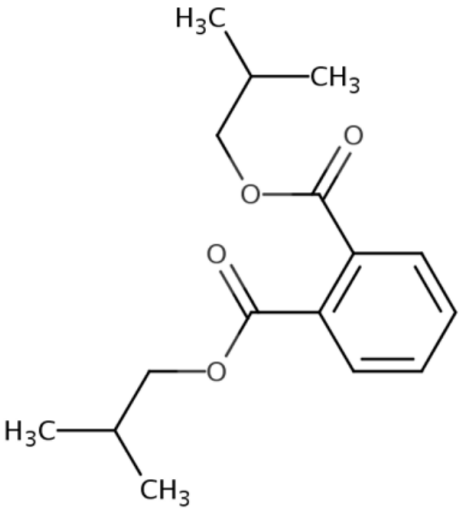
United States
Environmental Protection Agency

July 2025
Office of Chemical Safety and
Pollution Prevention

# Data Quality Evaluation and Data Extraction Information for Dermal Absorption for Di-isobutyl Phthalate (DIBP) (1,2-Benzenedicarboxylic acid, 1,2-bis(2-methylpropyl) ester)

# Systematic Review Support Document for the Draft Risk Evaluation

## CASRN: 84-69-5




***July 2025***

This supplemental file contains information regarding the data extraction and evaluation results for data sources that met the PECO screening criteria for the *Draft Risk Evaluation for Diisobutyl Phthalate (DIBP)* 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 *Draft Systematic Review Protocol for Diisobutyl Phthalate (DIBP)*.

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:** 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.
**HERO ID:** 675074

**EXTRACTION**

| Parameter | Data |
|---|---|
| Extraction ID; Chemical: | DIBP absorption in rat; Di-isobutyl phthalate (DIBP)-Parent compound |
| Species; Comments: | Rat; Not Reported; Notes: Not Reported |
| Sex; Covering used in Test System: | Male; Occluded |
| Vehicle; Concentration of Test Substance in Vehicle (percent): | absolute ethanol (USP grade); Not Reported |
| Mass per Surface Area on Skin (mg/cm2); Dose (include units (e.g., mg/kg bw))): | Not Reported; 30-40 mg/kg |
| Test Substance on Skin; Exposure Repeated (Days); Test Substance on Skin (Comments): | Other; Not Reported; Notes: 7 days |
| Time of Absorption Measured; Frequency; Time of Absorption Measured (Comments): | Other; every 24 hours; Notes: 7 days |
| Time Skin was Washed and Method used; Radiolabel Presence: | Skin was not washed; Yes |
| Total Recovery (percent); Dose Type: | 93; Finite |
| Percent Found in Skin Depot after Washing and Tape Stripping: | 35; Notes: Skin was not tape stripped. The dose was reported as a range (5-8 mg/cm2). |
| Percent Found in Urine ; Comments: | 51; Notes: Skin was not tape stripped. The dose was reported as a range (5-8 mg/cm2). |
| Percent Found in Feces ; Comments: | Not Reported; Notes: Skin was not tape stripped. The dose was reported as a range (5-8 mg/cm2). |
| Percent Found in Blood/Serum ; Comments: | Not Reported; Notes: Skin was not tape stripped. The dose was reported as a range (5-8 mg/cm2). |
| Percent Found in Air ; Comments: | Not Reported; Notes: Not Reported |
| Percent Found in Cage Wash ; Comments: | Not Reported; Notes: Not Reported |
| Percent Found in All Tape Strips, Excluding the Upper Two Strips: | Not Reported; Notes: Skin was not tape stripped. The dose was reported as a range (5-8 mg/cm2). |
| Total Percent Absorbed: | 51 |
| Steady State Permeability Coefficient (Kp) (cm/hr); Steady State Permeability Coefficient (Comments); Steady State Flux (ug/cm2/hr); Steady State Flux (Comments); Maximum Permeability Coefficient (Kp) (cm/hr); Maximum Permeability Coefficient (Comments); Maximum Flux (ug/cm2/hr); Maximum Flux (Comments); Additional Comments: | Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Not Reported; Notes: Not Reported; Notes: Not Reported |

**EVALUATION**

| 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. |

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**EVALUATION**

| Domain | Metric | | Rating | Comments |
|---|---|---|---|---|
| Domain 2: Test Design | | | | |
| | Metric 4: | Randomized allocation of animals | Low | The study did not report how animals were allocated into groups. |
| | 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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**EVALUATION**

| 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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**EVALUATION**

| 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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| | | | EVALUATION | |
|---|---|---|---|---|
| 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 ± 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