95 cm2. The missing information could have a significant impact on the results.
	Metric 9:	Reporting of concentrations	Medium	A nominal 0.4 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	Uninformative	The duration of exposure was dependent on when permeation reached a steady state. The durations were not reported for 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 (presumably 4 pieces total per group) 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 tape stripped 20 times to remove the stratum corneum. No information on thickness or skin integrity was provided.
	Metric 13:	Number/Replicates per group	Medium	The number of replicates per group was not specified in the methods. The data table reporting Kps indicates a n of 3-5. A sample size of 4 is the minimum sample size required, as specified in OECD 428.
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 cm2), so the applied volume was ~ 2.6 mL/cm2 which is appropriate for infinite exposure to a liquid, regardless of concentration. A molar concentration of 0.4 mM was reported. Based on a molecular weight of 312.4, and the 2.5 mL volume, approximately 0.312 mg of the test substance was added to the donor chamber with a 0.95 cm2 surface area (equivalent to ~0.328 mg/cm2).

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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: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 3859042
Unique ID: BBP - stripped (human) - BnP metabolite

Domain	Metric		Rating	Comments
	Metric 15:	Consistency of outcome assessment	Medium	Details regarding the outcome assessment protocol were limited. The same vehicle and receptor fluids were used for each replicate. Some information was not specified, including the duration of exposure, and 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. The skin was excised from animals from two donors. The skin was tape stripped, and the thickness was not reported. 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	There was insufficient information to determine whether there were confounding variables between replicates that were unrelated to exposure. The study did not indicate whether the test substance was soluble in the receptor fluid (PBS + 10% DMSO) although DMSO is expected to enhance the solubility of lipophilic substances. The study noted significant metabolism occurred and concentrations of two metabolites were assessed. This could cause additional variation across replicates.
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 metabolites 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 coefficient of variation across replicates could not be determined for several endpoints, including measurements in receptor fluid and in the skin. CoV for Kp was >25% for both metabolites.
	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).
	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 Uninformative

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:	Butyl benzyl phthalate
Exposure Type:	Parent compound
HERO ID:	675074
Unique ID:	BBP 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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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: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 675074
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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 cm2 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 cm2. 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/cm2 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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Chemical:	Butyl benzyl phthalate
Exposure Type:	Parent compound
HERO ID:	675074
Unique ID:	BBP absorption in rat

Domain	Metric		Rating	Comments
	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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Chemical: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 675074
Unique ID: BBP absorption in rat

Domain	Metric		Rating	Comments
	Metric 14:	Outcome assessment methodology	Low	There were several deviations from OECD 427 guidelines. For finite dosing 1-5 mg/cm2 is recommended, this study reported an application rate of 5-8 mg/cm2, 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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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: Butyl benzyl phthalate
Exposure Type: Parent compound
HERO ID: 675074
Unique ID: BBP 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